

HIV/AIDS DIAGNOSIS AND MANAGEMENT
A PHYSICIAN'S HANDBOOK

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Editor:
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**To My *Guru*,
Dr. Mohan Gharpuray**

He not only taught me dermatology but, by his own example, also taught how to keep learning all the time and to give, as much as possible, to others what one has learnt.

It is he who sensitized me to look beyond the mere signs and symptoms of the case and to understand the suffering of the human being who happened to be in the clinic as a patient.

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When a tree planted by you blooms it is due to several environmental factors that have contributed. However the most important of all of these is the ‘seed’. Not the seed of the concept itself, but the seed of the desire to sow something, the seed of the desire to respond to the needs of the people around you, of the necessity of being concerned about the problems of your own people, and of the motivation - not to wait for someone else to take the first step - but to take it yourself. The credit of the bloom may be attributed to the one who planted the seed but it actually belongs to the one who kindled this desire, who kept the fire burning, who cared for you whenever you felt ‘burnt out’. Dr. Sanjeevane Kulkarni, my best friend in life, has always remained the inspiration and motivation behind all my work. She has also provided the most candid and the best critique.

The quality of this publication is all due to these people. The responsibility of any shortcomings is entirely mine.

Dr. Vinay Kulkarni
Editor

PREFACE

HIV/AIDS epidemic has changed and challenged all the aspects of medicine during last two decades. It has also affected the society in many ways. It has proven that we are still vulnerable to epidemics of previously unknown pathogens. It has brought people from various fields, like social scientists, basic scientists, human rights activists, health care providers, together. It has made people think beyond the narrow restrictions of their fields and respond to the global challenge. One cannot understand the pandemic unless one understands its link with poverty, unemployment, displacement, globalization of the economies, changing sexual attitudes, increased travel, disintegration of families, taboos towards sexual behaviour, stigmatization of people with different life styles, intolerance, etc.

In our country the number of symptomatic HIV/AIDS patients is now increasing very sharply. Physicians and surgeons of all specialities are now required to manage them. On one hand it is true that most symptoms are due to opportunistic infections (OIs) and therefore could be diagnosed and treated by anyone, on the other hand the depressed immunological status alters the presentation of these diseases, as also hitherto uncommon disease entities are being seen more frequently. The physician needs to be updated regarding such manifestations.

Being a new phenomenon, most of the physicians in clinical practice have had no exposure to HIV medicine during their training. It is mainly based on their experience and information gathered in bits and pieces, that the cases are being managed.

About 13 years ago when I started looking around for information on HIV/AIDS it was difficult to obtain. Even after these many years – despite generation of tremendous amount of information in the form of text-books, journals, news-letters, networks and internet resources – the physician in the clinic is still starved of concise and simple guidelines based on the Indian experience and written from an Indian perspective. This is a humble attempt on my part to bridge this gap. Certainly there is a need for a text-book of HIV medicine written from our own country, but for a physician busy in clinical practice a text-book remains quite an unfriendly option. We have chosen a more 'user friendly' format, so that it could be used as a desk reference. The chapters have also been written in such a manner that the text would provide a symptomatology based guideline for in-office management of patients. This would also be useful in areas where investigative facilities are lacking.

We have attempted to cover the widest possible spectrum of presentation, yet more emphasis has been laid on common presentations. The diagrams, the flow-charts and the colour photographs would certainly be helpful.

We also feel that the text would be useful for medical students preparing for undergraduate examinations, as well as for those preparing to launch their clinical practice.

Many people believe and say that if an HIV/AIDS patient is destined to die “why treat?”

We believe that each and everyone has the basic human right to lead a reasonable quality of life – whether there is HIV or not. Life with care and support, and death with human dignity should not be denied to anybody. It is the stigma attached to HIV/AIDS, mainly due to its major mode of transmission (sexual), that raises such debates. There are several other ailments directly related to human behaviour which do not carry such a stigma. Secondly, our behaviour is not entirely determined individually. Several societal factors influence and determine it. So, emergence of such epidemics is, if at all, a manifestation of our collective failure. An affected individual should not be blamed and ostracised for that.

We have also seen, through years of experience of treating HIV/AIDS patients that prophylaxis against common opportunistic infections (OIs), prompt diagnosis and treatment of OIs definitely improves the quality of life of our patients. More experienced the physician, better the care. This book is intended to substantiate the experience of physicians caring for HIV/AIDS patients.

Availability of anti-retroviral drugs has added a new dimension to HIV/AIDS care. These drugs are extremely costly at present and need to be taken life-long. But everybody hopes that one day, there will be an affordable and easily available cure. We also hope that one day, we the people, will be so responsible in our acts that no virus could threaten us. Until such a day dawns – we will keep on trying to bring meaning to the lives of millions of friends infected with HIV and their families.

This book is a small step in that direction.

Dr. Vinay Kulkarni,
Editor.

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[Credits: Dr. Ajay Deshpande (54); Dr. Samiran Panda (60,61); others from the collection of Dr. Vinay Kulkarni]

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AIDS: HISTORY, ORIGIN AND EPIDEMIOLOGY

Dr. Sanjay Mehendale

HISTORY OF HIV/AIDS

Acquired Immune-Deficiency Syndrome (AIDS) was first described as a distinct clinical disease among men having sex with men (MSM, gay men or homosexual men) in 1981, who presented either with *Pneumocystis carinii* pneumonia and / or a rare type of cancer of skin, Kaposi's sarcoma. AIDS cases were subsequently reported in intra-venous drug users (IDUs) who were sharing needles and syringes, and hemophilia patients who had received blood products. Subsequently, AIDS cases were reported among blood transfusion recipients, adult males and females in Africa and children born to women having AIDS or those who were using injecting drugs.

Studies initiated to identify the cause of immuno-deficiency in AIDS patients and to study possible role of viruses like cytomegalovirus, Epstein-Barr virus and hepatitis B virus were inconclusive. Eventually, it became known that T helper lymphocytes get depleted in patients of AIDS. As human

T lymphotropic viruses (HTLV) were the only human viruses known to infect T cell lymphocytes and spread sexually as well as through contaminated blood or from infected mother to fetus, it was postulated that the agent causing AIDS was a variant of HTLV-III. The agent was subsequently described as Human Immunodeficiency Virus (HIV).

EXISTENCE OF HIV BEFORE 1981

Evidence from retrospective studies indicates that HIV was spreading for a few decades silently before AIDS was finally reported in 1981. Sera collected in 1959 from cases of haemorrhagic fever in Zaire, Africa, specimens from a British seaman who died in 1959 of an unexplained immunodeficiency along with certain opportunistic infections and samples collected from a Norwegian seaman and his wife in 1960, who died later in 1976 showed reactivity to HIV-1. AIDS might have occurred simultaneously in Africa as well as Europe and studies on stored serum samples suggested that the virus might have started causing the disease in

human beings around mid 50s or might have been introduced to cities through migration of a few resistant carriers from previously isolated tribes as a part of population movement. If the average incubation period of AIDS is believed to be 8-10 years, and the fact that the first AIDS cases were reported in 1981; it is certain that HIV was circulating in the previous decade, but was not diagnosed in years before 1981.

THEORIES OF ORIGIN OF HIV

Extreme controversies exist with respect to the theories of origin of HIV. They range from HIV being agents of biological warfare introduced by the racist people to its entry from outer space. Some of the following theories may be considered significant in the context of origin of HIV

1. Mutations or recombination may have occurred in case of organisms that were silently infecting the population or were causing a totally different disease and this might have led to evolution of virulent strain of HIV.
2. The disease might have been existing at a low level causing occasional or sporadic cases in some isolated pockets and relatively inaccessible areas. The presence of the disease might not have been noticed due to its low virulence and prevalence. Invasion of such areas by unaccustomed humans might have brought the agent from such isolated pockets into the outside susceptible populations.
3. The organism may have been introduced to humans from other species. Similarity has been described between the simian immunodeficiency virus(SIV) of sooty mangabey monkeys(SIVsm) and HIV-2 and SIV of chimpanzees(SIVcpz) and HIV-1. A possibility of evolution of HIV from SIV of wild-caught mandrill in Africa(SIVmnd), has also been hypothesized. It is possible that HIV might have emerged from the monkey viruses. However, the mechanisms to explain such a cross-species transfer are not precisely understood. This may have occurred naturally due to passage of the virus from wild monkeys to monkey species observed close to human dwellings and then to human beings. On the contrary, human behaviour or some scientific experiments may have been responsible for iatrogenic transfer of these monkey viruses to human beings. It may have happened due to entry of the virus in humans through human vaccines like Polio vaccines made from primary kidney cultures of African Green Monkeys and a suggested use of this vaccine against recurrent herpes by gay men. In addition, practice of injecting monkey blood for sexual stimulation in pubic area in certain African tribes and conduct of some human experiments involving injection of blood containing malaria parasites from Chimpanzees into humans for

studying its transmission, may have been some other possible mechanisms for emergence of HIV.

However, there is no agreement on how HIV originated as yet.

EPIDEMIOLOGY OF HIV/AIDS:

Global scenario

The HIV epidemic went through many transitions. In the earlier part of the HIV pandemic, three patterns were described. In most of the industrialized countries, the HIV transmission was predominantly among MSM and in IDUs, and males were more commonly affected. The African continent was witnessing heterosexual transmission of HIV and both the sexes were equally affected. In some countries, the transmission was observed to be mixed. Over a decade, clear-cut boundaries between the patterns gradually faded and the focus of the epidemic shifted from the western industrialized world to the developing countries.

Major changes that have been observed in the epidemiology of HIV/AIDS over the last decade include increasing spread and reporting among women, children, minorities and in economically unprivileged communities. It has also become evident that the disease is not restricted to specific high-risk groups like sex workers, STD patients and truck drivers; but has reached the general population and also in the rural areas.

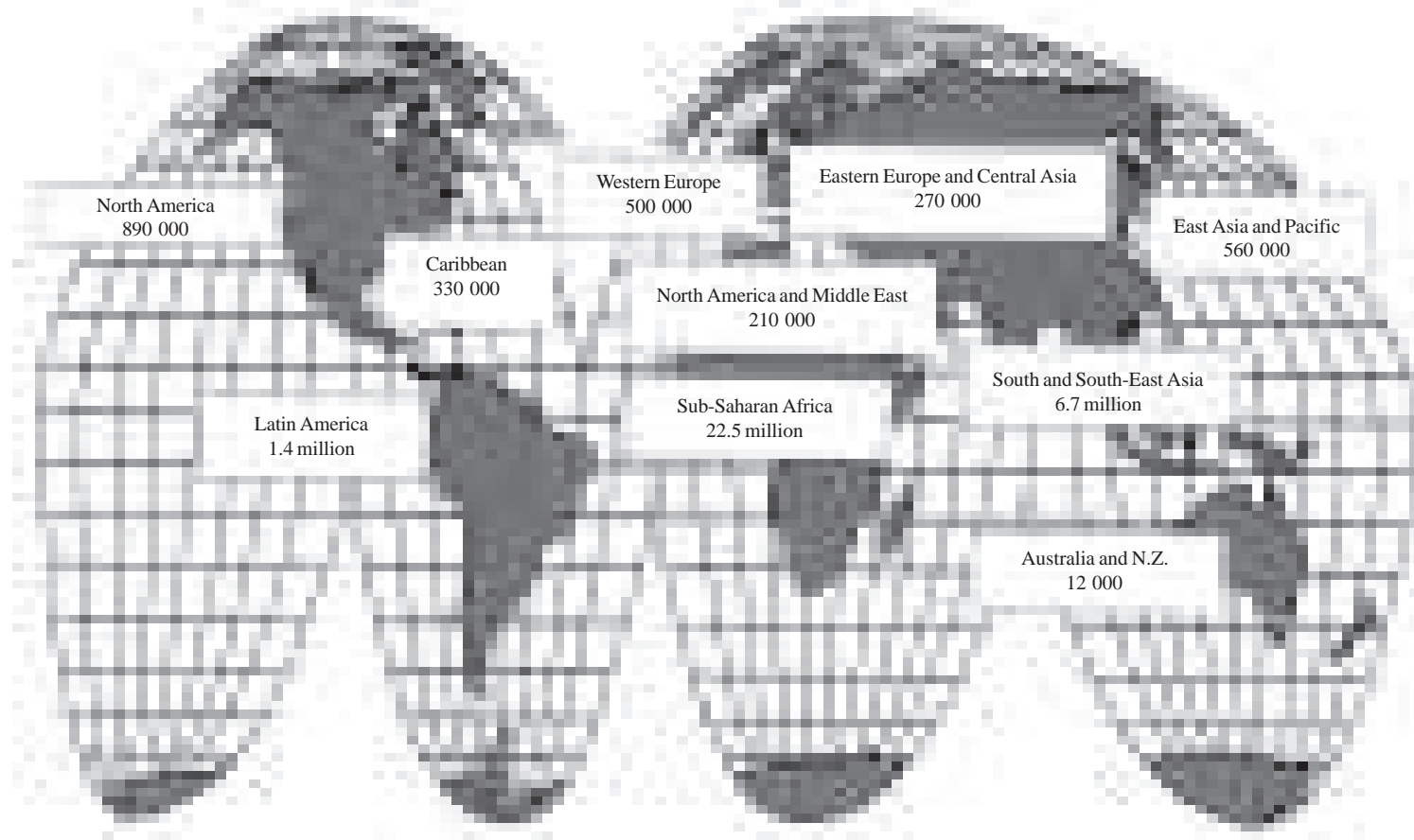
The emphasis is no more on high-risk groups alone, but also on the practice of at risk behaviour by anybody.

It has been estimated that almost 5.8 million people acquired HIV infection both in 1997 and 1998 and 1% of them were children. Nearly 16000 new infections occurred every day during the year. Estimated deaths due to AIDS increased from 2.3 million in 1997 to 2.5 million in 1998.

The present UNAIDS estimates indicate that around 33.4 million or 3.34 crore people were living with HIV infection at the end of 1998 (Figure 1). One in every 100 adults in the sexually active age group of 15 to 49 is believed to be HIV infected world-wide. More than 90% of HIV- infected people in the world live in the developing countries and as most of these do not know that they are infected; there may be over 30 million people in the world today who have no idea that they are infected. It has been predicted that more than 40 million people will be living with HIV in the year 2000. The cumulative total of deaths due to AIDS since the beginning of the epidemic has gone up to 13.9 million. Thus, since the beginning of the epidemic almost 18 years ago, over 47 million people have been infected with the Human Immuno-deficiency Virus.

In most parts of the world, majority of new infections has been occurring in young people between the ages of 15 and 24. An increase in STDs among

**Figure 1: Persons living with HIV/AIDS as of 1998 end
Global total: 33.4 million, Source: UNAIDS**



young people has been reported from Mongolia, Russia, Namibia and United States. Young women appear to be especially vulnerable to infection. In South Africa, the proportion of pregnant 15-19 year old girls infected with HIV rose two times reaching 13% in 1996 in just two years. In Botswana the prevalence rate was observed to be around 28% in the same group in 1997. In Maharashtra State in India, where the epidemic is in its early years, 3.5% of pregnant teenagers tested HIV-positive in a recent study.

Sub-Saharan Africa

Two-thirds of the HIV infected people in the world are living in Sub-Saharan Africa and the spread of HIV has been predominantly by heterosexual route. The prevalence (burden of the disease at a specific time point) of HIV infection in the sexually active population is reported to be as high as 7.4%. Around 530000 children (almost 90% of the global total) acquired HIV directly from their infected mothers due to poor access to programmes for the prevention of mother-to-child transmission and indirectly due to factors like high fertility and lack of awareness. Large burden of HIV infection in this region in the previous decade has resulted into a large number of AIDS cases and deaths. In the year 1998, four fifth of the global deaths due to AIDS occurred in Africa. Southern Africa has been the worst affected part of this continent. By early 1997, it was reported that 43% of pregnant women in Francis town and

32% of pregnant women in Harare, Zimbabwe were HIV infected. In Zimbabwe, one in five adults are presently estimated to be infected with HIV. Some densely populated countries like Nigeria in Western Africa are severely affected, with estimated 2.2 million people currently living with HIV. East Africa suffered a massive regional epidemic initially. But a developing country like Uganda, with its limited resources, succeeded in arresting the spread of the virus by adopting safer sexual behaviour like late initiation of sex, having fewer partners and more frequent condom use by young people.

Latin America and the Caribbean

HIV is concentrated in less educated and lower social and economic classes of society, in MSM and IDUs primarily. In Brazil, a very limited information is available in these groups. However, it is believed that almost 50% IDUs in both Brazil and Argentina are HIV infected. Mexican studies showed that up to 30% MSM and 5-11 % IDUs may be living with HIV.

Rising HIV prevalence rates in women indicate that heterosexual transmission is becoming more prominent. In Brazil, the male : female ratio of AIDS cases has dropped from 16:1 in 1986 to 3:1 in 1997. Level of HIV infection in pregnant women has reached up to 1% in Honduras and more than 3% in Porto Alegre, Brazil. However, the rates are substantially higher in the Caribbean and over 8% of pregnant women were HIV

infected in 1993.

In Mexico and Brazil, AIDS has emerged as a major cause of death in men between 25 and 34 years of age. However, a recent drop in AIDS mortality has been recorded in Sao Paulo, Brazil and is attributed to the increasing use of antiretroviral therapy. A favourable indication is that the incidence rates (rate at which new cases occur in a defined population) in some of the South American countries are stabilizing and might be reflecting successful implementation of HIV prevention strategies.

Newly Independent States (NIS) in Eastern Europe

Nearly 100000 new infections have occurred in several Eastern European nations like Ukraine and Russia in 1997; mostly as a result of sharing injecting equipment. However, increasing trends in STDs, especially syphilis have been observed in Russia, Belarus and Moldova and they may be important in HIV transmission.

Industrialized countries

In 1997, 44000 new HIV infections are estimated to have occurred in North America compared to 30000 in the Western Europe. Although in the United States, a decrease in HIV incidence was observed among homosexual men and IDUs due to acceptance of preventive interventions and change in behaviour, heterosexual spread of HIV among

African-Americans and the Hispanic community actually increased. This may be due to failure of prevention efforts in minority communities where transmission is often predominantly heterosexual. Only in Portugal and Greece in Western Europe, new cases due to unsafe drug injecting have shown a substantial increase.

Use of newly available anti-retroviral drugs and Highly Active Anti-Retroviral Therapy (HAART) has resulted in reducing the mortality and rate of progression from HIV infection to AIDS in North America, Western Europe, Australia and New Zealand.

Asia

The epidemic is more recent in Asia than in Africa and has not been uniformly monitored. However, with almost half of the world's population, even though HIV prevalence is low, disease burden faced by individual countries is high. In countries such as Indonesia, Malaysia, the Philippines and Singapore, HIV infection rates are well under 1%. The HIV prevalence in India is believed to be close to 1%, however, that in Thailand, Cambodia and Myanmar has been estimated to be over 2%. It has been observed that higher frequency of commercial sex, STDs and drug injecting have been the major determinants in the spread of HIV infection in Asia. Approximately 6.7 million (nearly 20% of the global total) people are currently believed to be living with HIV in Asia and the Pacific and this proportion of

HIV infected people in Asia is expected to rise to 25% by 2000 AD.

In Thailand, around 750 000 persons are infected with HIV, representing 2.3% of the adult population. However, sustained prevention efforts directed at increasing condom use, discouraging men from visiting sex workers, and offering young women better education and other prospects so as to discourage their entry into commercial sex industry have resulted in a decline in new infections. In Cambodia, 5% pregnant women, 6% soldiers and policemen and 50% sex workers were found to be HIV infected in sentinel surveillance for HIV. A rapid spread of HIV has been observed in Viet Nam and Myanmar. In Myanmar, 20% of sex workers and 65% of injecting drug

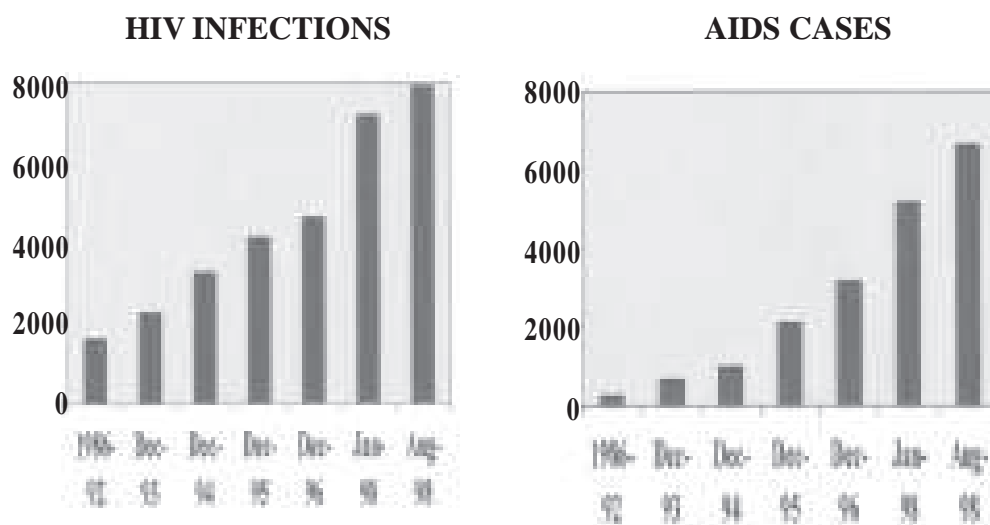
users are HIV infected. Although the reported HIV prevalence in China is low, it is likely to be grossly under reported.

EPIDEMIOLOGY OF HIV/AIDS IN INDIA

Surveillance for HIV/AIDS

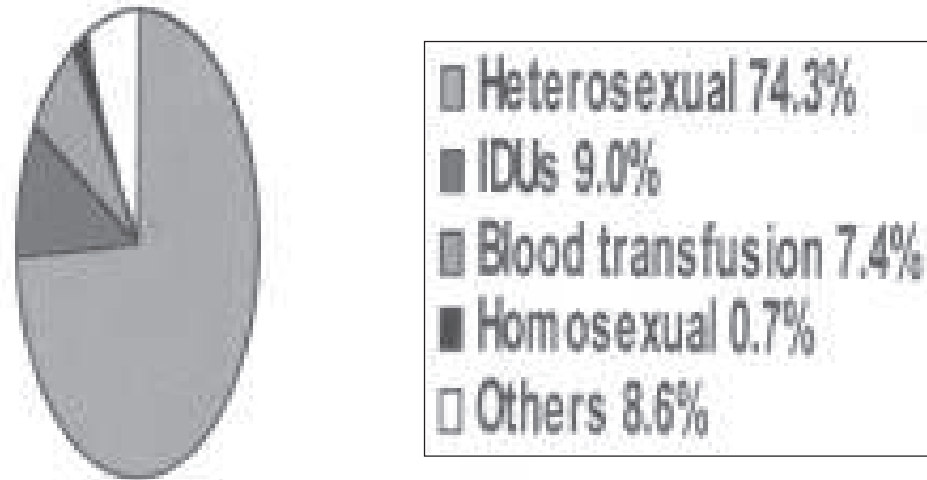
Surveillance activities began in India in 1986 with advocacy as the major objective. The first report of HIV infection was from commercial sex workers in Chennai in 1986 and the first AIDS case in India was reported from Bombay in 1986. By the end of August 1998, 79237 HIV infections and 6600 AIDS cases have been reported to the National AIDS Control Organization in India (Figure 2). With estimated infection rates of 0.6-1% of the total

Figure 2: Cumulative HIV infections and AIDS cases in India



Source : National AIDS Control Organization, Ministry of Health, Government of India

Figure 3: Probable source of infection in AIDS cases in India
Source: National AIDS Control Organization, Government of India



adult population, almost 3-5 million people are believed to have been infected with HIV. India possibly has the highest number or HIV infected people of all the countries in the world. In all, 50,000-1,00,000 cases of AIDS may have already occurred in the country.

India is experiencing a rapid and extensive spread of HIV. The doubling time of AIDS cases in Vellore, South India was reported to be approximately one year and that in Pune STD patients to be up to two years. The HIV sero-prevalence in intravenous drug addicts in Manipur increased rapidly from 50% in 1991 to about 87% in 1996. The most rapid and well-documented heterosexual spread of HIV has been observed in the states of Tamilnadu and Maharashtra and that through intravenous drug use in Manipur and the adjoining north-eastern states. HIV infection has spread to all the states in India. Around 75% of HIV

infection reported in India is due to heterosexual transmission (Figure 3). It appears that the distribution of problem is highly varied in different part of the country. The sero-prevalence of HIV infection has been reported to be low in East & North India. Although the prevalence of HIV infection in rural areas is not precisely known, there is an evidence of percolation of the problem from persons with high-risk behaviour to the general population and rural areas. STD prevalence in rural areas has been reported to be 3-4%.

The HIV sero-prevalence among the pregnant women primarily attending the public and Government hospitals has been reported to be between 0.5-1.5% in various parts of the country. HIV prevalence among voluntary blood donors in the metropolitan cities in India during the period of 1990-93 was reported to be 0.3 to 0.9% and in some

areas of the western state of Maharashtra, it has been reported to be up to 6% in 1997-98.

Sero-epidemiological studies

In Vellore, the sero-prevalence of HIV-1 antibody among sex workers was reported to increase from 1.8% in 1986 to 28.6% in 1990, while in Pune and Mumbai in western India, the HIV sero-prevalence among female sex workers has also greatly increased to up to 50%. Such a high prevalence is probably a result of a very high incidence of over 25% per year as reported among the sex workers attending STD clinics in Pune. High prevalence and incidence of HIV has also been noted in women attending STD clinics who denied being sex workers. Sexual contact with their partners (who often had sexual contact with female sex workers and suffered from STDs) was found to be the only risk factor in such women.

The prevalence of HIV infection in STD patients increased from 0.19 per cent in 1986 to 3.9 per cent in 1992 in South India. However, HIV sero-prevalence among STD patients in Bombay and Pune has been reported to be close to 20%. An incidence rate of 7.8% per year was reported among STD patients in Pune and the rate was higher among those who reported a recent visit to sex workers. Sexually transmitted diseases have been found to be strongly associated with high HIV incidence and prevalence. Factors like number of sex partners, lack of condom use and

previous or present STD have been found to be important predictors of HIV prevalence and incidence.

A high HIV prevalence of 5.2% was found in a study done on 500 truck drivers and helpers in West Bengal in 1994 who had little or no awareness about AIDS and were routinely practicing high risk behaviour. Among truck drivers in Chennai, HIV infection increased four times from 1.5% in 1995 to 6.2% just one year later.

Mandatory testing of blood and blood products was initiated in late 1980s. However, studies among thalassaemic and other children who received multiple transfusions have reported a high HIV sero-prevalence ranging between 8.9% and 30.4%, mostly due to transfusions of commercially available cryoprecipitate. Data from Mumbai showed that the HIV seropositivity in tuberculosis patients increased from 2.6% in 1988 to 10.2% in 1993-1994 and then to 28% in 1996, while in Delhi and Chennai, HIV seropositivity among tuberculosis patients was reported to be 0.4% and 3.4% in 1992-1993 respectively. Almost 20% of the newly diagnosed tuberculosis patients attending a tuberculosis clinic at Pune were found to be HIV infected in 1997. Infection due to HIV-2 and dual infection of HIV-1 & 2 has been reported predominantly from Western India. Of the persons infected with HIV, 1.7-4.6% have been reported to be due to HIV-2 alone and 3.3-20.1% due to HIV 1 and

2. Presence of dual infection of HIV-1 and 2 and not of HIV-2 alone has been also reported among IDUs from Manipur.

Although the infection rates in India are still low in comparison to many neighbouring countries, they are well over 10 times higher than in China. There has been ample evidence that the epidemic is no more restricted to persons with high-risk behaviour. It has already reached people having low risk behaviour and is expanding in women. Some of the important factors which might have contributed significantly to rapid spread of HIV in India are multiple partner sexual relationships and a high prevalence & incidence of sexually transmitted diseases.

IMPACT OF THE AIDS EPIDEMIC

The HIV/AIDS pandemic has produced a tremendous impact on familial, social, cultural, economic and demographic levels. It has been projected in nine countries (Botswana, Kenya, Malawi, Mozambique, Namibia, Rwanda, South Africa, Zambia and Zimbabwe) where more than 10% adults are infected with HIV, the average life expectancy is likely to be reduced by 17 years. In some parts of the world, the proportion of the total adult population has been observed to be actually shrinking. AIDS has become one of the most leading causes of death in adults. In the United States, AIDS is the second leading causes of death in people aged 25-44. In rural Uganda, AIDS was reported to account for 7 out

of every 10 deaths among men between 25 and 44 and women 20 and 44 years. In Namibia, HIV causes nearly twice as many deaths across all ages as malaria, the next most common killer.

The impact on the families has been very significant. It is estimated that since the beginning of the epidemic more than 8 million children have lost their mothers and many of these also lost their fathers to AIDS. It is estimated that this figure will almost double by the year 2000. For majority of the people living with HIV in the developing world, access to anti-retroviral and even to treatment of opportunistic infections is often difficult or impossible. Thus, many if not most of the 30 million currently infected people may die within the next decade. Infant and child survival in developing nations is being seriously jeopardized by HIV. Already, 25% more babies below one year are dying in Zimbabwe and Zambia. By 2010, Zimbabwe's infant mortality rate is expected to rise by 138% because of AIDS, and its under-five mortality rate by 109%. Substantial rise in the childhood mortality is also adversely affecting the life expectancy.

With the onus of the epidemic shifting to the developing world, the problems for AIDS prevention and control have grossly increased. HIV infections, AIDS patients and tuberculosis cases are increasing in great numbers in developing countries. Loss of adult productive population is adding a further pressure on the already stressed economy.

Even if newer drugs or vaccines will be developed, it is likely that they may not be affordable and easily available in these resource poor countries. It is possible that the gap between the developed and the

developing countries will continue to widen. To try and bridge this gap will be a real challenge for the scientific community, policy makers and programme managers both at the national and international level.

SELECTED BIBLIOGRAPHY

Origin and history of HIV/AIDS

1. Essex M. Origin of AIDS in AIDS: Aetiology, Diagnosis, Treatment and Prevention. Published by JB Lippincott Company, USA. Third Edition. 1992; p 3-10.
2. Pavri KM. The Origin of AIDS : How did HIV evolve? CARC Calling. 1994; 7:2-12.
3. Siefkes D. The origin of HIV-1, the AIDS virus. Med-Hypotheses. 1993 Oct; 41(4): 289-99
4. Horowitz LG, Strecker R, Cantwell A, Vid D & Grossman G. The mysterious origin of HIV: reviewing the natural, iatrogenic, and genocidal theories of AIDS. Int-Conf-AIDS. 1996 Jul 7-12; 11(2): 173 (abstract no. We.D.3678)
5. Hayflick L. Origin of HIV-1. Lancet. 1992;340:484-5.
6. McClure MD and Schultz TF. British Medical Journal. 1989;298:1267-8.

Global epidemiology

7. UNAIDS. UNAIDS- Report on the Global HIV/AIDS Epidemic- Dec; 1997.
8. MAP Network (Monitoring the AIDS Pandemic Network). Report of the Symposium on the Status and Trends of the HIV/AIDS Epidemics in the World. Veyrier du Lac, France. June 1998.

9. UNAIDS-WHO. AIDS Epidemic Update : December 1998.
10. Mertens TE and Low Beer D. HIV and AIDS : Where is the epidemic going? Bulletin of the World Health Organization. 1996; 74:12-9.
11. AIDS in the World II. Published by Oxford University Press. Edited by J Mann & D Tarantola. New York, Oxford. 1996.

Epidemiology of HIV/AIDS in India

12. NACO (National AIDS Control Organization), Ministry of Health and Family Welfare, Government of India. HIV/AIDS in India: A Status Report. Workshop on Biopsychosocial Aspects of HIV/AIDS : Mind - Body Reactivity. September 1998, New Delhi.
13. Jain MK, John TJ & Keusch GT. A review of human immunodeficiency virus infection in India. J Acquir Immune Defic Syndr. 1994 Nov; 7(11):1185-94
14. Jain MK, John TJ & Keusch GT. Epidemiology of HIV and AIDS in India. AIDS. 1994; 8 Suppl 2:S61-75.
15. Narain JP, Jha A, Lal S & Salunke S. Risk factors for HIV transmission in India. AIDS. 1994; 8 Suppl 2:S77-82
16. Dietrich U, Maniar JK & Rubsamen-

Waigmann H. The epidemiology of HIV in India. *Trends Microbiol.* 1995 Jan; 3(1): 17-21

17. Bollinger RC, Tripathy SP & Quinn TC. The human immunodeficiency virus epidemic in India. Current magnitude and future projections. *Medicine.* 1995 Mar; 74(2): 97-106

Prevalence, Incidence and risk factors in North-Eastern, Western and South India

18. Sarkar S, Das N, Panda S, Naik TN, Sarkar K, Singh BC et al. Rapid spread of HIV among injecting drug users in north-eastern states of India. *Bull Narc.* 1993; 45(1): 97-105.
19. Pal NK, Chakraborty MS, Das A, Khodakevich L, Jana S & Chakraborty AK. Community based survey of STD/HIV infection among commercial sex workers in Calcutta (India). Part IV: Sexually transmitted diseases and related risk factors. *J Commun Dis.* 1994Dec; 26(4): 197-202
20. Rodrigues JJ, Mehendale SM, Shepherd ME, Divekar AD, Gangakhedkar RR, Quinn TC et al. Risk factors for HIV infection in people attending clinics for sexually transmitted diseases in India. *BMJ.* 1995 Jul 29; 311(7000): 283-6.
21. Mehendale SM, Rodrigues JJ, Brookmeyer RS, Gangakhedkar RR, Divekar AD, Gokhale MR et al. Incidence and predictors of human immunodeficiency virus type 1 seroconversion in patients attending sexually transmitted disease clinics in India. *J Infect Dis.* 1995 Dec; 172(6): 1486-91.
22. Mehendale SM, Shepherd ME,

Divekar AD, Gangakhedkar RR, Kamble SS, Menon PA et al. Evidence for high prevalence & rapid transmission of HIV among individuals attending STD clinics in Pune, India. *Indian J Med Res.* 1996 Dec; 104: 327-35

23. Gangakhedkar RR, Bentley ME, Divekar AD, Mehendale SM, Gadkari D, Shepherd ME, et al. Spread of HIV Infection Among Married Monogamous Women Attending STD clinics in India. *JAMA* 1997; 278:2090-2092
24. Salunke S et al. Rapid rise in HIV prevalence among women attending government STD clinic in Mumbai (Bombay), India [letter]. *Int-J-STD-AIDS.* 1997 Apr; 8(4): 280
25. John TJ, Babu PG, Saraswathi NK, Jayakumari H, Selvaraj R, Kaur A et al. The epidemiology of AIDS in the Vellore region, southern India. *AIDS.* 1993 Mar; 7(3): 421-4
26. Solomon S, Anuradha S, Ganapathy M & Jagadeeswari. Sentinel surveillance of HIV-1 infection in Tamilnadu, India. *Int J STD AIDS.* 1994 Nov-Dec; 5(6): 445-6
27. Jacob M, John TJ, George S, Rao PS & Babu PG. Increasing prevalence of human immunodeficiency virus infection among patients attending a clinic for sexually transmitted diseases. *Indian J Med Res.* 1995 Jan; 101: 6-9
28. Srikanth P, John TJ, Jeyakumari H, Babu PG, Mathai D, Jacob M et al. Epidemiological features of acquired immunodeficiency syndrome in southern India. *Indian-J-Med-Res.* 1997 May; 105: 191-7

Cases before 1981

AIDS was first identified as a distinct syndrome in 1981 as the consequence of a cluster of cases amongst gay men in large US cities with highly visible and established gay communities. Subsequent review of the medical literature has revealed a plethora of inexplicable AIDS-like illnesses dating back to the late 1940s in the United States and Europe.

Pre-1981 cases fall into two categories: those for which stored blood samples have revealed HIV infection, and those for which no stored blood samples exist, but where the pattern of symptoms reported is nevertheless highly suggestive of AIDS.

The oldest AIDS case for which an HIV diagnosis has been confirmed is that of a Manchester sailor who died in 1959. Nothing is known about him except for the fact that he visited Africa. Doctors thought his death from multiple opportunistic infection so odd they wrote it up in *The Lancet* and stored tissue and blood for future investigation.

An American youth who died in 1969 has also been retrospectively diagnosed, as have a Norwegian family-father, mother and child-who all died in 1976. A Portuguese man who fell ill in 1978 has been retrospectively diagnosed as one of the earliest cases of AIDS caused by HIV-2.

The identified cases in which HIV was present are important because they challenge the belief that HIV is a virus which was introduced into the West in the 1970s. although some of these cases indicate contact with Africa, the 1969 case of an American youth shows no evidence of an African connection.

Clinical records have also been used to identify pre-1981 cases. Historians have looked for unusual cases recorded in the medical literature which appear to fit the existing definition of AIDS. A surprising number of such reports exist, dating back to at least 1940s in North America and Europe. Prior to 1960, all the cases identified in North America were men, but thereafter women begin to account for possible cases too, and at least one married couple has been identified.

(contd.)

Similar detailed reports do not exist for Africa, except for data concerning Kaposi's sarcoma, which became epidemic in equatorial Africa in the late 1950s. This form of KS, which took the lethal only in about 10% of cases, was not associated with HIV or with immune suppression, and affected Africans but not Westerners resident in Africa. It has recently been suggested that a number of different forms of KS may exist, perhaps with radically different causes, so it is as well to be sceptical of the appearance of KS as a marker for the widespread presence of HIV in Africa before the 1970s. African doctors tend to agree that AIDS did not appear in Africa before the late 1970s, and that it became epidemic only in the early 1980s. In the early years of the epidemic only in the syndrome was known as 'Slim' in Uganda and other central African countries; it first appeared in Uganda on the north shores of Lake Victoria, in Burundi and Rwanda (states to the west of Lake Victoria), and in Kinshasa (the capital of Zaire), which lies at the crossroads of trade routes linking East Africa, West Africa, Angola and Zaire.

Isolated cases of AIDS-defining illnesses began to appear among gay men and injecting drug users from the early 1970s in New York and San Francisco. These were not linked by doctors until the beginning of 1981. Although the cluster of PCP cases was identified in 1981, it is possible that a low level of 'pneumonia' cases were treated with standard antibiotics and hence went undetected by the Center for Disease Control for some years before 1981.

Researchers argue that AIDS cases could have occurred at a low level in the population before the 1940s without exciting much suspicion, due to a greater frequency of infectious diseases. It was only when infectious disease became less common that immune deficiency became more remarkable and worthy of note. Prior to the introduction of antibiotics, tuberculosis and syphilis may have masked minor clusters of HIV disease.

[Mirko Grmek: History of AIDS: Emergence and origin of a modern Pandemic (Princeton University Press, 1990)]

2

VIROLOGY OF HIV

Dr. Srikanth Tripathy

The retroviruses comprise of a large family of viruses. They are associated with many diseases like malignancies, wasting diseases, neurological disorders and immunodeficiencies. The history of retroviruses began in 1908 with the discovery of a filtrable transmissible agent associated with disease in chickens. In the next few decades, significant research work was carried out on murine leukemia viruses. In 1970, the reverse transcriptase enzyme present in retroviruses was discovered by two different scientists separately (David Baltimore and Howard Temin). In 1980, Robert Gallo and his colleagues reported the isolation of the first human retrovirus, which they named Human T-Leukemia virus or HTLV-1, due to its tropism for T-lymphocytes. So far, two evolutionary distinct groups of human retroviruses have been found : The leukemia virus (HTLV-I and HTLV-II) and the immunodeficiency viruses HIV-I and HIV-II viruses were first isolated in 1983 and 1986 respectively. Retroviruses have been traditionally divided into three subfamilies based on their pathogenicity,

i.e. Oncovirinae, Lentivirinae and Spumavirinae. Their classification is given in table 1.

The HIV replication cycle can be divided into two phases.

The *first phase* involves:

1. Interaction between viral envelope proteins and specific host cell receptors
2. Fusion of viral and cell membranes
3. Entry of the virion core into the target cell cytoplasm
4. Synthesis of double stranded DNA by reverse transcription using the single stranded RNA genome as template
5. Transport of the DNA, associated with the virion proteins to the nucleus of the cell
6. Integration of the viral DNA into host chromosomal DNA using the integrase enzyme to form the provirus

The *Second phase* involves:

- 1) Synthesis of viral RNA by RNA polymerase II using the integrated provirus as the template

Table 1. Classification of Retroviruses

Subfamily	Group	Examples
Oncovirinae	Avian Leukosis Sarcoma	Rous Sarcoma Virus (RSV)
		Avian Myeloblastosis Virus (AMV)
	Mammalian C-type	Avian Erythroblastosis Virus (AEV)
		Rous associated virus (RAV)-1to50 RAV-O
		Moloney murine leukemia virus (Mo-MiLV)
		Harvey murine sarcoma virus (Ha-MSV)
B type viruses	Abelson murine leukemia virus (A-MuLV)	
	AKR-MuLV	
	Feline leukemia virus (FeLV)	
D type viruses	Simian sarcoma virus	
	Reticulo-endotheliosis virus (REV)	
HTLV-BLV group	Spleen necrosis virus (SNV)	
	Mouse mammary tumor virus (MMTV)	
	Mason-Pfizer monkey virus (MPMV)	
Lentivirinae	Lentiviruses	“SAIDS” Viruses
		Human T-cell leukemia (or lymphotropic) virus (HTLV)
		Bovine Leukemia virus (BLV)
		Human Immunodeficiency virus (HIV-1&2)
		Simian Immunodeficiency virus (SIV)
		Feline Immunodeficiency virus (FIV)
		Visna-maedi virus
Equine infectious anemia virus (EIAV)		
Spumavirinae “Foamy” Viruses		Caprine arthritis-encephalitis virus (CAEV)
		Simian Foamy viruses(SFV)

- 2) Processing of the transcripts of the HIV genomic RNA as well as mRNAs
 - 3) Production of the spliced and unspliced viral mRNA transcripts that encode the regulatory and structural viral proteins
 - 4) Assembly of the precursor structural proteins along with genomic length RNA and budding of the virion particles from the host cell surface
 - 5) Maturation of the precursor poly proteins to form the infectious viral particle.
- Although HIV is one of the most recently discovered retrovirus, CD4 was the first retrovirus receptor to be identified. Another receptor called galactosyl ceramide can also serve as a receptor

for HIV in glial and neuroblastoma cell lines. The only other retrovirus receptor to be identified so far is that of moloney murine leukemia virus. However, expression of CD4 receptor on the cell surface is not sufficient to allow HIV entry into the cells since HIV-I cannot infect mouse cells that have been engineered to express CD4. Other human-specific accessory factors appeared to be required for CD4 mediated viral entry. This problem was overcome recently when Feng et al showed that a protein designated “fusin”, which is a putative G protein-coupled receptor with seven transmembrane segments, enabled CD4 expressing nonhuman cell types to support HIV-I envelop mediated cell fusion and HIV-I infection. Antibodies to fusin blocked cell fusion and infection of normal CD4 positive human target cells by HIV. Fusin messenger RNA levels correlated with HIV-I permissiveness in diverse human cell types. Fusin or CXCR4 acted preferentially as a coreceptor for T cell line tropic HIV-I isolates, in comparison to its activity with

macrophage tropic HIV-I isolates. Another coreceptor used by macrophage tropic HIV strains to infect CD4 containing cells is CCR5. A homozygous deletion of a 32 base pair sequence in the CCR5 gene has been associated with protection from HIV-I infection.

VIRUS STRUCTURE

HIV comprises of a nucleoprotein core surrounded by other protein coats. On its outer surface is a bilipid layer containing viral surface (gp120) and transmembrane (gp41) envelope proteins. gp120 contains viral determinants that bind to the receptor present on the host cell surface. gp41 contains the transmembrane and cytoplasmic domains that anchor the gp120 onto the surface of the viral bilipid layer.

The nucleoprotein core of the HIV virion comprises of the copies of the genomic RNA (positive strands, which are identical) and associated RNA molecules, together with gag and pol

Figure 1. HIV virion.

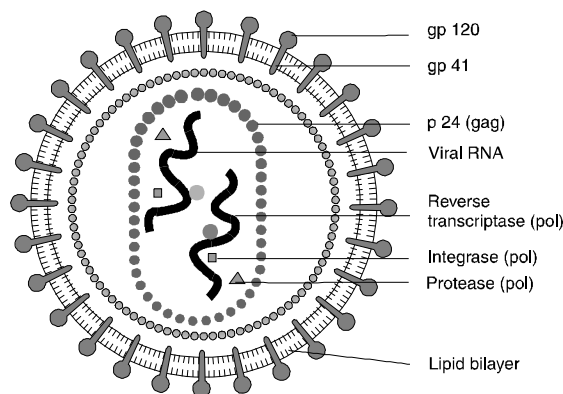
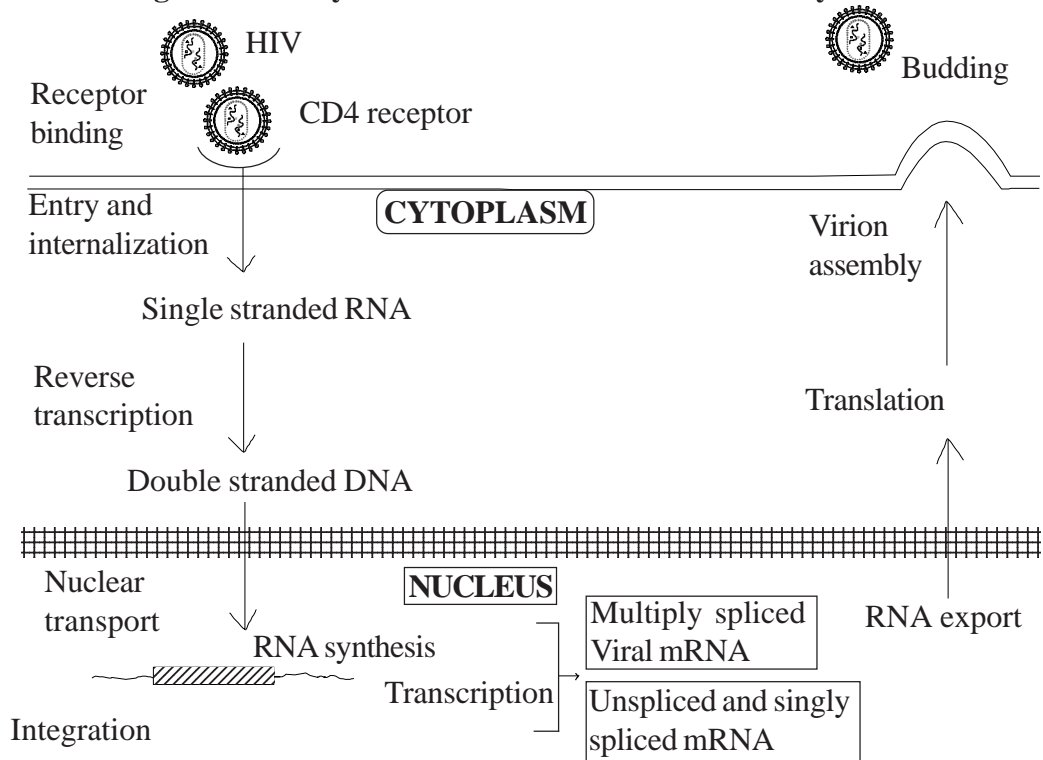


Figure 2. Life cycle of the human immunodeficiency virus.



protein products, i.e. the NC protein, the CA protein and a fraction of the RT activity. The matrix (MA) gag protein lines the inner surface of the lipid bilayer. It is the only HIV protein that can be chemically cross-linked to lipid in the HIV virions. The amino-terminus of most matrix (MA) proteins is modified by the addition of a fatty acid (usually myristic acid) group, a modification which is characteristic of many proteins that lie on the internal face of the cell membrane. The MA (P17) polypeptide is derived from the myristylated end of the gag precursor and so remains membrane bound, thus anchoring the HIV viral core particle that has been formed to the plasma membrane, facilitating virus budding and stabilising

the virus particle within its surrounding lipid envelope.

The capsid (CA) gag protein forms the icosahedral viral core. It is hydrophobic and forms the major internal structural feature of the virion, i.e. the shell of the viral core. Mutations in the CA protein may result in elimination of virus assembly during the late stage of viral replication. During the final steps of virion maturation, the CA (p24) protein is formed when the 55 kilodalton (KD) gag precursor protein is cleaved by the virally encoded protease enzyme (a product of the pol gene) into four smaller proteins designated P17 (matrix or MA protein), p9 (nucleocapsid or NC protein) and p6 protein.

ENZYMES IN HIV VIRION

The pol gene product finally results in the formation of the HIV virion enzyme. The primary pol product is cleaved by the virion protease to yield the amino-terminal RT peptide and the carboxy-terminal IN (or integrase) protein. The RT peptide has activities necessary for DNA synthesis which includes RNA and DNA directed DNA polymerase, ribonuclease H and some other nucleolytic activities. The high degree of nucleotide sequence variation between different HIV-I strains makes it a difficult target for therapeutic intervention. This variability is in part due to the absence of the 3'-5' exonuclease proof reading activity, which could result in upto ten incorrect bases being incorporated during each round of HIV-I replication. Thus, reverse transcription results in formation of a variety of HIV-I quasispecies that can have altered cell tropism and drug resistance patterns and that can escape the neutralization by the host immune system. The HIV-I RT enzyme is a heterodimer made up of two subunits, i.e. p66 and p51.

After the viral genomic RNA is reverse transcribed into viral DNA by the reverse transcriptase enzyme it is transported to the host cell chromosomal DNA to form the provirus. This step requires the activity of the viral IN (integrase) protein. The site of integration of the retroviral DNA into the host chromosomal DNA is usually random,

although some target sites may be preferred.

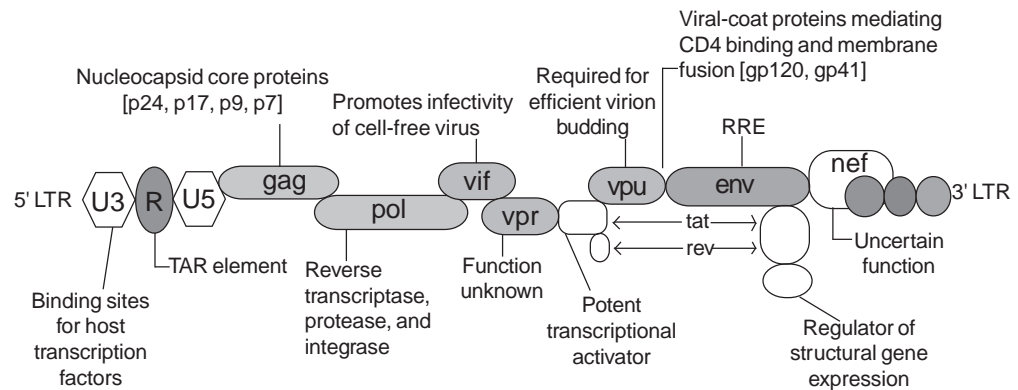
ENVELOPE PROTEINS

The envelope gene is 2.5 kb in size and encodes for a 160 KD precursor glycoprotein composed of 850 amino-acids, which is cleaved by an endopeptidase into two glycoprotein, i.e. gp120 and gp41. Despite the considerable variability of the HIV-I envelope, there are regions that are highly conserved. All 18 residues located within gp120, as well as most cysteines in gp41 are conserved, indicating that cysteine residues are necessary to maintain the three dimensional structure of the envelope protein. There are several highly conserved areas interspersed with regions of high variability in the gp120 region. It is a high degree of variability in the envelope region which makes it difficult to prepare a vaccine which will protect against all strains of HIV-I. Based on the sequence variability in the sequence of the envelope and gag genes, the HIV-I isolates have been grouped into group M (major group), group O (outlier group) and group N. Most HIV-I isolates fall into group M (subtypes A to J). Group N is the newest group to be described and has been found from Cameroon.

STRUCTURE AND EXPRESSION OF THE HIV-I GENOME:

The proviral DNA form of the HIV-I genome consists of 8.5 kb of protein coding information, flanked on either

Figure 3. HIV genome map.



side by a pair of identical long terminal repeats (LTRs). The coding portion encodes for a least 9 recognised genes. They are :

1. The virion structural genes-gag, pol and env genes
2. The regulatory genes-tat, rev and nef genes
3. The accessory genes-vpu, vpr and vif genes. The genomic structure of HIV-2 is similar to that of HIV-I but instead of vpu, which is present in HIV-I, there is the VPX gene in HIV-2.

Transcription of the provirus is controlled by a single promotor in the 5' LTR region and gives rise to a 9 kb primary transcript containing all nine genes. This primary transcript can be either packaged as such into virion particles to form the viral RNA genome or can be spliced into various mRNAs specifying the individual gene products. The primary HIV-I transcript contains at least four donor (5')

(3') potential splice sites. HIV-I mRNAs fall into three size classes, each with specific functions :

- a. The unspliced 9 kb primary transcript that can be packaged into virions or serve as mRNA for gag and pol
- b. A heterogeneous class of partially spliced mRNA which code for env, vif, vpu, vpr proteins and for a single exon form of tat. Each of these mRNA, is 4 to 5 kb long.
- c. Another heterogeneous class of viral mRNA, each about 2 kb long and spliced at all potential splice sites. These code for viral proteins rev, nef and the two exon form of tat.

During the early phase of HIV infection, only the fully spliced regulatory mRNAs can be detected in the cytoplasm of the infected cell. Cytoplasmic expression and subsequent translation of the structural mRNAs leading to the production of virions from the infected cell occurs only late in the viral life cycle in response to the viral regulatory protein

rev. The regulatory proteins tat, rev and nef proteins together act to either up regulate or down regulate the rate of HIV viral replication in the infected host cell.

The nef gene has been detected in all known retroviral genomes. In HIV, the nef gene (previously termed 3' ORF gene or the F gene) encodes for an approximately 27 kd protein containing 206 amino acids which is myristylated at the N-terminal end and is located at the 3' end of the HIV genome. A well established function of nef is the downregulation of CD4, which is the primary receptor for HIV. Nef acts by inducing CD4 endocytosis resulting in its degradation in lysosomes. The CD4 down-regulation is strongly enhanced by the association of nef with cell membranes through myristylation. Some studies have revealed that deletion in the nef gene could alter the progress of disease in a HIV infected individual. The nef genes of HIV and SIV are dispensable in vitro but are essential for viral spread and disease progression in vitro. Nef has been found to be necessary for the

maintainance of high viral loads and for the development of AIDS in macaques. A nef containing HIV-I molecular clone induced severe depletion of human thymocytes in immunodeficient (SCID) mice containing human lymphoid tissues (SCID-hu) within 6 weeks of infection but a nef deleted HIV-I did not.

DIFFERENCE BETWEEN HIV-1 AND HIV-2

HIV-2 was first isolated in 1986 in persons with AIDS originating from West Africa. Isolated cases of HIV-2 have been reported from all countries. In India majority of the infections is due to HIV-1, some cases have dual HIV-1 and HIV-2 infection and a few have HIV-2 infection alone.

HIV-2 causes similar illnesses but appears to progress more slowly. It is not possible to diagnose HIV-2 infection clinically. Transmission of HIV-1 is more efficient than HIV-2, especially early in the course of disease. Rates of mother-to-child transmission of HIV-2 are approximately 20 times lower than of HIV-1.

3

IMMUNOLOGY OF HIV INFECTION

Dr. Ramesh Paranjape

HIV infection is unique in that the virus infects the cells that are at the centre stage of body's immune system i.e. CD4 positive T lymphocytes. Also the virus bears capacity of undergoing structural mutations at an amazingly high rates. These two facts make the host-virus interaction in HIV infection very complicated. Prior to the discovery of HIV the laboratory diagnosis of AIDS was primarily based on the dramatic decrease in the CD4 positive lymphocytes and the reversal of ratio of CD4 positive cell and CD8 positive cells in the peripheral blood. Hence from the beginning of AIDS era it was known that AIDS is primarily a disease that affects the immune system of the body. The discovery of HTLV-III in 1983 and the availability of newer tools of molecular biology and immunology opened the floodgates of investigations in the host-virus interaction in HIV infection. These investigations have revealed the finer aspects of the immunopathogenesis of HIV infection and AIDS.

Like all other infectious agents, HIV also elicits immune reactions in the infected

persons. The three predominant immune responses recognized in an HIV infected individual are cytolytic T lymphocytes (CTL) that are capable of destroying HIV infected cells in an antigen specific manner; neutralizing antibody response as measured by the inactivation of virus particles *in vitro* by incubation with patient's serum, thus rendering them incapable of producing productive infection in the lymphocytes; and CD8 suppressor factors. These immune reactions, the genetic make up of the host i.e. host factors and the virus strain variation ultimately decide the outcome of the HIV infection.

HIV SPECIFIC IMMUNE RESPONSES

HIV-specific CTLs : HIV antigen-specific CTLs have been demonstrated in HIV infected persons. The CTL response to HIV antigens has assumed significance due to various reasons.

- Strong CTL responses are seen consistently in the persons showing good control of viremia such as long term non-progressors and the

responses are absent or minimal in patients in AIDS stage.

- CTL responses is one of the earliest response seen in acute primary HIV infection i.e. during the window period and often precedes the sharp decline in viremia seen at the time of seroconversion.

HIV-specific CTL responses have been reported in persons who are exposed to HIV infection but are not infected.

Neutralizing antibodies

HIV infected persons demonstrate the presence of antibodies that can neutralize the laboratory strains of HIV *in vitro*. These neutralizing antibodies are rarely seen in acute primary HIV infection, but are seen more commonly in clinical asymptomatic period. However, they rarely neutralize prevalent autologous strain. Also the neutralizing antibodies are capable of neutralizing laboratory strains of HIV more efficiently compared to the primary isolates of HIV. Hence the contribution of neutralizing antibody response to control of viremia is considered limited. However, broadly reactive neutralizing antibodies induced by HIV vaccines may be important in preventing new HIV infection in the vaccinee.

CD8 cell suppressor factors

CD8⁺ cells, on stimulation with HIV antigens produce certain soluble factors that down regulate HIV infection in CD4

cells and cell lines. They also produce factors that down regulate the virus multiplication. In some of the recent studies β -chemokines also have been shown to inhibit virus multiplication in cell lines. High levels of β -chemokines in circulation have been shown to be associated with better prognosis in the patient and down regulate HIV multiplication in cell lines in culture. The receptors for β -chemokines may play very important role in HIV infection. This has been discussed further under the section on host factors.

Besides the above-described immune responses in HIV infected persons, the pattern of cytokines produced by the lymphocytes may also be important. Interactions between interleukins and HIV have been studied in HIV infected persons. Interferon- γ is expressed early and throughout acute primary HIV infection. On the basis of the effect on virus expression and replication, cytokines may be classified into three groups: inducers of virus expression, suppressors of virus expression and bi-functional. The cytokines produced in response to antigen may follow two different patterns, namely Th1 and Th2. Th1 cytokine pattern is essentially with production of IL2, interferon- γ and Th2 cytokine pattern predominates production of IL4 and IL5. The Th2 type of response seems to be seen in late AIDS stage. It has been suggested that the switch from Th1 to Th2 type of cytokine response is critical in progression of HIV disease to AIDS

stage. It may be critical to find out exact trigger for this switch. It may offer new therapeutic approach towards maintaining disease free state for longer time period.

One of the areas in HIV immune response that is relatively less explored, but is very important is mucosal immunity. HIV gains entry into the host through mucous membranes of genital tract as the predominant mode of transmission of HIV infection is through sexual contact. HIV-specific antibodies have been detected in vaginal secretions in HIV infected women. While IgG antibodies predominated in cervico-vaginal secretions and correlated with serum antibodies, secretory IgA antibodies were seen predominantly in salivary secretions. However, HIV-specific IgA and secretory IgA have not been detected in all women tested. Immunization with vaccines can induce antibody response at the mucosal surfaces. Little is known about the HIV-specific CTL response in mucosal tissue. Studies in women exposed to HIV but are uninfected failed to reveal the presence of HIV-specific antibodies in cervico-vaginal secretions.

HOST GENETIC FACTORS

HLA haplotype

There are reports of association between HLA antigens and the course taken by the HIV infection. HLA class I alleles A2, A3 A28, A23, B17 and B27 favour prolonged asymptomatic stage of HIV

infection. Alleles B52, B58 and B70 have been shown to be associated with greater HIV susceptibility and rapid progression of the disease among infected individuals.

Accessory receptors

For a long time it was known that CD4 molecules on the surface of lymphocytes is primary receptor for HIV. However, there were strong evidences that there is a second receptor required by HIV for infecting the cell. The family of these elusive second receptors has been recently identified and may have a significant importance for the pathogenesis of HIV infection. The receptors for β -chemokines are utilized by HIV as accessory receptors. These receptors may be specific according to the tropism of the virus. While T-lymphotropic viruses use receptor CXCR4, Macrophage-tropic (M-tropic) viruses preferentially utilize receptor CCR5. Receptor CCR3 is used by a variety of T-, M- and dual-tropic viruses. The identification of over 13 different accessory HIV receptors has opened newer avenues for therapeutic strategies. It has been seen that a deletion of 32 base pairs by mutation in CCR5 results in the changes in the susceptibility of individuals to HIV infection and the course of the disease. Persons homologous for CCR5 32 allele with deletion of base pairs are relatively refractory to HIV infection and individuals heterozygous for CCR5 are often long-term non-progressors.

T-cell receptor V β alleles in HIV infection

Variations in the response to the HIV antigens amongst different individuals also manifests in the expression of V β alleles of the T cell receptor. T cells recognize the antigens of the pathogens by virtue of a receptor and V β chain of this receptors is present in a polymorphic (allelic) form. With the antigenic stimulation as a result of infection, T-lymphocytes with different allelic V β chains may expand differently. The response in some patients is restricted to dramatic expansion of one or two of the 20+ V β alleles, whereas in others it may be oligoclonal involving more alleles. It is believed that this response early in the infection may predict the outcome of infection, that is whether a person will be a rapid progressor or a long term non-progressor or will follow average course of infection.

THE VIRUS STRAIN VARIATIONS

HIV viruses are classified into two main groups group M and group O based on the similarities in the genome. While group M is further classified in 10 subtypes A to J, group O has only one subtype, subtype O. The distribution of subtypes is geographical in nature. There is no definite evidence of subtypes differing from each other biologically. It is not clear whether immunotypes i.e. classification of HIV strains according to specificity of immune response match the genotypes. Such information is of great importance as immunotypes may

have greater relevance in context with the development of HIV vaccine. HIV genome has certain sections that are highly variable, thus giving rise of the strain variation. Some parts of genome are highly conserved the variations between the different virus strain are minimal in these regions.

The virus strain variations and the specificity of the immune response have a bearing on the progression of the disease. Greater variation in HIV viruses in an individual i.e. quasi species may indicate a stronger immune response and better prognosis.

As the body mounts immune response against the virus, virus also tries to undermine the immune system of HIV infected persons. One of the most lethal effects of HIV on immune system is the destruction of CD4 positive lymphocytes in infected individuals. Inability of detecting the virus in many infected individuals during the asymptomatic period was considered to be due to the decrease in virus production in the asymptomatic phase of infection. Recent data shows that virus multiplication continues unabated even during the asymptomatic phase. However, virus multiplication in this phase is more restricted to the lymph nodes. The destruction of CD4+ lymphocytes also continues in this phase and the drop in CD4+ cell number is made up by the overproduction of CD4+ cells in lymphopoietic tissue. However the rate of generation of new CD4+ cells cannot

match the rate of destruction of the cells, hence causing gradual decline in CD4+ cells. The destruction of CD4+ cells occurs by many mechanisms such as destruction due to virus multiplication, induction of apoptosis by HIV proteins, antibody dependent cell cytotoxicity, Superantigen like actions of HIV proteins and the toxicity of HIV proteins. HIV not only affects CD4+ cells that are key to specific immune response but it also brings about down regulation of other cells and effector mechanisms of immune system. It thus renders immune system incapable of combating the opportunistic infections that are never a threat in immunocompetent individuals.

One of the reasons why the immune response is not able to eliminate HIV infection is due to the fact that the virus has propensity to changing the antigen structure. In some of the experiments it has been shown that a substitution in one single amino acid in the envelop can abrogate the specific CTL response. This indicates to the fact that the responses are fine-tuned and minor variations can lead to non-recognition of virus strain.

Although HIV infection in an individual invariably leads to the death of the individuals, some of the observations have raised the hope of control of HIV multiplication if not eradication. A percentage of HIV infected persons show no sign of clinical progression for many years, often more than twelve years. They have their CD4 cell counts stable and virus load very low. These individuals show very strong HIV-specific CTL responses. These individuals are known as **long term non-progressors**. A group of commercial sex workers with very high risk of contracting HIV infection have been found to be free of HIV infection even after seven years in the trade. They are exposed, but not infected, persons and have been shown to exhibit HIV-specific CTL response. And lastly, as a result of mounting of effective immune response, virus set point i.e. baseline plasma virus load, is set very low and these individuals are more likely to be long term non-progressors. These observations have pointed to one fact that it is possible to control HIV multiplication. However, the mechanisms for control of viremia are not yet clearly defined. Further research in this area is very likely to lead to immunological interventions for the control of HIV infection.

4

THE NATURAL HISTORY OF HIV INFECTION

Dr. Vinay Kulkarni

The natural history of HIV infection is divided into the following stages:

1. Viral transmission
2. Primary HIV infection
3. Sero-conversion
4. Clinical latent period with or without persistent generalized lymphadenopathy (PGL)
5. Early symptomatic HIV infection (previously known as “AIDS-Related Complex” or ARC and more recently referred to as “B symptoms” according to the 1993 CDC classification)
6. AIDS (AIDS indicator condition according to the 1987 CDC criteria and revised 1993 CDC criteria that include a CD4 cell count $<200/\text{mm}^3$); and
7. Advanced HIV infection, characterized by a CD4 cell count $<50/\text{mm}^3$.

In an average patient, the entire sequence of events (in the absence of antiretroviral treatment) is approximately seven to ten years from seroconversion to death.

Patients with symptomatic primary HIV infection progress more rapidly than person without. Age at which the person gets infected is also an important variable. Younger the age better the prognosis. For patients aged 16-24 years at seroconversion, the median time from seroconversion to AIDS was 15 years; for those ≥ 35 years at seroconversion, it was 6 years.

Some patients may remain asymptomatic, with CD cell counts in the normal range, for many years. These patients are sometimes called “long-term non-progressors.” These are defined as patients with HIV infection and CD4 counts that remain normal and stable, (without antiviral therapy) for >7 years.

Factors associated delayed progression are:

1. Low viral burden,
2. Preserved lymph node architecture,
3. Increased CD8 cytolytic activity,
4. Nonsyncytium inducing HIV.

Stages

- 1. Viral Transmission:** HIV infection is usually acquired through sexual intercourse, exposure to contaminated blood, or perinatal transmission.
- 2. Primary HIV Infection** (also called: “acute HIV infection” or “acute seroconversion syndrome”):
The time from exposure to onset of symptoms is usually 2-4 weeks, but the incubation may be as long as 6 weeks.
- 3. Seroconversion:** Seroconversion with positive HIV serology generally takes place at 6-12 weeks following an established transmission event.
- 4. Early HIV Disease:** This represents the period from seroconversion to 6 months following HIV transmission. Clinical studies show considerable variation in CD4 cell counts and viral burden. At 6 months the viral burden establishes a “set point”. When followed over a period of years (in the absence of antiretroviral therapy); it shows minimal variation. This set point correlates strongly with prognosis.
- 5. Asymptomatic Infection:** During this period the patient is clinically asymptomatic and generally has no findings on physical examination except for “Persistent Generalized Lymphadenopathy” (PGL), defined as enlarged lymph nodes involving at least two non-contiguous sites other than inguinal nodes.
- 6. Early Symptomatic HIV Infection (“ARC” or “B Conditions”):** “B conditions” include conditions that are more common and more severe in the presence of HIV infection; by definition these are not AIDS-indicator conditions. Examples are thrush; vaginal candidiasis that is persistent, frequent, or difficult to manage; oral hairy leukoplakia; peripheral neuropathy; idiopathic thrombocytopenic purpura (ITP), etc.
- 7. AIDS:** The 1987 definition of AIDS utilized a tabulation of conditions indicative of severe immunosuppression, especially defective cell-mediated immunity. The more recently revised CDC classification (1993) is given elsewhere in the book.
- 8. Advanced HIV Infection:** These patients have CD4 cell count of $<50\text{mm}^3$. They have limited life expectancy with a median survival of 12-18 months.

Although the person has no symptoms -it does not mean that the virus is dormant. About 30% of the total body virus burden is turned over daily. The turnover of CD4 cells represents 6-7% of the total body CD4 cells so that the entire supply turns over every 15 days. The implication of these observations is that “AIDS is primarily a consequence of continuous, high-level replication of HIV-1, leading to virus and immune-mediated killing of CD4 lymphocytes.”

Correlation of Complications with CD4 Cell Counts

CD4 cell count > 500/mm³

Infectious	Acute retroviral syndrome Candidial vaginitis
Non-infectious	Persistent generalized lymphadenopathy (PGL) Guillain-Barre syndrome Myopathy Aseptic meningitis

CD4 cell count > 200 – 500/mm³

Infectious	Pneumococcal and other bacterial pneumonias Pulmonary TB Herpes zoster Thrush (Candidiasis) Candidial esophagitis Cryptosporidiosis (self-limited) Oral hairy leukoplakia (Kaposi's sarcoma)
Non-infectious	Cervical intraepithelial neoplasia Cervical cancer B-cell lymphoma Anemia Mononeuritis multiplex Idiopathic thrombocytopenic purpura Hodgkin's lymphoma Lymphocytic interstitial pneumonitis

CD4 cell count < 200/mm³

Infectious	<i>P. carinii</i> pneumonia Disseminated/chronic Herpes simplex Toxoplasmosis Cryptococcosis Disseminated histoplasmosis and Coccidioidomycosis Cryptosporidiosis (chronic) Microsporidiosis Miliary/extrapulmonary TB Progressive multifocal leukoencephalopathy (PML) Candidial esophagitis
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(contd.)

Non-infectious	Wasting Peripheral neuropathy HIV-associated dementia CNS lymphoma Cardiomyopathy Vacuolar myelopathy Progressive polyradiculopathy Immunoblastic lymphoma
CD4 cell count < 50/mm³	
Infectious	Disseminated CMV Disseminated <i>M. avium</i> complex

5

TRANSMISSION OF HIV AND PREVENTION

THE MECHANISMS OF HIV TRANSMISSION

It has now been proved that for HIV transmission to happen, three conditions need to apply:

1. Live virus has to be present either in the body of an infected person or in a contaminated body fluid or body tissue (Presence).
2. There has to be a sufficient amount of the virus present (often called technically 'tissue culture infectious dose') (Quantity).
3. It has to get into the body of the uninfected person through an effective route for transmission to occur. In this respect HIV is no different from any other virus; it can only be transmitted through certain now well understood routes. There must be susceptible receptor cell at the site of entry and inadequate host defences (Route and Susceptibility).

Additionally, there are two sets of co-factors that may be said to

encourage transmission or make it more likely:

4. Physical co-factors.
5. Social co-factors.

These principles can be used to determine:

- The established and predominant modes of transmission
- Biologically possible but unlikely modes of transmission
- 'Impossible' modes of transmission and reassurance against unfounded concerns about HIV and AIDS.

THE PRESENCE OF HIV

HIV will inevitably be more prevalent in some groups of people than others because of the history of the epidemic.

This will mean that the same act will carry different levels of risk in different groups of the population and different places.

Identification and avoidance of people

with HIV is not an effective or desirable line of defence against HIV for individuals who engage in activities which can transmit the virus. This is because, at any time the majority of people with HIV cannot be identified by external physical signs. Moreover, any attempt to fit individuals into broad and blunt risk categories (although useful in the planning of public health services) is likely to fail on an individual level most of the time. It is not always possible to detect the sexual or drug using history of partners with sufficient accuracy for this to offer sufficient protection.

Similarly, the HIV antibody test is not a safe and effective tool for making such judgements as mass testing is not feasible and selective testing will only ever reveal a small proportion of people with HIV.

Blood

HIV has been isolated from blood at levels of up to 5,000 infectious particles per ml, but some researchers have found it much more difficult to isolate HIV from the blood of HIV-positive individuals. This is due to the dramatic fall in HIV levels after primary infection and the confinement of HIV to lymphoid tissue (the lymph nodes, spleen, tonsils and adenoids). Rising levels of HIV in the blood usually signal that cellular immunity is declining and are an important marker for progression to symptomatic HIV disease.

Semen

Between 10 and 30% of seminal fluid studied has been shown to contain either free infectious virus or cell-associated virus (infected lymphocytes). However, levels of cell-associated virus are much higher; there are up to one million lymphocytes in each millilitre of semen; even if only one per cent of these lymphocytes are infected with HIV, this means that each millilitre of semen may contain up to 1,000 infected lymphocytes. The average male ejaculation is 5 ml of semen, although this varies considerably.

Lymphocytes and cell-associated virus are most likely to be present in individuals suffering from infections that cause inflammation in the urethra and other regions of the genital tract. Untreated sexually transmitted infections, even those that cause no detectable symptoms, are likely to increase the viral load in semen.

Vasectomy does not reduce levels of HIV in semen.

HIV-infected cells have been detected in pre-ejaculatory fluid (pre-cum) in a significant proportion of HIV-infected men. It is unclear whether the quantities isolated are sufficient to lead to infection.

Vaginal and cervical secretions

Levels of HIV in the vagina increase at the time of menstruation due to the presence of blood and other cell-associated virus. Levels of macrophages that could harbour HIV also increase in the vaginal fluid at the time of menstruation. It is believed that sexually transmitted infections and inflammation in the vagina will boost the level of lymphocytes.

Brain tissue and cerebrospinal fluid

HIV was cultured from the cerebrospinal fluid of 13 out of 14 people suffering from AIDS-associated neurological disorders, in much higher quantities than any other body fluid apart from blood. Another study was able to isolate HIV from brain tissue and cerebrospinal fluid in 24 out of 33 people suffering from AIDS-associated neurological disorders.

Bronchoalveolar fluid

HIV has been isolated from the fluid of the lungs; in one study it was found in every one of 23 AIDS patients studied. This has clear implications for the cleaning of bronchoscopes in hospitals.

Faeces

HIV has never been isolated from faeces in an infectious form. Genetic material from HIV has been detected, but it has been impossible to culture the virus in the laboratory.

Saliva

HIV has been successfully isolated from saliva on only a handful of occasions despite many attempts, and even then in tiny quantities compared with blood, semen and vaginal fluid. This low recovery rate is probably explained by the presence in saliva of substances that inhibit HIV from infecting new cells.

Tears

Researchers have found it difficult to isolate HIV from the tears of HIV-positive people. In one experiment it was possible to find HIV in the tears of only one person with AIDS out of seven tested, and impossible in five HIV-positive people with no symptoms. Another experiment using highly sensitive techniques looked at 50 HIV-positive people and failed to find HIV in the tears of any of them.

Urine

Although HIV antibodies are detectable in urine, HIV capable of infecting cells has not been isolated from urine; in one study HIV could not be isolated from the urine of any of 48 people studied.

THE ROUTE OF TRANSMISSION

HIV can only be transmitted and cause infection if it gets into the body via a route where vulnerable cells are plentiful.

Summary

HIV is not present in:

- Urine, faeces, stool, vomit, sweat

HIV is present in negligible quantities in:

- Saliva (only rarely detected in very small quantities in the saliva of a very small number of people)
- Tears
- Blister fluid

HIV is present in infectious quantities in:

- Blood and blood-derived products
- Semen and possibly pre-cum
- Vaginal and cervical secretions or juices
- Breast milk

These are, the key body fluids and materials to take precautions against.

In addition, HIV has also been detected in sufficient quantities in:

- Amniotic fluid
- Cerebro-spinal fluid
- Skin transplants
- Bone marrow transplants.

All of these are only a potential risk in invasive surgical procedures and may be covered by the same precautions and guidelines.

On a cellular level, HIV infects CD4 cells and CD8 cells in the blood as well as cells in the lungs, the brain, the gastrointestinal tract, the kidneys. But to reach these cells, HIV must pass through cells in the mucous membranes called dendritic cells and Langerhans cells.

Blood splashed onto the skin will not come into contact with the Langerhans

cells beneath the skin because these are not exposed. The skin must be damaged, lacerated or deeply wounded for this to happen. In the rectum and vagina by contrast, infected blood or semen will reach the Langerhans cells for more easily because they are close to the surface and lack the covering of the thick dead epithelial layer which is the dry surface of the skin.

The effective routes for transmission to occur are:

1. Directly into the blood (parenterally) through a wound:
 - Through a cut or sore or damaged skin
 - An injection using contaminated and unsterilized injection equipment
 - An invasive surgical procedure such as an organ transplant or blood transfusion.
2. Through particular 'interior' sections of skin called mucous membranes:
 - In the rectum
 - In the vagina and cervix
 - In the urethra (which is in front of the vagina in women and the tube of the penis in men)
 - In the eyes and mouth in rare circumstances.

It should be noted that in these cases, trauma or damage to the tissue is not always necessary for infection to occur. These mucous membranes will allow HIV to be absorbed into cells which facilitate infection. In the early years of the epidemic it was thought that damage

to these tissues might be the precondition. We now know that infection occurs without such damage, although damage will certainly increase the chances of infection.

Physical co-factors which encourage transmission

Factors in increasing the risk of infection if exposed to the virus may include:

- Having other sexually transmitted diseases at the time, such as herpes, syphilis, hepatitis B, especially, but not only, if they cause genital ulceration. Genital ulceration provides an enhanced route of infection. It also increases the quantity of HIV-bearing cells present in the vaginal fluid, blood or semen
- Pre-existing immune deficiency for some other reason
- The health status or disease progression of the infected partner
- The strain of virus
- Local immunity in the vagina
- Alkalinity/acidity in the vagina
- Lack of vaginal lubrication
- In men, it may be that being uncircumcized increases the risk

There are only four proven, substantial routes of transmission:

1. Unprotected intercourse with someone who is infected.
2. Sharing unsterilized injection equipment which has been previously used by someone who is infected.
3. Injection or transfusion of contaminated blood or blood products, and donations of semen (artificial insemination), skin grafts and organ transplants taken from someone who is infected.
4. From a mother who is infected to her baby (this may be during the course of pregnancy, possibly at birth and through breast-feeding).

- Damage to tissue in the throat or mouth may facilitate infection; in reported cases of infection through oral sex, inflammation of the throat due to allergy and frequently bleeding gums have been cited along with pharyngeal gonorrhoea as co-factors for infection.
- In women, oral contraception can sometime cause cervical ectopy, in which cells in the cervix are exposed on the surface where they can easily be broken, allowing for easier HIV transmission
- Generalised immune system activation may play some role, as yet unclear, in facilitating HIV infection.
- Genetic predisposition or susceptibility.

SOCIAL CO-FACTORS THAT ENCOURAGE TRANSMISSION

Whilst it has been important to focus down onto the specific details of how transmission occurs at a cellular and bodily level, it is important for the purposes of prevention and reassurance in the real world to be aware that all transmission is by definition always interpersonal i.e. it involves two or more people. As such, it needs to be understood as a social phenomenon as much as a biological one.

THE ESTABLISHED MODES

Unsafe sex

Established and common routes:

- Unprotected anal penetration
- Unprotected vaginal penetration.

Possible but uncommon routes:

- Oral transmission: a very small number of cases have been reported, all of which suggest that oral transmission depends on either damaged tissue in the mouth or throat, or on ulceration of the penis
- Any sexual activities where blood may be shared (e.g. involving piercing, shaving, etc)
- Through blood in otherwise uncontaminated body fluids: in the mouth or the rectum, during menstruation
- Through shared sex toys etc.

Shared injecting equipment

Established and common routes:

- Sharing injecting equipment

Possible but uncommon routes:

- Needle-stick and sharps injuries.

Blood and blood products

Between mother and baby

- Antenatal
- Through breast-feeding
- At birth.

POSSIBLE BUT UNCOMMON ROUTES

- Blood transfusions, blood products and donations (organs, skin). Since 1985 blood donations in the UK have been screened, and screening began at roughly the same time in most other countries which could afford such programmes. Organs and

COMPARING RISKS

Highest risk activities

- Anal sex receptively
- Vaginal sex receptively
- Anal sex actively
- Vaginal sex actively
- Blood-sharing recreational activities
- Sharing unsterilized injecting equipment
- Being born to an HIV-infected mother
- Being breast-fed by an HIV-positive mother.

Much less risky activities

- Penetrative sex with appropriate barrier (condom or Femidom):

residual risk because the condom may fail

- Oral sex receptively (because of individual claimed case reports and inadequate size of epidemiological sample if there is a small risk)
- Sharing injection equipment if *improperly* sterilised
- Occupational risks in invasive surgical and medical contexts
- Laboratory work with superconcentrates of HIV.

Very low risk activities

- Sharing penetrative sex toys
- Sharing razors, toothbrushes, etc.
- Rimming if blood present in stool.

tissues for donation have also been screened since that time, whilst blood products such as Factor VIII have been heat treated since 1984.

- Surgical and other invasive procedures: fortunately very uncommon and the risk needs to be seen in the light of the far greater risks involved routinely in these invasive health care procedures
- Occupationally through blood splashes onto broken skin and needle stick injuries
- Donations of blood, organs, tissues, semen, breast milk and bone marrow-in each of these instances a very small number of cases have been reported
- Tattooing, acupuncture, electrolysis, shaving equipment. In these cases it

is assumed that infection is possible but unlikely. A case of infection through unsterilised acupuncture needles has been reported.

IMPOSSIBLE ROUTES OF HIV TRANSMISSION

The virus cannot be transmitted through:

- Unbroken healthy skin, because cells vulnerable to HIV infection do not exist on the surface of skin
- Breathing in (unlike the common cold, for instance, which can be spread through sneezing), because HIV cannot be airborne. It is not present in the tiny particles of moisture sneezed or coughed out of someone's mouth

- A healthy, undamaged mouth, because cells vulnerable to HIV infection are not present in the mouth
- Unbroken barriers such as a latex condom or the Femidom, because these barriers cannot be penetrated by HIV
- Corneal transplants because no blood vessels are present on the cornea
- Mosquitoes because although these insects suck blood, they do not regurgitate blood containing live HIV into the bodies of other victims
- Sharing cutlery, plates or cups because HIV cannot be transmitted in saliva
- Over-broad and imprecise categories such as 'sex' or 'promiscuity' or 'drug abuse' are not in themselves a risk
- Social contact with people with HIV, because HIV is not transmitted by touch or through the air
- Through animal bites because animals do not carry HIV
- By caring for people with HIV
- By association with blood
- By contact with small quantities of dried blood, because HIV will not be present in sufficient quantity (all infections through blood not injected or transfused have occurred where large quantities of blood splashed onto the broken skin of other people)
- Through swimming pools, showers, washing machines, because HIV will be killed by chemicals in disinfectant and detergent, or simply just washed away
- By mouth-to-mouth resuscitation,

because HIV is not present in saliva. Only if HIV is present in large quantities does it pose a risk.

- By touching objects such as telephones, because HIV is not transmitted by touch
- By using the same lavatory as people with HIV, because even if someone had bled into the lavatory, the water would immediately dilute the virus. Nor would HIV be picked up from blood on the lavatory seat.

Rarely, the virus may be transmitted through:

- The lining of the mouth if there are cuts, sores or ulcers or bleeding gums
- The nipples, if bitten by a child with bleeding gums while breast feeding
- The mucous membranes in the eye, if splashed there in large quantities.

HIGH RISK GROUPS AND HIGH RISK BEHAVIOURS

Epidemiologists use the phrase 'risk groups' to refer to people who may be vulnerable to a particular medical or social condition. For example, smokers are a risk group for lung cancer and need specially targeted health education. So the idea of risk groups is useful for identifying the need for particular resources and services.

While everyone is biologically susceptible to infection with HIV if they are exposed to the virus, this does not mean that gay man having unsafe sex is

at much greater risk of having unsafe sex.

To this extent, definable groups within the population may be accurately described as high-risk groups, because they are at the greatest statistical risk of HIV through unsafe sex. This recognition should be seen as benign, rather than stigmatizing or hostile, since

it allows a sense of priorities in HIV education and care service provision to be established. In a world of limited resources, it makes sense that resources are targeted to the areas of greatest risk.

Unfortunately, this benign concept has been misused throughout the epidemic. The identification of gay men and

SAFER SEX

Condoms and lubricants

Penetrative sex is the main way in which HIV is transmitted, through infected blood and sexual fluid. A condom acts as a barrier between the penis and the other person's body, and stops our partners and ourselves from being exposed to infected fluids.

Reliability of condoms

You may have heard a lot about condoms failing, or about them not being strong enough, or that they are not suited to anal sex. There is some truth in all of these statements.

Condoms are not totally safe sex: they reduce the risks of penetrative sex. Experience with birth control shows that over a period of a year about 6% of women using condoms will get pregnant. This is quite a high failure rate. Moreover, it is important to bear in mind that whilst condoms are required to provide protection during one week of each month in order to prevent pregnancy (the week during which a women is ovulating), a condom must provide protection on each and every occasion of sexual intercourse if it is to be a reliable form of protection against HIV infection.

However, the main reason that condoms fail is because they are used wrongly-they are torn during opening, oil-based lubricants are used, or they are put on wrongly, for example.

In general, condoms provide an effective barrier against HIV and other STDs, and given that so many people practice penetrative sex as part of our sex lives, it is important that they are used properly.

injecting drug users as high risk groups in the early 1980s did not result in education and care services being targeted to them; indeed, it was left largely to underfunded voluntary groups to 'look after their own'. Instead, members of the high-risk groups were falsely believed to be a risk to others,

rather than to be at increased risk themselves. So all that was targeted at gay men and drug users was hysterical blame, prejudice and discrimination.

The misunderstanding of 'high-risk groups' also contributed to the idea of bridging groups, and the related idea that

FEMALE CONTROLLED METHODS

Femidoms and microbicides

The most effective method to prevent HIV acquisition and transmission, the condom, is worn by men. Many women do not have relationships of equality with the men they have sex with, and they can experience difficulties 'persuading' men to use condoms. This can be particularly difficult in situations where HIV is not the priority concern (for example, when the woman experiences violence). However, it is also problematic for women in more equal relationships, since many men find condoms unpleasant, and as women are more vulnerable to HIV than men from vaginal intercourse, they may not afford the same priority to condom use.

The female condom, or Femidom, is the first product that has been developed to offer women more control over HIV prevention methods. However, it is not a method entirely within women's control. Although, in general, the woman inserts the device, it requires compliance and consent from the man for it to be used. It is extremely visible-many would say unattractive-as it extends beyond the labia. Currently Femidoms are not freely available in India.

Since there are no methods entirely within women's control, and as the vulnerability to HIV from vaginal sex increases for women, the need for new prevention methods is urgent. Microbicides (previously known as virucides) have been spoken about for several years, and are now receiving a fair degree of attention from some policy makers (such as WHO) and sectors of the research community. Currently no proven safe and effective microbicides are available, but research is underway. Microbicides are also beneficial because they offer the potential to protect against sexually transmitted infections, which are a significant contributor to death, illness and infertility around the world.

HIV spreads from gay men *through* bisexual men and hence *through* women into the general public. This view even appeared in an advisory report to the government a classic example of not thinking of women as part of the general public! It reveals an unconscious assumption that heterosexual men are more important than other groups. Instead of showing concern for the needs of the groups most affected by HIV, it inaccurately labels them as the risk to others.

HIV PREVENTION METHODS

The case for risk reduction

Since the beginning of the epidemic we have been faced with two competing philosophies about the relationship between acceptable levels of risk and sustainable degrees of behaviour change and public health measures.

One model, that of risk reduction, has sought to demonstrate that the risks of HIV transmission are identifiable and that proven methods of protection against infection exist. These include:

- Use of condoms in penetrative sex
- Screening of the blood supply
- Heat treatment of Factor VIII
- Avoidance of breast feeding where feasible and necessary
- Adoption of universal precautions in medical settings where invasive procedures take place.

All these measures to some extent involve changes in behaviour which require the sacrifice of liberties or pleasures. It is unrealistic to imagine that people will adopt guidelines on their behaviour which appear to be punitive, coercive or moralistic.

Thus HIV prevention based on a risk reduction philosophy involves substituting less harmful activities for those which pose the greatest risk. For example, the promotion of needle exchanges is a form of risk or harm reduction; it does not *eliminate* the potentially harmful activity of injecting drugs, but it does offer a means of *reducing* the risk of HIV infection.

Similarly, the promotion of condoms to gay men for having sex is seen as preferable to a policy of discouraging gay men from having sex altogether. It offers gay men a choice of ways in which to reduce their level of risk, and offers substitutes which are proven to be of lower risk, e.g. oral sex instead of unprotected anal sex. Exactly the same strategy has been employed with workers in the sex industry in many countries.

Risk elimination

Risk elimination on the other hand depends on the belief that protecting public health requires the elimination of risk. Risk elimination approaches take two forms:

HARM REDUCTION

Injection Drug Use

Most injecting drug use is both illegal and socially driven underground. Research shows that punitive or coercive attempts to try to ‘stamp out’ drug use don’t succeed. What’s worse is that they drive drug use even further underground and make HIV prevention services inaccessible to the majority of drug users.

If our primary aim is the reduction of HIV transmission and the provision of quality services to drug users with HIV or AIDS, then it is essential to adopt an approach that recognises the difficulties of accessing drug users and the dangers of alienating them. In other words it is important to begin with advice and with services that drug users will themselves value. It is important to give the minimum necessary advice about risk and harm reduction rather than maximal advice requiring drug users to make total changes to their lives in a very short space of time.

Advisors and those wishing to provide relevant and appropriate services should:

- Advice about not sharing injecting equipment
- Advice about cleaning injecting equipment for those situations where there is no option but sharing
- Advice about safer sex.

The above factual advice is all that anyone needs to know in principle in order to protect themselves and others from HIV infection. In the real world, however, this factual advice cannot be put into practice without attention to wider issues:

- Advice about the wider health context of safer injecting
- Advice about preventing and dealing with an overdose
- Advice about and referral to accessible services
- Advice about implementing harms reduction techniques in the real world.

If users are looking for services to help them give up drug use then clearly it is important to provide speedy and reliable referrals to these and to ensure that they are as user-friendly as possible. However, the great danger is of alienating and losing touch with drug users by trying to ram abstinence down their throats!

Injecting drug users face a number of threats to their health as a result of injecting, one of which is HIV infection. To stop using or injecting drugs is not always an acceptable or realistic option and therefore it is vital to find ways to reduce the potential harm associated with drug use.

- The promotion of abstinence over condoms and needle exchanges. This approach questions the efficacy of safer sex, and suggests that injecting drug use is just as harmful as the sharing of injecting equipment
- The highlighting of very low risks as unacceptable risks.

The highlighting of very low risks can have the paradoxical consequence of inducing fatalism about past sexual practices and reducing adherence to current tried and tested safer sex guidelines, as a 1992 Dutch study showed amongst gay men. Those who became worried that oral sex was risky were most likely to abandon the use of condoms in anal sex, believing them to be already exposed to the virus through oral sex.

Another example is the emphasis upon the testing of health care personnel in order to protect the public from the tiny risk of infection through an invasive procedure. This draws attention away from the need for universal precautions to be employed in all invasive procedures, and undermines confidence in such precautions.

Of course, we have to make allowance for what we do not know and err on the side of caution in predicting the risks of the developing epidemics. Worst case predictions are intended to be treated as such precisely in order to prevent such scenario from coming about. However, when such scenarios interfere with

demonstrably effective health education, they become almost as dangerous as denial of any risk whatsoever.

A further principle associated with risk reduction is that of minimal disruption. Changes in behaviour are thought to be more sustainable if they involve the least possible change in behaviour required to protect oneself. This is why for many people, cutting down the amount of fat one eats is likely to be a far more realistic, if minimal, form of risk reduction than giving it up altogether. Advice of this sort works with the grain of long established and pleasurable behaviour, rather than against it. Sexual habits are deeply rooted in everyone's lives, and require rather more than will power to change.

Those who advocate risk elimination argue that the public have the right to be aware of all the risk associated with HIV infection, and to make up their own minds on the basis of such information. Such an argument presupposes:

- That everyone makes up their mind about potential risks on the basis of all the available facts
- That perceptions of risk in the community are all formed by the same factors, leading to an even perception of risk. An example might be sexually transmitted disease: some people regard these as more disastrous because they have less sex, or because they interfere with an existing relationship, or because the consequences of a sexually

transmitted disease might be more serious for a woman than a man

- That the facts are presented neutrally
- That information about AIDS and HIV is not received by people in the light of previous prejudice, misinformation or blaming
- That the information is presented in such a way as to be easily understood
- That everyone is equally capable of acting upon that information to protect themselves
- That there are unlimited resources to present information about even the tiniest theoretical risks. An example of this might be the choice between educating gay men about the dangers of unprotected sex and the much smaller danger from oral sex.

Realistic risk reduction advice

Following on from the criticisms of risk elimination, it is important that risk reduction advice should be:

- Easily understood by those it is intended to reach
- Implementable. In other words, people have to be willing and able to take the suggested precautions. To suggest that all sex is risky is to invite denial of any risk attached to sexual activity
- Persuasive, not punitive
- Not more disruptive than absolutely necessary.

Advice about risk reduction is most useful when targeted at those most at risk. This may seem a blindingly obvious statement, but it is not necessarily the

case that those most at risk will automatically be targeted with information tailored according to their needs. Predicting in advance who is at risk is possible at least in the part by looking at which groups are already most affected, and comparing the existing prevalence with information we have about factors which increase the likelihood of transmission.

Nevertheless there is considerable disagreement about who is at greatest risk and how risk should be defined:

- Should risk be defined according to epidemiological criteria?
- Should risk be defined according to socio-economic criteria which affect access to health care?
- Should risk be defined according to pre-existing criteria of social vulnerability and disadvantage at all?

INEFFECTIVE MEASURES AGAINST HIV TRANSMISSION

Following are some of the ineffective measures against HIV transmission:

- Vaccines
- Specific agents
- HIV antibody testing
- Coercive measures
- Fear
- Once only education
- Inappropriate targeting

Vaccines

Many teams around the world are working to try to develop vaccines

against HIV and vaccine 'breakthroughs' have already been hyped for several years now.

But there are serious reasons why they probably offer no solution for the next few years.

It will take two to three years at the very least before we will know if a particular vaccine actually offers protection in the human body, as opposed to under laboratory conditions. Even when a vaccine gets developed, we don't know how long it will remain effective. To put this in context, HIV may change its genetic code about five times as fast as the influenza virus. And there may be thousands of slightly different forms of HIV. Efficacy studies will need to run for a number of years before we can be sure that a vaccine works.

HIV attacks cells (with CD4 receptors) in the nervous system as well as T-cell in the blood: this makes a vaccine much harder to develop. There are also serious ethical problems in testing such a vaccine on human beings: how can you ask someone to be a control (i.e. receiving no vaccine) in such a trial without trying your hardest to persuade them about safer sex or safer drug use? How would we then know whether the vaccine has worked or whether it is the health education that has worked to prevent infection?

What about other diseases? There are already two types of HIV reported; there

may be others, and of course we may discover that HIV is simply the first of a number of viruses which cause this kind of damage.

World-wide vaccination programmes also cost a lot of time, money and organisation: they do not happen overnight. Thus even when a vaccine is prepared it may be many years before it is fully available world-wide, and possibly never in some poorer countries.

Specific agents

These are often based on precautions which may be effective against sexually transmitted diseases or in preventing pregnancy, they include the following:

- Nonoxynol-9 and other spermicides. There continues to be no clear proof that nonoxynol-9 is effective enough to serve as sole form of protection against HIV infection, either in the vagina or the rectum. However, this is a form of protection which merits continued attention
- AZT for needle-stick injury prophylaxis. It was assumed that the administration of AZT immediately after a needle-stick injury might prevent seroconversion. Studies have now show this method to be ineffective.

HIV antibody testing

HIV testing has been assumed to be a means of protection, both on an individual basis and as a social solution

to the spread of HIV infection.

HIV testing has been advocated as a substitute for generalized safer sex education, yet it is clearly inappropriate and impractical to test the whole population.

A negative HIV test result does not confer immunity against HIV. It is also a retrospective result, and does not cover the most recent three months, since antibodies may take up to three months to form in most people.

It assumes that the act of testing will, of itself, develop a sense of responsibility previously absent in those having unprotected sex. Yet there is very little evidence of behaviour change as a result of HIV testing without safer sex counselling at the time of the test.

HIV testing provides the means for other forms of discrimination, which are also mistaken methods of HIV prevention. For example, many countries, will not admit people with HIV. This is assumed to protect the country from an external threat.

Yet the isolation and quarantine of people with HIV in all sorts of subtle and not so subtle ways ignores the fact that any person with HIV who has not been tested automatically slips through this false and faulty net.

Coercive measures

One of the first responses demanded to the AIDS epidemic was the quarantine of people with AIDS, closure of bathhouses and other commercial sex facilities, mandatory testing and registrations of HIV-positive people. All of these measures had been used in the past to control other public health problems, particularly sexually transmitted diseases, but all of these measures would exacerbate the AIDS epidemic. All were presented as self-evidently sensible restrictions on human rights, and little attention was paid to the way in which these proposals all interfered with health education, treatment or care.

Fear

Many countries used fear as one of the first tools in attempting to change behaviour. In the UK the Government campaign of 1987 used the image of a crashing tombstone with the message 'Don't Die of Ignorance'. In Australia the government used the image of the Grim Reaper in its campaign. They relied on the assumption, drawn both from drink-driving campaign and a misperception of the experience of gay communities around the world, that fear was the prime motivator of behaviour change.

Whilst it is likely that fear plays some part in behaviour change amongst a

proportion of those addressed through advertising messages, fearful images are not as effective in encouraging or sustaining behaviour change as those which offer positive and rewarding alternatives.

When fear-laden imagery did not work amongst heterosexuals, this was explained away as a result of the lack of proximity of heterosexuals to death and illness. It was assumed that gay men had begun to change their behaviour only as a result of seeing their friends die. This is a misreading of how behaviour changed amongst gay communities around the world, and undermines the importance of community-based education.

Once only education

It has been assumed that simply by informing people of the risks they face, this will lead to an irrevocable change in their behaviour. One burst of information does not inoculate against HIV infection however, and encouragements to sustain safer sex are needed. These should not be limited to exhortations to 'keep it up'. Such messages ignore the complex

difficulties faced in relationships; they also ignore the way in which sexuality develops and changes with age. The issue of sustaining safer sex is particularly crucial for gay men-a population with high HIV prevalence and a high rate of partner change.

One of the results of a lack of 'sustenance' has been a phenomenon that has been labelled 'relapse'. This is an unrigorous response to an unrigorous approach to health education. Such a label lumps together a range of different phenomena related to the failure to practise safer sex amongst gay men after ten years of the epidemic.

Inappropriate targeting

There have been a series of failures to educate and these reflect shifting and contested perceptions of who is most at risk.

In India, now that the epidemic has gone way out of the 'red light areas', the targeting of sex workers and their clients is proving to be an inappropriate methodology.

(Modified from: AIDS reference manual, NAM Publications 1995)

6

HOW TO TAKE SEXUAL HISTORY?

The major mode of transmission of HIV in India is sexual. In clinical practice more than 90 % HIV positive patients give history of sexual behaviour that may have put them or their sexual partners to risk. Thus it becomes essential that a proper history of sexual behaviour be obtained in order to diagnose HIV infection, especially if we intend to diagnose it early. However it is a common experience that health care workers are not properly trained in this field. It is understandable that clinicians and patients alike may be uncomfortable initially in discussing many issues of sexuality.

Two approaches are taken.

- a) To skip the sexual history part,
- b) To take a short cut and order testing for anti-HIV antibodies without informing the patient.

Both the options are usually followed with disastrous after effects.

Many a times the clinician's approach is highly judgmental and authoritarian. A 'true' history may not be elicited then.

So:

- Be non-judgemental.

- Try to make the patient comfortable, and do not intimidate the patient
- Assure the patient that confidentiality will be strictly maintained
- Any patient has the right to refuse discussion regarding sexuality. So ask only those questions that are related with patient's welfare, and not those being asked for the clinician's curiosity.
- It is essential we develop empathy. Explain the rationale for taking this form of history. Patient's co-operation is essential to get maximum 'true' information.
- Use language which the patient understands, do not assume that every word is understood the way it is intended to be.
- It is often useful to talk about the most recent contacts first and then go working backwards.
- Be sensitive about the psychological state of the patient.
- Try to elicit details of sexual practices.
- Do not assume heterosexuality/monogamy.
- Remember about the " Window-Period " for testing the patient, as well as patient's sexual partners.

7

COULD IT BE HIV?

Dr. Vinay Kulkarni

“The term AIDS is obsolete. HIV infection more correctly defines the problem. The medical, public health and community leadership must focus on the full course of HIV infection rather than concentrating on the later stages of the disease [ARC (AIDS Related Complex) and AIDS.] Continual focus on the later stages of disease rather than the entire spectrum of HIV infection has left our nation unable to deal adequately with the epidemic.”

- From the report of the Presidential Commission on the HIV Epidemic (USA). 1988.

The situation in India, even today, is not very different. A substantial percentage of people with HIV infection are detected only after they have developed AIDS. This is partly because of lack of awareness among the people who have had behaviour putting them to risk of being infected with HIV and the long asymptomatic phase. It is also out of concern for the implications of being ‘ HIV positive.’ In addition to this, it is also because of lack of awareness among

the physicians who have failed to identify the early ‘markers’ of HIV infection and due to lack of adequate index of suspicion.

The experience gained over the years definitely suggests that the clinical events occurring during the natural course of HIV infection follow a reasonably predictable chronological order. It is possible to decide on the basis of clinical finding-regarding antimicrobial chemoprophylaxis, to predict the prognosis, to decide about institution of antiretroviral therapy and to discuss optimum care.

Why is it important to diagnose HIV infection early?

The costs of missed diagnosis are tremendous : both for the individual and to the community. During the initial phase of HIV epidemic the concept of ‘High Risk Groups’ was very popular and people from such groups alone were under the scrutiny. But it soon became apparent that high-risk behaviour was the risk factor and such ‘high risk

behaviour' was widely prevalent in large populations outside the so-called 'high risk groups'. To give just a dramatic example, a commercial sex worker practising safer sex was certainly at a lower risk than an unsuspecting spouse of a man having multiple sexual partners. HIV has thus become a part of differential diagnosis for several problems in any sexually active person. Though the most common mode of transmission is sexual (hetero/homosexual) there are certain other modes too. It has been seen very often that the diagnosis of HIV is missed just because the physician does not think of the same, in say a 58-year-old person. From the patient's point of view early diagnosis is important because interventions like chemoprophylaxis for certain opportunistic infections and treatment with antiretroviral drugs definitely offer better quality of life. For the health care worker-earlier the detection, better are the chances that the course of the disease could be influenced, the patient could be counselled and further spread of HIV may be prevented.

Benefits of Early HIV Diagnosis

To individual patients

- Prolongation of asymptomatic period
- Delayed disease progression
- Prevention of opportunistic infections (OIs)
- Optimal maintenance of health through patient education and counselling

Cures of OIs are only likely with early intervention

Benefits of antiretroviral treatment

Chance to participate in research and clinical trials and help in developing appropriate intervention strategies.

To the community

Documentation of and advocacy based on changes in the epidemiology

Behaviour change interventions

Contact tracing

Control of the epidemic

There is great personal and professional satisfaction in caring for patients with HIV related disease and in ameliorating attitudes towards them. Early diagnosis gives the best chance for positively influencing the course of the disease.

Primary HIV infection

Also called as the seroconversion illness. It is characterised by an onset 2-4 weeks after infection and "mononucleosis - like" syndrome. It reflects the initial encounter of HIV with the host immune system. This is a phase of very rapid viral replication and viraemia. Most manifestations are self-limited and resolve, as anti-HIV antibodies become detectable in the patient serum.

There is fever (with or without night sweats), pharyngitis, lymphadenopathy, arthralgia, myalgia, lethargy/malaise, anorexia and weight loss. The skin may show erythematous maculopapular or roseola-like rash, headache, retro-orbital

pain, meningoencephalitis, peripheral neuropathy, radiculopathy, Guillain-Barre syndrome, cognitive/affective impairment. There could be mucocutaneous ulceration, oral/oropharyngeal candidiasis, nausea/vomiting or transient diarrhoea.

Early HIV Disease

Apart from a very few exceptions the primary infection is followed by a prolonged (usually 5-7 years) asymptomatic phase. Though HIV is replicating inside the lymph nodes (and that too to the tune of several billion copies everyday) the levels of virus in the blood are low. Only generalised persistent lymphadenopathy (PGL) may be noted. Disappearance of PGL may be a poor prognostic sign.

The course may be marked by recurrent episodes of illness. Recurrent illnesses, multiple illnesses and abnormal features and usually delayed response to standard treatment should alert the physician about the possibility of underlying HIV infection.

Idiopathic thrombocytopenic purpura (may also occur in late disease), Guillain-Barre syndrome, chronic demyelinating peripheral neuropathy, mononuritis multiplex, cranial nerve palsies, autoimmune salivary gland disease, ideopathic polymyositis may occur in a few patients.

Moderately advanced HIV disease

This is characterised by less severe infections of the skin and mucosal surfaces (tinea, seborrhoeic dermatitis, warts, molluscum contagiosum, folliculitis and gingivitis, oral candidiasis, oral hairy leukoplakia indicated this stage. Reactivation of herpes zoster and herpes simplex viruses, tuberculosis (usually with typical clinical features - the atypical variety occurring in more advanced stage of the disease) are definitely more sensitive markers of possible HIV infection.

Advanced HIV disease

This is characterised by development of AIDS defining opportunistic infections or malignancies. The 'viral load' in the blood and in the semen is high. This is associated with increased virulence and accelerated rate of further immune destruction. Pneumocystis carinii pneumonia, toxoplasma encephalitis, atypical and widespread tubercular infection, cryptococcal meningitis, mycobacterium avium complex, CMV retinitis, cryptosporidial enteritis, non-Hodgkin's lymphoma, primary CNS lymphoma, have all been seen in Indian AIDS patients. Kaposi's sarcoma is quite rare. Cervical (invasive) carcinomas, too, have not been reported that frequently.

Further reading: Could it be HIV? The clinical recognition of HIV infection. 2nd edition. Edit.: Graeme Stewart, Australian Medical Publishing Co. Ltd., 1994.

8

LABORATORY DIAGNOSIS OF HIV INFECTION

Dr. Suniti Solomon

INTRODUCTION

Two distinct Human Immuno Deficiency viruses (HIV) types 1 and 2 (HIV-1,2) are the etiologic agents of AIDS- (Acquired Immunodeficiency Syndrome) the plague of the 20th century. AIDS due to HIV-1 infection is most prevalent in the America, Western Europe and Africa whereas, most AIDS cases due to HIV-2 are reported in West Africa. Phylogenetically, HIV-1 is divided into 9 sub types and HIV-2 into 2 sub types.

The first case was reported in 1981. Dr. Luc Montagnier discovered the virus in 1984.

Sexual contact is the major route of transmission. The virus can also be transmitted by blood or blood products both to individuals who share contaminated needles for drug use and to those who receive transfusions of blood or blood products. Infected mothers efficiently transmit the virus to their infants perinatally and as early as the first and second trimesters of pregnancy.

Once in the blood stream, the virus enters several types of cells including lymphocytes, macrophages, Langerhans cells and neurons within the central nervous system. The prime targets however CD4+ cells, which include T. lymphocytes and their precursors, resulting in their depletion.

LABORATORY PROCEDURES

Laboratory procedures for the diagnosis of HIV infection include tests for immunodeficiency as well as specific tests for HIV.

Immunological tests

The following parameters help to establish the immunodeficiency in HIV infection:

1. Total leukocyte and lymphocyte count to demonstrate leukopenia and lymphopenia (lymphocyte count usually below 2,000/c mm)
2. T cell subset assays:- Absolute T4 cell count will be usually less the 200/mm. T4: T8 cell ratio is reversed.

3. Platelet count will show thrombocytopenia.
4. Raised IgG and IgA levels.
5. Diminished CMI (Cell Mediated Immunity) as indicated by skin tests.
5. Surveillance for sero epidemiology.
6. Research
7. Screening donors of tissue, organs, sperms etc.

Specific tests for HIV infection

1. Antigen detection - P₂₄ antigen
2. Virus isolation - Virus is isolated from the peripheral lymphocytes
3. Antibody detection - Like anti HIV antibodies (anti P₂₄)

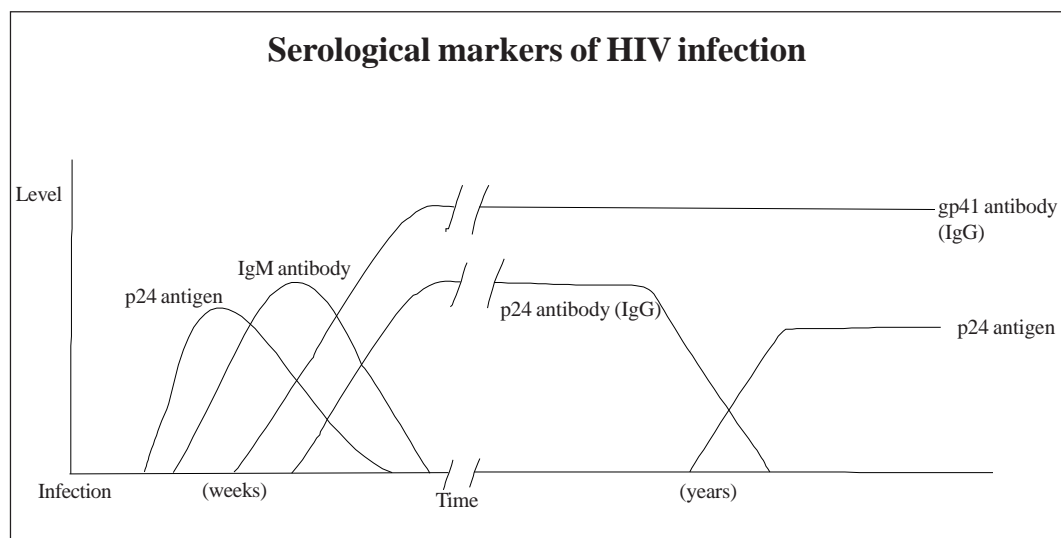
Objectives of HIV antibody testing

1. Diagnosis of HIV infection in clinically suspected persons.
2. Voluntary testing in persons with high-risk behaviour.
3. Persons immigrating overseas.
4. Blood/blood products safety.

Detection of antibody

HIV serological testing is the most common approach for identifying HIV infected individuals or HIV contaminated blood products. HIV antibody testing has gained popularity because anti-HIV antibodies usually occur relatively early in the disease process and normally persists throughout the course of HIV disease progression. Also, these assays are relatively inexpensive and most can be easily adapted to accommodate large screening test volumes.

Every individual who is tested for HIV should receive pre and post test counselling and if found positive for HIV



antibodies should continue to have psychological support, counselling on nutrition and regular medical check-up etc. They should be encouraged to join self-help groups to meet others in a similar situation. No HIV testing should be done without the individuals consent.

Seroconversion (Development of detectable levels of HIV antibody)

- a. A few weeks after primary HIV infection there is a burst of virus replication and high levels of viremia (HIV-1 p24 Ag). This period is referred to as the “window phase”, where an individual is infectious but HIV antibodies cannot be detected by serological assays.
- b. HIV antibodies are normally detected 3 to 12 weeks following infection. But in rare cases, this may be longer, prolonging the window phase.
- c. Depending on the assay used, the first antibodies detected may be directed against core p24 or envelope gp41 antigens.
- d. Normally, following seroconversion HIV antibodies will persist throughout the disease process. However, antibodies directed against viral core antigen may disappear with HIV disease progression into AIDS, and in rare cases, complete loss of HIV antibody production can occur during the total collapse of the immune system in terminally ill AIDS patients.

Classes of immunoglobulin (Ig) detected in HIV diagnostic assays

Three of the 5 known classes of the immunoglobulins are detected in various HIV diagnostic assays (IgG, IgM, IgA)

1. IgG Class

The majority of the HIV assays are designed to detect this class of immunoglobulin.

Most of IgG sub-classes can cross the placenta, therefore transplacental maternal HIV antibodies can confuse and confound the diagnosis of HIV infection in neonates.

2. IgM Class

Documentation of anti-HIV IgM production in early HIV infection is not consistent and technical problem with IgM specific serological assays lead to problems of reduced specificity, therefore the application of HIV IgM assays in diagnostic testing is limited.

HIV IgM specific assays are useful in neonatal diagnosis and identification of early seroconversion in patients who demonstrate indeterminate western blot results.

3. IgA Class

This class of immunoglobulins does not cross the placenta. So they are useful in diagnosis of HIV-infection in neonates.

Antigen types used in diagnostic testing

1. **Viral lysate** - Most Common Antigen type used

Viral particles are produced in continuous T-Lymphocyte cell lines and are purified by density gradient ultracentrifugation. Contaminating cellular antigens and host cell membrane glycoproteins account for a portion of decrease in specificity observed when using HIV assays based on viral lysate antigen preparations.

2. **Recombinant antigens**

Recombinant antigens are produced by genetic engineering methods, when a portion of HIV genome is inserted into a biological vehicle or vector and then transfected into an appropriate host cell expression system where large quantities of HIV gene products are produced and purified with improved sensitivity and specificity.

3. **Synthetic antigens**

Synthetic peptide antigens or chemically synthesized amino acid residues, corresponding to specific viral antigen epitopes.

Because of their inherent purity and exquisite specificity, these antigen preparations are most useful in confirmatory assays.

Screening assays for HIV antibody

Screening assays are usually highly sensitive assays, which are not completely specific. These assays are designed to detect the vast majority of specimens containing HIV antibodies and then more specific secondary / supplement assays are performed to confirm or refute the initially reactive results, in order to distinguish true HIV antibody containing specimens from falsely reactive samples.

Selection of the most appropriate test or combination of tests to use depends on 3 criteria:

- a. Objective of the test
- b. Sensitivity and specificity of test being used
- c. Prevalence of HIV infection in the population being screened.

Basic types of HIV screening assays

1. ELISA/EIA (Enzyme Linked Immuno Sorbent Assay)
2. Rapid assays
 - a. Dot blot
 - b. Particle agglutination (latex, red cell, gelatin particles)
 - c. Fluorometric micro particle technologies.

ELISA/EIA

Enzyme Linked Immunosorbent Assay. ELISA's remain the most common type of HIV screening immuno assay.

Advantages

1. Easy to perform
2. Large number of samples can be done at a time.
3. Highly sensitive
4. Highly specific

Disadvantage

1. False positives may occur
2. Needs to be read in an ELISA reader.

Types of ELISA

1. Indirect

HIV antigens are attached to a solid support allowing HIV antibodies in the sample to bind, which are subsequently detected by enzyme-labelled anti-human immunoglobulin. A specific substrate is then added to produce a colour reaction when HIV antibody is present in the test serum.

2. Competitive

- a. Competitive ELISA are like indirect ELISA method, except an enzyme labelled HIV antiserum reagent is mixed with a dilution of the patients test sample before adding it to the solid phase antigen support.
- b. If HIV antibodies are present in the patient's sample, they compete with the labelled HIV antiserum and reduce the binding of the enzyme labelled antibodies to the HIV antigens on the solid phase.

- c. Unlike the indirect assay in the competitive ELIAS, the reduction or absence of colour development indicates the presence of HIV antibodies in the patient's serum. Strong colour development in the competitive assay indicates the absence of HIV antibodies in the patient's sample, allowing the enzyme labelled antibody to non-competitively bind to HIV antigens on the solid phase (i.e., inverse relationship between O.D. [Optical Density] and HIV antibody concentration in the patient specimen.)

3. Antigen sandwich ELISA

The antigen sandwich is a modification of classical indirect ELISA to improve sensitivity and specificity. This is accomplished by reducing the density of antigen molecules attached to the solid phase. (Ag molecule/unit area.) Bivalent or multivalent antibodies binding to the HIV antigen molecules will have a free antigen combining site (S). A labelled HIV antigen is then attached to antibody molecules, allowing these antibodies attached to the solid phase to be detected. The sandwich assay detects all classes of HIV antibodies.

4. Antigen and antibody capture ELISA

Principles-A monoclonal antibody directed against HIV antigen is bound to the solid support.

HIV viral lysate antigen mixture is added and specific HIV antigens are captured by monoclonal antibodies present in the serum binding to the HIV antigen captured on the solid support. This technique improves the specificity of the assay by capturing only specific HIV antigens and; therefore, does not detect antibodies in patient serum directed against unimportant antigens or contaminants in the lysate, antibody capture. E.g. : - Gacelisa, Marcelisa.

These assay are used to test specimens with low concentration of antibody i.e. urine or to detect the concentration of specific classes of immunoglobulins directed against HIV. (i.e. IgG, IgM).

For example, an anti-human Ig (anti-IgG or IgM) immunoglobulin (mono or polyclonal is attached to solid support; the patients serum is added binding a certain class of Ig's to the solid support. After washing, a labelled HIV antigen is added, binding to the patients HIV antibodies attached to the solid phase by the anti immunoglobulins.

5. Interpretation of results

a. Cut-off value

Each kit manufacturer has devised a method of calculation of the cut off value, to classify a test sample as positive or negative.

b. Grey zone identification

All infected individuals start with low levels of antibody and gradually the level of HIV antibody increases as the

infection progresses. Therefore, some laboratories testing high risk, high incidence populations institute “grey zone” identifications where specimens which are just below the cut-off (i.e. cut-off multiplied by 0.9) are classified as “grey zone reactive”, which are re-tested and subjected to confirmatory testing. This method may identify sero-converting patients early in the course of disease.

c. Repeat testing

Reactive and “grey zone” reactive specimens are normally repeated in duplicate and the consensus results are accepted. Initial reactive specimens, which are not reproduced, are usually the result of technical error and are subsequently not tested in confirmatory HIV assays.

6. Performance variables/trouble shooting

ELISA tests are generally easy to perform but require careful adherence to procedures, any deviation in incubation times and /or temperature of pipetted volume can dramatically change test results.

7. Biological false positive and false negative EIA/ELISA results

a. False positive

1. Hematological malignant disorders
2. DNA viral infections
3. Autoimmune disorders

4. Multiple myeloma
5. Primary biliary cirrhosis
6. Alcoholic hepatitis
7. Influenza vaccination
8. Hepatitis B Vaccinations
9. Passively transferred antibodies
10. Antibodies to class II leucocytes
11. Renal transplantation
12. Chronic renal failure
13. Stevens - Johnson Syndrome
14. Positive rapid plasma reagin test (Syphilis).

b. False negatives

1. Incubation “Window” period before antibody development
2. Immunosuppressive therapy
3. Replacement transfusion
4. Malignant disorders
5. B-cell dysfunction
6. Bone marrow transplantation
7. Kits that detect primarily antibody to p²⁴
8. Starch powder from laboratory gloves.

Rapid assays

These assays were developed as alternatives to ELISA for HIV screening. Generally require less than 30 minutes to perform. Do not require sophisticated laboratory equipment and are easy to perform. Positive results must be confirmed by standard HIV screening and confirmatory tests.

Particle agglutination assays

Agglutination assays may lack specificity due to antibodies in the patient’s samples reacting against the carrier particles to which the specific antigens are attached. Agglutination assays for HIV antibody screening use 4 major particle types : gelatin particles, treated sheep red blood cells, latex particles or microbeads.

Prozone reactions

Prozone reactions are false negative reactions that occur in agglutination tests. When an excess of antibody exists binding to the antigen-coated particles occurs without bringing, this prevents the lattice formation. Dilution of sera will resolve this.

Dot blot EIAs

This is a rapid and easy test to perform. It usually yields results in less than 10 minutes.

Many of these assay incorporate HIV-1 and HIV-2 synthetic peptide antigen. These tests can differentiate between HIV-1 and HIV-2 infections.

Examples of dot blot EIA

1. Micro particle based assays
2. Membrane spotted assays
3. Dip stick method

Advantages

1. Time only 10 minutes
2. No elaborated equipment needed
3. No specialized training necessary

Disadvantages

1. Expensive
2. Indeterminate results may occur
3. Needs confirmation

Fluorometric microparticle technologies

Microparticles are coated with HIV antigen, incubated with serum and reacted with antihuman immunoglobulin labelled with a fluorochrome. The microparticles are trapped on a membrane and fluorescence emitted by conjugated antihuman immunoglobulin is measured using a fluorometer.

CONFIRMATORY TESTS FOR HIV ANTIBODY

Confirmatory assays must be highly specific to ensure that individuals who test reactive in screening assays are correctly identified as being HIV infected. Western Blot (WB) is the most commonly used confirmatory test.

WHO recommends a second screening test to confirm a reactive initial test but the second assay must be different in principle from the first test.

These confirmatory (supplemental) assays do not always yield conclusive results but may produce “indeterminate” results that require additional testing to resolve.

Confirmatory tests

1. Western Blot (WB)

2. Line immunoassays
3. IFA (Indirect Fluorescent antibody assay)
4. RIPA (Radio Immuno Precipitation Assay)

Western Blot

Western Blot (WB) assays are the most widely accepted HIV confirmatory assays. WB’s highly specific, but expensive and labor-intensive. The WB technique owes its exquisite specificity to two factors: Component separation and component concentration.

The technique involves separating viral proteins electrophoretically by their molecular weights. After separation, the proteins are transferred, or “blotted” onto nitro-cellulose paper, which is then incubated with the patient’s serum sample.

After incubation and washing of the specimen, specific bound antibodies are detected by antihuman globulins conjugated to an enzyme or a radioactive probe. The spectrum of bands present is used as the interpretative criteria.

Interpretation of the Western Blot for HIV-1 has not been universally established. The majority of laboratories have accepted the recommendations of the Association of State and Territorial Public Health Laboratory Directors (ASTPHLD) and the Center for Disease Control. These criteria require two of three key bands to be present for a positive result.

When assessing Western Blot results, physicians should be aware of the criteria used by the laboratory performing the test.

Specimens from high-risk patients that are repeatedly reactive on ELISA are usually unequivocally positive on western blot. However, false - positive and indeterminate results can occur because of cross-reactivity with other proteins.

Interpretation of test results

Differences in laboratory criteria and variation among results of different Western blot kits may cause a patient serum to test positive in one laboratory and negative in another. Thus incidences of inaccurate results vary from a false-positive rate of 1 in 20,000 tests to indeterminate results in 20% to 40% of cases in which the ELISA test was serum negative. The incidence of indeterminate results is one reason Western blot is not used as a screening test.

In patients with known risk factors for HIV, one indeterminate result on the Western blot test following a positive ELISA result may represent early infection; sero-conversion is incomplete in patients with early HIV infection. Also, patients presenting in the late state of infection may have severe immune incompetence, causing an indeterminate result. Such patients would be expected to be clinically symptomatic and usually indicates a poor prognosis. In patients with no identifiable risk factors who have

an indeterminate result, follow-up testing may resolve the uncertainty.

Evidence suggests that low-risk patients with consistently indeterminate western blot results do not have HIV infection. The recommendations of the Center for Disease control state : a person whose western blot results continue to be consistently indeterminate for at least 6 months in the absence of any known risk factors, clinical symptoms, or other findings may be considered negative for antibodies to HIV-1.

In low-risk persons concerned about HIV infection, a negative ELISA is a good indicator that HIV antibody is not present. For persons with known exposure to the virus, the combination of negative ELISA and the absence of all bands on western blot at 3, 6, 9 and 18 months after exposure provides good evidence that HIV antibody is not present.

Criteria for interpreting western blot results for HIV ASTPHLD/CDC

Negative: no bands

Positive: at least two of key bands p23, gp41 and gp120/160

Intermediate: Single band or combination of bands that does not confirm to a positive result.

American Red Cross

Positive: - Three or more bands, one from each of gene groups gag, pol and env.

Causes of false-positive and indeterminate Western Blot results for HIV

- Normal Human ribonucleoproteins
- Other human retroviruses
- Antibodies to mitochondrial, nuclear and T-cell leutocyte, antigens
- Globulins produced during polyclonal gammopathy
- Proteins on filter paper
- Anti-carbohydrate antibodies
- Heat - inactive serum
- High concentration of bilirubin in serum
- Passively acquired antibodies

Line immuno assays

Viral antigens (usually recombinant or synthetic) are mechanically applied (sprayed) onto membrane support.

These assays do not contain the contaminating cellular components, which may lead to indeterminate results.

ImmunoFluorescence Assays (IFAs)

In the hands of properly trained, experienced technician with a quality microscope, this assay's performance is equal to the western blot assay.

Types

Direct: To detect HIV antigen using specific HIV antibody labelled with a flourochrome.

Indirect: To detect HIV antibody-sandwich-technique

Reading and interpretation

- a. Subjective grading of intensity
 1. Negative: No specific fluorescence of infected or uninfected cells.
 2. Positive: A minimal % of infected cells must demonstrate specific fluorescence (usually 20-40%) to a reaction to be considered positive.

Radio Immuno Precipitation Assay (RIPA)

This is an expensive and elaborate test to perform requiring cultivation of HIV in tissue culture and handling radioactive material. Consequently, RIPA is not used in many clinical laboratories and has been found to be difficult to standardize from one laboratory to another. RIPA is a highly sensitive assay and can detect antibodies to HIV envelope antigens earlier in the course of disease than western blot assays.

Alternative specimens for HIV antibody testing

Although serum / plasma are the primary specimens for HIV antibody testing, recently two alternate samples have been proposed for routine diagnostic testing. Saliva is an alternative body fluid for detecting HIV antibodies to HIV envelope antigens earlier in the course of disease than western blot assays.

Saliva HIV test is not as sensitive in detecting recent seroconversion as

screening blood specimens. It is a convenient alternative method for conducting seroprevalence surveys.

Antibody specific for HIV-1 can also be detected in the urine of infected individuals, even in the absence of demonstrable proteinuria.

Saliva HIV test

Saliva has been used successfully as a diagnostic specimen and has several advantages over blood in the diagnosis of HIV infection.

Advantages

1. It is easier to collect
2. There is no need for trained technicians and it can be used in drug users with collapsed peripheral veins.
3. It is less infectious than blood.
4. Safer to manipulate.
5. It has better subject compliance because it causes no needle injury and no religious or ethnic objections.
E.g. In countries like Guinea - Bissau where ethnic opposition makes the use of blood specimens difficult, saliva could represent an alternative in surveillance studies.

Procedure

GACELISA is commonly used for testing antibodies to HIV in saliva.

Saliva should be collected by dribbling into a sputum disposable pot and diluted (1:2) in a solution of 0.1% sodium azide

in water. Salivary production, which is impaired in some HIV infected subjects, should be stimulated by chewing a mentholated chewing gum for 1 min, without swallowing the saliva. Diluted saliva should be clarified by centrifugation (1500 g./10min) and the supernatant can be stocked at 20°C or processed.

Salivary antibodies to both HIV-1 and HIV-2 can be detected by GACELISA.

Saliva - based HIV - antibody testing in Thailand

In a survey, conducted in Thailand by Ralph R Frerichs, Narumol Silarug, Nora Eskes, Prasong Pagcharoempol, Amron Rodklai, Somchai Thangasupachai and Chainarong Wongba, found that the sensitivity of the GACELISA with saliva was 98.0% in the field (298 HIV - positive specimens) 100% after correction of errors (300 HIV - positive specimens), and 100% among the quality assurance samples (95 HIV - positive specimens). The specificity of the GACELISA was 99.4% in the field (1653 HIV- negative specimens), 99.6% after correction of errors (1654 HIV - negative specimens) and 100% among the quality assurance samples (96 HIV - negative specimens).

Urine antibody to HIV-1

Antibody specific for HIV-1 can be routinely detected in the urine of infected individuals, even in the absence of demonstrable proteinuria. Antibody in

urine is the intact IgG class of immunoglobulin. Antibody levels in urine are much lower than those in matched plasma. The low antibody titres in urine create the potential for a false negative result. At present additional studies are necessary to determine the usefulness of urine in HIV testing.

Detection of HIV nucleic acids

The detection of HIV antibody has generally been a very reliable tool for diagnosing HIV infection. However, there are specific situations where the direct detection of viral nucleic acids may improve the capability of a clinical laboratory to diagnose HIV infection (i.e. congenital HIV infections, “Window phase” and sero-converting individuals).

Additionally, molecular biological techniques, which characterize HIV nucleic acids may be useful in identifying genetic variability among isolates and enable direct measurement of viral load.

Polymerase chain reaction (PCR)

A variety of techniques have been developed to amplify the nucleic acid target sequence of the molecular probe attached to the target sequence to improve the sensitivity of nucleic acid detection.

- a. PCR is a highly sensitive and specific assay. If correctly performed it can be used in the following areas of HIV diagnosis.
1. Detect early infection (Window period) prior to seroconversion.

2. Resolve indeterminate WB or serological results.

3. Congenital HIV diagnosis (detected HIV infections of infants born to seropositive mothers).

4. Monitor viral load in patients undergoing antiviral therapy.

5. Detect genetic variability among HIV isolates, identify mutations of RT enzymes, associated with AZT and other nucleotide analog antiviral drugs.

6. Detect infection in Antibody positive individuals who are culture negative and / or negative by antigen detection assays.

PCR is yet to be used for routine diagnosis of HIV infections, it is primarily employed as a research tool.

Procedure

The polymerase chain reaction is a way of “amplifying” or making multiple copies of all or part of the DNA of genes.

1. First a double strand of DNA is separated into two single strands by heat.
2. Two rows of nucleotides are marked or “primed” by the addition of two short strands - oligonucleotides - designed to bind specifically on either side of the section of interest in the gene.
3. A polymerase enzymes, synthesizes a copy of the nucleotide sequence between the primers in the forms of a new double strand.

4. The process is repeated and at each stage the number of copies is doubled from the two to four to eight and so on. This can be done quite simply because all the reagents can be added to one tube and the reactions controlled by changing the temperature (the first reaction at 94°C, the second at 55°C, and the third at 72°C using a special heat stable Taq polymerase). As a cycle takes only a few minutes it is possible to generate millions of copies of the DNA in a day.

RNA can also be studied by making a DNA copy of the RNA using the virus enzyme reverse transcriptase. This approach allows us to study messenger RNA (mRNA) in cells that are using the molecule to synthesize specific proteins or for detecting the genome of RNA viruses. Originally, unstable and toxic reagents had to be used, but this can now be avoided.

Capillary polymerase chain reaction procedure for the rapid detection of HIV-1 DNA in blood

Polymerase chain reaction (PCR) is used increasingly in addition to serology for the diagnosis of HIV infection, particularly in infants of HIV-positive mothers. Many laboratories are now offering same-day testing for HIV antibodies.

Capillary PCR in which the reaction mixtures are held in glass capillary tubes is completed in a matter of minutes

compared to hours for conventional PCR.

Advantages

1. A reduction in overall cycling time (from 2h 20min in tubes to 20 min in capillaries) giving an overall time for the nested PCR of 5.5h.
2. A cost saving in reagents because of the 10 ml reaction volume.
3. A lack of over-amplification of the PCR product DNA favouring a clear sequencing pattern of DNA. Semi-capillary PCR, which can be performed on DNA extracted from clotted blood, can serve as a rapid confirmatory method for HIV serology offering the possibility of providing a result on the day the specimen is collected.

Detection of HIV infection during window period using polyclonal B-cell activation test (PBAT)

Detection of HIV infection both in mass screening and in patient diagnosis, relies on detecting HIV specific antibodies in the serum (serology). Although, very specific and sensitive, it does not solve the lack of detection during the “window period” between infection and the sero-conversion.

In a study conducted by T Jehuda Cohen, JM Mumo, JJ Bwaya and M Pezzella in Kenya, found that Polyclonal B Cell Activation Test (PBAT) offers a relatively simple tool for the detection of individuals in the window period. It

could be an important tool in better diagnosis and treatment of hospital patients in area endemic with HIV.

Evaluation of rapid on-site clinical HIV test

It is essential to have rapid, cost-effective assay methods to detect HIV, particularly in some developing countries where sophisticated equipment is not readily available.

Early on-site serodiagnosis of HIV infection should be possible at the peripheral of the health-care systems where it may be an advantage to enable patients to make informed decisions and health workers to decide on early prophylactic treatment and management strategies. This would also facilitate on-site counselling where relevant and benefit studies on epidemiological patterns and prevention interventions.

Common screening tests for HIV are enzyme - linked immuno sorbent assay (ELISA) which are suitable for batch testing of large numbers of specimens, but impractical for field conditions in some developing countries. They are time consuming (2-24h) require access to running water, electricity and entail the purchase and maintenance of sophisticated equipment. These tests may not be suitable for cost-effective for laboratories handling relatively small numbers of specimens.

The high specificity, sensitivity and predictive values on both positive and

negative samples indicate that this method (capillus) is suitable for rapid onsite HIV- investigations and offers performance characteristics comparable to the laboratory ELISA.

Advantages

1. Rapid testing requires minimum operator and does not require expensive equipment.
2. Low volumes of patient specimens from infants, emergency situations and any number of tests can be tested.

Rapid serologic testing with immune dissociated HIV p24 antigen for early detection of HIV infection in neonates

Serologic detection of HIV infection in neonates is complicated by the presence of immune complexes, consisting of passively transferred maternal antibodies and HIV antigens. A new rapid assay has been designed to disrupt these immune complexes in order to permit the detection of a specific HIV antigens.

Method to measure p24 antigen in blood samples from infected children of HIV infected mothers

The samples should be treated with glycine hydrochloride to dissociate the immune complexes. Followed by neutralization with TRIS - hydrochloric acid. A commercial HIV p24 antigen assay is available, with an optical density greater than 0.120 at wavelength of 450 nm defined as indicating a positive result.

Automation of an HIV proteinase enzyme assay

Introduction

The Scintillation Proximity Assay (SPA) is a highly sensitive homogeneous assay that eliminates the need for separations, washings or the use of liquid scintillates. SPA technology is ideally suited for high

output screening and can achieve optimum performance hence used with an automated laboratory workstation. High output is possible with uncompromized accuracy and convenience.

SPA offers a sensitive and easily automated means for screening large sample libraries.

HIV TESTING STRATEGIES FOR INDIA

WHO recommends 3 testing strategies or algorithms to maximize accuracy and minimize cost.

Strategy I

All serum is tested with one ELISA or Rapid / simple assay. Serum that is reactive is considered HIV antibody positive. Serum that is non-reactive is considered HIV antibody negative.

Strategy II

All serum is tested with one ELISA or Rapid simple assay. Any serum found reactive on the first assay is re-tested with a second ELISA or rapid/simple assay based on a different antigen preparation and/or different test principle (e.g. indirect versus competitive). Serum that is reactive on both tests is considered HIV antibody positive. Serum that is non-reactive on the first test is considered HIV antibody negative. Any serum that is reactive on the first test but non-reactive on the second test is also considered antibody negative.

Strategy III

As in the strategy II all sera is first tested with one ELISA or rapid/simple assay and any reactive sample is re-tested by using a different assay. In strategy III, a third test (WB) is employed for those sera found positive by the 2nd test. The 3 tests in this strategy should be based on different antigen preparation and/or different test principles. Serum reactive on all 3 tests is considered HIV antibody positive. Serum that is non-reactive on the first test is considered HIV antibody negative as is serum that is reactive in the first test but non-reactive in the second. Serum that is reactive in the first and second tests but non-reactive in the third test is considered to be equivocal.

Strategy adopted using Western Blot

As in the strategy II all sera is first tested with one ELISA or rapid/simple assay and any reactive sample is retested by using different assay. In strategy WB-II, a third test (WB) is employed for those sera found positive by the 2nd test. Only

those samples found positive by all the three tests. (ERS followed by 2nd ERS and WB) are only considered HIV antibody positive.

Recommendation by WHO and NACO

For diagnosis of HIV infection (asymptomatic) an individual test of high specificity should be used to minimize the rate of false-positive results. If the prevalence in the population being screened is >10 percent, the WHO testing strategy II should be used. If

prevalence is ≤ 10 percent, WHO testing strategy III is recommended. Individuals with clinical signs/symptoms of HIV infection / AIDS should be tested according to WHO strategy II regardless of the prevalence of HIV infection.

In conducting sero-epidemiological studies or surveillance two different strategies are recommended based on the prevalence of HIV infection in the population being screened. WHO testing strategy I should be used where the prevalence is >10 percent: and strategy II where the prevalence is ≤ 10 percent.

First Test	Second Test	Third Test	Result
Positive	Negative	Positive	Positive
Positive	Negative	Negative	Negative
Positive	Positive	Not requitred	Positive
Negative	Not requitred	Not requitred	Negative

9

CLASSIFICATION AND STAGING OF HIV DISEASE

Dr. Srikanth Tripathy

Early in the AIDS epidemic, clinical manifestations were frequently categorized as those meeting with the surveillance case definition of AIDS, and other less severe signs and symptoms were called ARC (AIDS related complex). With the knowledge about the full spectrum of HIV-disease the term ARC became obsolete and a more comprehensive phrase “HIV-disease”

was coined.

The most widely used classification systems used were drafted by Centre for Disease Control (CDC). The first one in 1986 which was later modified in 1993.

The 1986 classification scheme was for “public health purposes” and was not intended as a staging system.

Summary of 1986 CDC Classification system for HIV infection

Group I	Acute infection	
Group II	Asymptomatic infection	
Group III	Persistent generalized lymphadenopathy (PGL)	
Group IV	Other diseases	
	Subgroup A	Constitutional disease
	Subgroup B	Neurologic disease
	Subgroup C	Secondary infectious disease
	Category C-1	Specified secondary infectious diseases listed in the CDC surveillance definition of AIDS.
	Category C-2	Other specified secondary infectious diseases
	Subgroup D	Secondary cancers
	Subgroup E	Other conditions

CDC: AIDS DEFINING CONDITIONS.

Opportunistic infections.

Candidiasis of bronchi, trachea, lungs
Candidiasis, oesophageal
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (> 1 month's duration)
Cytomegalovirus (CMV) disease (other than liver, spleen, nodes)
including retinitis
Herpes simplex: chronic ulcer(s) (>1 month duration, or bronchitis,
pneumonitis, or oesophagitis)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Progressive multifocal leukoencephalopathy (PML)
Salmonella septicaemia, recurrent
Toxoplasmosis of brain

Malignancies

Kaposi's sarcoma
Lymphoma, Burkitt's (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary of brain
Cervical cancer, invasive

Encephalopathy, HIV related

Wasting syndrome due to HIV

Advanced immune deficiency (CD4 cell count < 200/ml)

Limitations of CD4 assay

It is expensive.

It is not readily available.

It needs to be repeated and monitored serially, as the rate of change is also important.

It needs to be emphasised that both, absolute CD4 counts and their percentage need to be taken into account and correlated with the clinical picture.

DEFINITION OF HIV DISEASE

The most specific diagnosis of HIV infection is by direct identification of the virus in host tissues by virus isolation. However it is difficult to do this, and the techniques are not readily available. It is not cost effective.

For public health purposes, patients with repeatedly reactive screening test for HIV antibody (e.g. enzyme-linked immunosorbent assay [ELISA]) in whom the antibody is identified by the use of supplemental tests (e.g. western blot) should be considered both infected and infective. Presumptive clinical diagnosis of HIV infection has been made in some situations depending upon the clinical manifestations fulfilling surveillance criteria.

PROPOSED WHO CLINICAL STAGING FOR HIV INFECTION AND DISEASE

CLINICAL STAGE 1: ASYMPTOMATIC

Asymptomatic/acute retroviral infection
Persistent generalized lymphadenopathy
History of acute retroviral infection

And /or performance scale 1 :
Asymptomatic, normal activity

CLINICAL STAGE II; EARLY (MILD) DISEASE

Weight loss < 10% of body weight
Minor mucocutaneous manifestations (seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulceration, angular cheilitis)
Herpes zoster within the last five years
Recurrent upper respiratory tract infection (e.g. bacterial sinusitis)

And/or performance scale 2:
Symptomatic, normal activity

(contd.)

CLINICAL STAGE III: INTERMEDIATE (MODERATE) DISEASE

Weight loss > 10% of body weight
Unexpected chronic diarrhea > 1 month
Unexplained prolonged fever (intermittent or constant) > 1 month
Oral candidiasis (thrush)
Oral hairy leukoplakia
Pulmonary tuberculosis within the past year
Severe bacterial infections (e.g. pneumonia, pyomyositis)

And or performance scale 3 : bedridden < 50% day time during the last month

CLINICAL STAGE IV: LATE (SEVERE) DISEASE, AIDS

HIV wasting syndrome, as defined by CDC
Pneumocystis carinii pneumonia
Toxoplasmosis of the brain
Cryptosporidiosis with diarrhea > 1 month
Isoproriasis with diarrhea > 1 month
Cryptococcosis, extra pulmonary
Cytomegalovirus(CMV) disease of an organ other than liver, spleen, or lymph node
Herpes Simplex Virus (HSV) infection : Mucocutaneous > 1 month or visceral any duration
Progressive Multifocal Leukoencephalopathy (PML)
Any disseminated endemic mycosis (e.g.histoplasmosis, coccidioidomycosis)
Candidiasis of the oesophagus , trachea, bronchi or lungs
Atypical mycobacteriosis, disseminated)
Non-typhoid salmonella septicaemia
Extra pulmonary tuberculosis
Lymphoma
Kaposi's Sarcoma (KS)
HIV encephalopathy, as defined by CDC

And/or performance scale 4 : bedridden > 50% of the daytime during the last month

CDC SURVEILLANCE CASE DEFINITION OF AIDS CLINICAL CATEGORIES (1993)

CD4+ T-CELL CATEGORIES	>= 500/ ul	200-499/ ul	<200/ ul
(A) Asymptomatic, Acute (primary) HIV or PGL	A1	A2	A3
(B) Symptomatic, Not (A) or (C) Conditions	B1	B2	B3
(C) AIDS-Indicator Conditions	C1	C2	C3

CATEGORY A:

- Asymptomatic HIV infection
- Persistent Generalised Lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

CATEGORY B:

- Bacillary angiomatosis
- Candidiasis, oropharyngeal
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe) / cervical carcinoma in situ
- Constitutional symptoms, such as fever or diarrhea lasting > 1 month
- Oral hairy leukoplakia
- Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
- Peripheral neuropathy

CATEGORY C:

Includes the clinical conditions listed in the AIDS surveillance case definition.

THE WALTER REED STAGING CLASSIFICATION

Stage	WR0	WR1	WR2	WR3	WR4	WR5	WR6
HIV Antibody and/or virus	—	+	+	+	+	+	+
Chronic lymphadenopathy	—	—	+	+/-	+/-	+/-	+/-
T-helper Cells / mm	>400	>400	>400	<400	<400	<400	<400
Delayed hypersensitivity	N	N	N	N	P	C	P/C
Thrush	—	—	—	—	—	+	+/-
O I	—	—	—	—	—	—	+

P= Partial defect in immunity
 C= Complete defect in immunity

WHO STAGING SYSTEM FOR HIV INFECTION AND DISEASE:

(CLINICAL AND LABORATORY CLASSIFICATION)

	(A)	(B)	(C)
Total lymphocyte count	>2000	1000 - 2000	<1000
CD4+count	>500	200 - 500	<200
(1) Asymptomatic persistent generalized lymphadenopathy	1A	1B	1C
(2) Early	2A	2B	2C
(3) Intermediate	3A	3B	3C
(4) Late	4A	4B	4C

Strata by laboratory values = A,B,C
 Strata by clinical status = 1,2,3,4

WHO CASE DEFINITION FOR AIDS SURVEILLANCE WHERE HIV TESTING IS NOT AVAILABLE (FOR ADULTS AND ADOLESCENTS)

The case definition for AIDS is fulfilled in the presence of at least 2 major signs and at least one minor sign

MAJOR SIGNS

- 1) Weight loss > 10% of body weight
- 2) Chronic diarrhea for more than 1 month
- 3) Prolonged fever for more than 1 month

MINOR SIGNS

- 1) Persistent cough for more than 1 month
- 2) Generalised pruritic dermatitis
- 3) History of Herpes Zoster
- 4) Oropharyngeal Candidiasis
- 5) Chronic progressive or disseminated Herpes Simplex infection
- 6) Generalised lymphadenopathy

For patients with tuberculosis, persistent cough for more than 1 month should not be considered as a minor sign

The presence of either generalised Kaposi's Sarcoma or Cryptococcal Meningitis is sufficient for the case definition of AIDS

Advantage : Simple to use and inexpensive

Disadvantages : Low sensitivity and specificity

WHO CASE DEFINITION FOR AIDS SURVEILLANCE WHERE HIV TESTING IS AVAILABLE (FOR ADULTS AND ADOLESCENTS)

The case definition for AIDS is fulfilled in the presence of a positive HIV test and one or more of the following conditions :

- 1) Weight loss > 10% body weight, or cachexia, with diarrhea or fever, or both, for at least one month, not known due to a condition unrelated to HIV infection
- 2) Cryptococcal meningitis

- 3) Tuberculosis (pulmonary or extrapulmonary)
- 4) Kaposi's sarcoma
- 5) Neurological impairment which prevents independent daily activities, not known to be due to a condition unrelated to HIV infection
- 6) Oesophageal candidiasis
- 7) Life threatening, or recurrent episodes of pneumonia
- 8) Invasive cervical cancer

Has a higher specificity but requires the availability of HIV of serological testing

WHO CASE DEFINITION FOR AIDS SURVEILLANCE WHERE HIV TESTING IS NOT AVAILABLE (FOR CHILDREN)

The case definition is fulfilled in the presence of at least 2 major and 2 minor signs (if no other cause of Immuno-suppression exists)

MAJOR SIGNS

- 1) Weight loss or abnormally slow growth
- 2) Chronic diarrhea >1 month
- 3) Prolonged fever > 1month

MINOR SIGNS

- 1) Generalised lymph node enlargement
- 2) Oropharyngeal candidiasis
- 3) Recurrent common infections, e.g. ear infections, pharyngitis
- 4) Persistent cough
- 5) Generalised rash

Confirmed HIV infection in the mother counts as a minor criterion.

MODIFIED CLINICAL CASE DEFINITION FOR AIDS IN AFRICA (DE COCK & COLLEAGUES)

In this classification, an adult would be classified as having AIDS. If the CDC surveillance case definition

For AIDS was fulfilled or patients had a positive test for HIV infection plus one or more of the following:

1. Greater than 10% body weight loss or cachexia, with diarrhea and or fever, intermittent or constant cough for at least one month, not known to be due to a condition unrelated to HIV infection
2. Tuberculosis that is disseminated involving at least two organs or miliary TB: or extrapulmonary TB that may be presumptively diagnosed
3. Kaposi's Sarcoma
4. Neurological impairment sufficient to prevent independent daily activities not known to be due to a condition unrelated to HIV infection, such as trauma

AIDS DIAGNOSIS CRITERIA APPROVED FOR INDIA (NACO)

- A) Positive test for HIV infection by two tests based on preferably two different antigens
- B) Any one of the following :
 - 1) A) Weight loss >10% of body weight or cachexia
(Not known to be due to a condition unrelated to HIV infection)
 - B) Chronic diarrhea > 1 month
(Intermittent or constant)
- 2) Disseminated or miliary or extrapulmonary tuberculosis
- 3) Kaposi's sarcoma
- 4) Neurological impairment preventing daily activities, not known to be due to a condition unrelated to HIV (e.g. trauma)
- 5) Candidiasis of the oesophagus (diagnosable with a dysphagia, odynophagia and oral candidiasis)

CDC AIDS CASE DEFINITION FOR SURVEILLANCE : DEFINITIVE AIDS DIAGNOSIS (WITH OR WITHOUT LABORATORY EVIDENCE OF HIV INFECTION)

1. Candidiasis of the oesophagus, trachea, bronchi or lungs
2. Cryptococcosis, Extrapulmonary
3. Cryptosporidiosis with diarrhea , persisting > 1 month
4. Cytomegalo virus disease of an organ other than liver, spleen or lymph nodes
5. Herpes Simplex virus infection causing a mucocutaneous ulcer that persists longer than 1 month, or bronchitis, pneumonitis or oesophagitis of any duration
6. Kaposi's Sarcoma in a patient < 60 years of age
7. Lymphoma of the brain (primary) in a patient < 60 years of age
8. Lymphoid Interstitial Pneumonia or Pulmonary Lymphoid Hyperplasia affecting a child <13 years of age
9. Mycobacterium avium complex or Mycobacterium kansasii disease, Disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
10. Pneumocystis carinii pneumonia
11. Progressive multifocal leukoencephalopathy (PML)
12. Toxoplasmosis of the brain

DEFINITIVE AIDS DIAGNOSIS (WITH LABORATORY EVIDENCE OF HIV INFECTION)

1. At least 2 bacterial infections, multiple or recurrent, within a 2 year period, affecting a child < 13 years of age
2. Coccidioidomycosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
3. HIV encephalopathy
4. Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
5. Isosporiasis with diarrhea persisting > 1 month
6. Kaposi's sarcoma at any age
7. Lymphoma of the brain (primary) at any age

(contd.)

8. Other non-Hodgkin's lymphoma of b cell or unknown immunologic phenotype
 9. Any mycobacterial disease caused by mycobacteria other than *M. tuberculosis*, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
 10. Disease caused by extrapulmonary *M. tuberculosis*
 11. *Salmonella* (non-typhoid) septicaemia, recurrent
 12. HIV wasting syndrome
-

PRESUMPTIVE AIDS DIAGNOSIS (WITH LABORATORY EVIDENCE OF HIV INFECTION)

1. Candidiasis of the oesophagus (a) recent onset of retrosternal pain on swallowing and (b) oral candidiasis
2. Cytomegalovirus retinitis: a characteristic appearance on serial ophthalmic examinations
3. Mycobacteriosis: specimen from stool or normally sterile body fluids or tissue from a site other than lungs, skin, or lungs or hilar lymph nodes showing acid fast bacilli of a species not identified by culture
4. Kaposi's sarcoma: erythematous or violaceous plaque like lesion on skin or mucous membrane
5. Lymphoid interstitial pneumonia: bilateral reticulonodular interstitial pulmonary infiltrates present on chest x-ray for more than 2 months with no pathogen identified and no response to antibiotic treatment
6. *Pneumocystis carinii* pneumonia: (a) history of dyspnea on exertion or non-productive cough of recent onset within the last 3 months and (b) chest x-ray evidence of diffuse bilateral interstitial infiltrates or gallium scan evidence of diffuse bilateral pulmonary disease and (c) arterial blood gas analysis showing an arterial oxygen partial pressure of <70 mm hg or a low respiratory diffusing capacity of < 80% of predicted values or an increase in the alveolar-arterial oxygen tension gradient and (d) no evidence of a bacterial pneumonia
7. Toxoplasmosis of the brain (a) recent onset of a focal neurological abnormality consistent with intracranial disease or a reduced level of consciousness and b) brain imaging evidence of a lesion having a mass effect or the radiographic appearance which is enhanced by injection of contrast medium and c) serum antibody to toxoplasmosis or successful response to therapy for toxoplasmosis

THE CARACAS AIDS CASE DEFINITION

Symptoms/sign/diagnosis	Assigned points
Kaposi's sarcoma	10
Tuberculosis, disseminated/ Extrapulmonary/noncavitary pulmonary	10
Oral candidiasis or hairy leukoplakia	5
Tuberculosis, cavitary pulmonary or TB unspecified	5
Herpes zoster, <60 years of age	5
Central nervous system dysfunction	5
Diarrhea for > 1 month	2
Fever > 38° C for > 1 month	2
Cachexia or > 10% weight loss	2
Asthenia > 1 month	2
Persistent dermatitis	2
Anemia, lymphopenia, thrombocytopenia	2
Persistent cough or any pneumonia (except TB)	2
Lymphadenopathy > 1 cm. At 2 or more non-inguinal sites for >1 month	2
Required point score	10 or more

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HIV/AIDS COUNSELLING

Dr. Jacob K. John,
Dr. Joseph J. Samuel

The emotional responses to HIV/AIDS, both among the affected individuals and their family members, are varied and spread over a long time frame. The psychosocial implications affect almost all aspects of life and professional help may be needed to help live and cope with these. In addition, the life style of the person concerned may include high-risk behaviour like multiple sexual partners or injecting drug use, and if this is not addressed, the risk for further spread continues. Information and education through mass media does provide awareness. However, it seems clear that additional inputs would be required for those at risk, and counselling to empower safer behaviour is an important prevention strategy.

Counselling is a special form of interpersonal communication in which feelings, thoughts and attitudes are expressed, explored and clarified. It is a treatment strategy that enables the individual to help oneself. Counselling is both an art and a science, a “science” because of its underlying principles, an

“art” because of the blend of the counsellor’s personality, technique and skill. The counsellor and client meet to solve a problem or make decisions involving highly personal matters and behaviours. It is not ‘brain washing’, ‘advise giving’ or a ‘process to stem emotions’.

HIV/AIDS counselling has two general objectives:

- (1) Prevention of HIV infection and its transmission to self or to other people.
- (2) Supporting the infected individuals and their families.

The focus for counselling thus can be towards risk-assessment and risk-reduction, before and after testing and diagnosis as well as long term in the care of the affected.

Counselling for prevention :

Prevention as an objective in counselling shares a lot of ground with health education. This process is very important in a situation where the numbers at risk

are high and behaviour change is not uniform. This particular objective is also important because of the cost effectiveness of prevention. Even though information regarding HIV/AIDS is widely disseminated, this knowledge alone does not necessarily bring about the desired behavioural change. Hence it is important that interested volunteers from varying sections of society viz. health workers, social workers, teachers, etc. use basic counselling skills to help people identify their own risk and appropriately change behaviour.

Risk assessment :

The process of risk assessment involves bringing a person to the understanding that HIV poses a personal threat as a result of his or her behaviour.

Raju works as a lorry assistant or cleaner. Each round trip takes about 15 days. He was married 6 months ago. He has been hearing a lot about HIV/AIDS from his colleagues. He becomes concerned and is very anxious and someone directs him to meet a counsellor.

How to assess risk?

Risk assessment involves discussing intimate and personal matters. It also involves an ability to be non-judgmental, have the skill and vocabulary to ask sensitive questions and preferably some knowledge about the prevailing risk related practices in society.

In Raju's case, it is wise to be direct and ask him about the frequency and type of sexual behaviours and specific practices. Unprotected penetrative intercourse (vaginal or anal) carries risk. It is also useful to evaluate other behaviour like drug abuse since this can directly or indirectly influence the risks. Apart from the direct risk of virus transmission with injection use, alcohol consumption and other drug abuse may promote risk-related behaviour and should be enquired into. Being on the road most of the time, the possibility of severe wounds requiring emergency blood transfusion may be asked for.

All these are also risks for Raju's wife if she is being assessed. Hence remembering to check on the behaviour of the spouse in particular is important.

Risk assessment is not mere information gathering or going through a checklist of risk factors. The goals of risk assessment are to help the client :

- (1) Assess his/her current and past risk of HIV infection.
- (2) Personalize his/her risk of HIV infection.
- (3) To help him/her decide about risk reduction behaviours.

Risk reduction :

It is difficult to clearly separate risk assessment and risk reduction. In effect, risk reduction counselling automatically follows risk assessment. The important point is to help the client internalize that

HIV infection and its transmission are avoidable and that he/she has a choice in that.

Risk reduction includes

1. Planning behaviour changes.

It may not be practical for Raju to change his job. It is equally difficult for him to change his behaviour suddenly. Changing behaviour is difficult; it takes time, effort and commitment both on the part of Raju and the counsellor. It would be better if Raju's peers were also involved in discussion about HIV/AIDS to promote behaviour changes as a group.

2. Identification of potential obstacles and developing strategies to overcome them.

In Raju's case, any effort on his part to change his behaviour like avoiding sexual contact with his peers or trying to use a condom may cause him to be ridiculed and isolated. It is essential to probe into these details for Raju may not voluntarily share those concerns for fear of displeasing the counsellor. Often in these circumstances, the sense of individuality is lost. Hence it is important to empower him without affecting his routine life and interactions with his colleagues.

3. Sustain the new behaviours and reinforce positive changes.

Follow up is essential to sustain the new behaviours. There are inherent

difficulties in following up people on the move and people who are illiterate. Greater effort and innovative ways are needed if good results are to be seen over a period of time.

The HIV test :

Testing may be preliminary or screening like the ELISA, and supplementary or confirmatory like the Western blot. Two screening tests selected from different principles can also be used for diagnostic confirmation. All these tests detect antibodies that are produced by the body in order to overcome the HIV rather than looking for the virus itself.

There is a time interval taken by the body to produce antibodies to the virus. From the time the virus enters and establishes itself in body, it takes about 6 to 12 weeks for the antibodies to appear in the blood and to be detected by the HIV test. This period of time from infection to when antibodies are detectable in the blood is commonly called as the 'window period'.

The virus per se can be detected from the initial stages but these special tests are expensive, formidable and cannot be easily done. These tests are usually done for research.

Pre-test and post-test counselling :

The psychosocial implications to the testing and diagnosis of HIV/AIDS are so distressing, that the test should be done only when absolutely necessary.

Again, considering these implications, involving the patient in the decision-making, and getting informed consent is critical. Helping in that decision making is the main aim of pre-test counselling. Post-test of course is to help break the news to the patient and to start the process of helping him/her cope with it. **This exercise is not unique to HIV testing and should form the basis of good clinical practice wherever the implication of a test or procedure is serious enough to impact on the life of an individual.** The social and personal implications of the HIV test are manifold and hence this precaution.

Circumstances in which the test is usually done :

- (1) Surveillance. Here the identity of the individual is not required and the test is recommended only as unlinked and anonymous. No counselling is required.
- (2) Blood banks. The recommendation is that blood has to be tested and discarded if positive, but the identity of the individual is not required. Hence no supplementary tests or diagnosis is made. However, some hospitals that do not have a blood bank, screen and prepare volunteers for direct donation. Here the implications are different.
- (3) Voluntary, where the patients requests it.

- (4) Health Care - When patients actively seek health-care for various STDs, drug abuse or associated symptoms like unexplained glandular enlargement, progressive weight-loss, persistent fever etc.
- (5) Pre-requisites for a visa, pre-employment, pre-surgery, etc where the indication is unclear and often untenable.

Pre-test counselling :

Pre-test counselling focus on two main issues :

- (1) Risk-assessment : the client's understanding of how his/her personal behaviour increases his/her risk of contracting or transmitting HIV infection.
- (2) The client's understanding of HIV/AIDS and an informed consent to the test. Information should also include exploring the social and personal implications of a positive test, assessment of ability to cope with a positive result, awareness of available social supports and provision of adequate preventive strategies.

Ramesh is a computer software specialist. He has a good job in a reputed firm. His marriage is planned for the next month. Though some of his colleagues have been involved with multiple sexual partners, Ramesh has

not done that or taken any drugs. He underwent emergency surgery two years ago when blood was transfused to him.

Not only is he getting married next month, he may also have to go to USA for further training six months from now. Being aware that the HIV could be transmitted via blood transfusion he desires to test himself.

During pre-test counselling, Ramesh can be asked details of risk factors : sex, drugs, transfusions and strategies he used for risk reduction, if any. Also about illnesses to suggest sero-conversion or immune suppression. It may be rather embarrassing for a person of his standing to be asked or even to acknowledge history of high-risk behaviour. Ramesh is also likely to hold the opinion that his sexual encounter(s) were not with prostitutes but with respectable colleagues of his.

It is good to review with Ramesh his knowledge about HIV/AIDS, especially means of prevention and the distinction between HIV infection and AIDS. The concept of 'window period' has to be explained particularly in case the risk behaviour was within that. Testing may be negative now and there may be a need to retest afterwards.

The potential implications of a positive test for him are :

- (1) Deferment or cancellation of marriage

- (2) Possible emotional reactions. He may go either into severe depression or become extremely angry.
- (3) Being denied a visa to USA
- (4) Possible loss of job or curtailed promotions in his firm.
- (5) Social consequence for his family.

The counsellor can review with Ramesh his experiences in dealing with crisis situations in the past to get an idea about his coping skills. If Ramesh decides that he wants to go through with the test, check out the social supports, either family or friends, who else should be informed the test result. If then Ramesh can bring that person with him for the result, not only is the counsellor able to leave the patient with someone trusted in a crisis, but also save some time in explaining things twice over.

After internalizing the implications of a positive result it is possible that Mr. Ramesh decides to abandon the idea of testing himself. Irrespective of his decision, this may be the only opportunity you have with him to discuss preventive aspects.

In reality, no pre-test counselling occurs and the first contact a counsellor has with a client is after the test has been done and sometimes even after the result has also been given. The principles involved do not really change even then, and taking a step backwards to explore these issues are well worth the effort. There

should be a clear understanding of the policy on consent in HIV testing at every instance, and those recommending the test should understand the limits and potential consequences of testing.

Post-test counselling :

Discussing the results of the test is always a serious process. These sessions must be scheduled when the counsellor can spend adequate time with the client. It is also sensible that the same counsellor who built up rapport with the client in the pre-test session continues on to the post test. Generally the aims of this session are to help the client :

- (1) Cope with immediate reactions to the test result (shock, denial, sense of loss, depression etc.)
- (2) Integrate and understand the meaning of the test result at all levels (rational, emotional, medical and behavioural)
- (3) Develop a plan for risk reduction
- (4) Maximize healthy coping skills and strategies.

Counselling after a negative result :

Conveying a negative result is relatively easy. Most counsellors share a sense of relief with the patient in this situation. A few points need to be kept in mind.

From the time of possible exposure, at least three months (the window period) must have elapsed before a negative test can be considered truly negative. The

need for a re-test must be assessed if there have been potential risk factors in the previous three to six months.

Those involved with high risk behaviour have to be helped to internalize and operationalise the behaviour changes that will minimize risks for them. Even encourage them to be peer group educators and change-agents.

Counselling after a positive result :

The first reaction to a positive result is likely to be a state of shock or denial and the client should be given enough time to absorb the news. The result should be conveyed clearly and non-ambiguously, under conditions of confidentiality. Following this, some people feel emotionally overwhelmed and experience a feeling of loss of control or helplessness. Other reactions which may be expressed are depression, guilt, self-blame, anger, fear and suicidal thinking. The counsellor should not stem the outpouring of emotions but should support the client and provide reassurance. Time invested during pre-test counselling, a sound knowledge and judgement of the client's background viz. social supports, psychological condition and the cultural and spiritual strengths is of immense value in helping break bad news and in tailoring the support needed.

Wait for client's responses before continuing with the session. Post-test counselling is usually a long process. The test result is only the first part of it. Next comes integrating this in different parts

of life, making behaviour changes, emotional and interpersonal adjustments, at work, family & health. Often the counsellor gets involved with the family as well. Supporting the needs of the family become important in these situations, frequently starting from education, partner protection, testing, etc. Ideally counselling then goes on to help during different phases of the client's life, disease, death and even after that in terms of supporting the family through much of this. If there is an infected spouse or child who survives, the sessions do not end even there.

The following points need to be highlighted :

- HIV infection and AIDS are not synonymous. Encourage normal living and it is essential to recruit the support of those concerned to make it possible.
- General health measures such as good hygiene and nutrition and early treatment of opportunistic infections can prolong life.
- Spouses and partners will support. Counselling them is essential.
- There is no cure at present but let us keep hoping.

In a country like ours where social acceptance plays a big role, confidentiality has to be maintained both on the part of the client and the counsellor. Presently support networks in India are scarce but wherever

necessary and possible referrals should be made.

Post-test counselling in case of a positive result should ensure that the person understands what a positive result means; should provide support to the person and their spouse/partner. Follows-up counselling is essential and often forms the beginning of a long-term supportive relationship.

Counselling after an equivocal result:

When the result is equivocal or 'indeterminate' the technicalities of a retest have to be worked out with consultants in the field. Modern methods of testing reduce the frequency of equivocal results but are expensive and not universally available. During this period of uncertainty clients need a lot of support. The essential preventive messages should be emphasized and the person will need to take precautions recommended for HIV positive patients until proven otherwise.

Crisis counselling :

A crisis is where the normal coping strengths of an individual are compromised. This usually results in a sense of loss of control and helplessness. These crises constantly threaten the individual and the gains made through counselling. The counsellor may need to take on a more directive role for the client rather than only relying on his coping. In situations like this it may be necessary for the therapist to be more

directive and temporarily even take on some of the decision making.

Ramesh of our story tested positive and he has postponed his marriage. But there is intense pressure from his relatives and those of the girl to take matters forward. Colleagues are constantly reminding him of the party that he should host to celebrate his engagement and they are teasing him about his 'honeymoon plans'. Ramesh is perplexed. The company sent him a reminder to send his 'acceptance' to visit USA for further training. Ramesh turns to the counsellor for help in this crisis.

Some basic principles of counselling in crisis are :

- (a) Stay in the "here and now", i.e. focus on the client's expression of feelings and anxieties
- (b) Clarify what the client regards as the crisis
- (c) Show that the seriousness of the crisis is appreciated
- (d) Ascertain what the client regards as the most, as well as the least threatening aspect of the crisis.
- (e) Check and attempt to reduce feelings of helplessness, hopelessness and loss of control by asking questions and making observations. False reassurance cannot be offered.
- (f) If the client is using denial as a defence mechanism or is too distressed to understand what is

being said, reinforce information that is understood.

- (g) Select one aspect on which to begin work and work out an action plan.

In the case of Ramesh, at stake are his marriage, his opportunity to go abroad for further training, his social position and even his employment. He has tough decisions to take. The counsellor can help Ramesh list and prioritise the problems and options:

- (1) taking his parents into confidence
- (2) postpone/cancel the marriage
- (3) postpone/decline the offer to go abroad for training.

The counsellor may suggest a plan of action and even take on some of the components. It may be that he uses contacts to determine whether HIV testing is a factor for visas to that country. Or in bringing Ramesh's parents over to help in informing them about his status and thus take off the pressure for marriage. Once the pressure is off and the crisis settles, the process of helping Ramesh to take on his own responsibilities can function better.

Supportive counselling:

HIV/AIDS has brought to the forefront the challenge of living as normally as possible an otherwise shortened life. Most of us have a system of supports that help buffer us through the stressors of life. The family is a very important

support system in a country like ours where other resources are scarce. Indeed the support required by the infected person from the counsellor is minimal as much of the stress is taken off by the family. This also means that the family needs all the help possible to maintain this function.

The stress of having HIV infection may precipitate tensions in other aspects of life viz. relationship with the spouse and other family members, with friends and in the workplace. The burden of carrying the knowledge of the disease confidentially can generate a lot of stress and the person tends to isolate himself either consciously or subconsciously. In addition, to imagine or experience family members especially children, suffer discrimination is a painful experience.

The counsellor helps the client to maintain hope and engage in constructive life patterns. It is good to establish short-term goals and long term goals and discuss the same. Quality living has to be emphasized. Simple measures like good hygiene, exercise, rest and relaxation, work-satisfaction, good nutrition, recreation, spirituality and regular medical check ups in a friendly social setting go a long way to a wholesome life.

Ramesh, the software specialist who tested positive in our earlier story was very disheartened. His marriage was cancelled. He was not able to discharge his day to day responsibilities both at

home and at office. He resented the attention his parents gave him at home. He stopped interacting with his colleagues at office and stopped even having coffee with them. He becomes furious if anyone enquired of his wedding plans. Finally he resigned his job and decided to be at home.

At home also he would lock himself in his room refusing to meet anyone who come to visit him. He developed a cough in between and he began to despair that his end was drawing nearer. The medical examination and investigations ruled out tuberculosis or other HIV related illnesses.

Even minor illness like fever and diarrhoea can frighten the HIV infected individual. Not all the private practitioners and hospitals are keen on taking the responsibility of their health care. It is useful for a counsellor to help the client in identifying resources like a doctor who is willing to care for a positive patient, or a lawyer who is sensitive to his needs. Other supportive resources have also to be thought of. Self-help groups of HIV positive people are known to be very effective. Similarly, the spiritual and religious foundation of the client is an important resource that needs to be strengthened.

Eventually Ramesh has come to terms with his HIV positive status. He started his own work; he offers consultation on software related matters. Five years passed by and now he is directing a

reputed firm of his own and he openly declared his HIV positive status. Now he is a happy man who is enjoying sharing his 'sense of hope' with those who are newly detected to be HIV infected.

End stages of HIV related diseases and AIDS :

The counsellor's role here is primarily supportive. Disbelief or denial, anger, depression, 'bargaining' and acceptance are common psychological reactions to the threat of death. The relationship between the client and counsellor at the beginning and through the various stages sets the tone for counselling in the terminal stages. Support for the family along with the patient in the end stage of the disease is important. Hospices replacing the traditional hospitals in the care of terminal patients with AIDS is a concept gradually gaining favour at least in the west. Such caring places would be a great resource.

Conclusion :

HIV/AIDS is proving to be a great challenge in our country at this time. The need of the hour is for intensive promotion of education and behaviour change towards prevention as well as compassionate caring of those affected.

Counselling efforts are being complemented by the advances in medical therapeutics. The use of 'triple drug therapy' seems to have reduced the mortality from AIDS in the western nations. Nevertheless, the adage 'prevention is better than cure' is so true in the case of HIV/AIDS. Though the universal goal of 'health for all by 2000A.D.' is significantly challenged by HIV/AIDS, counselling serves as a formidable weapon to counter this. Counselling promotes 'quality living' in an otherwise shortened life and in the totality of caring, counselling is a service which uses the relationship between the carer and the client to help the latter live his life with dignity.

How to tell patients that they have HIV disease?

Honesty

Realistic optimism

Practical support

11

OUTPATIENT MANAGEMENT OF HIV INFECTION

Dr. Vinay Kulkarni

It should be possible to provide most of the primary care to the HIV infected persons in an out patient setting.

Challenges to the primary health care provider

1. Tremendous variability in clinical manifestations and patient's stage of illness.
2. Compliance to treatment and regularity of follow up.
3. Level of understanding of the illness by the patient.
4. Functional status and morbidity.
5. Home support.
6. Psychosocial needs.

Goals of primary health care

1. Collect initial history, physical and laboratory data.
2. Manage urgent needs, symptoms.
3. Educate, inform regarding safe sexual practices, needle sharing etc. and also guide towards 'positive' living.

4. Institute appropriate chemo-prophylaxis.
5. Diagnose and treat opportunistic infections and malignancies.
6. Seek collaboration form other specialities and plan interventions.
7. If appropriate and affordable plan and initiate antiretroviral treatment.
8. Prepare the patient and the family members for the anticipated eventualities, seek collaboration with other social agencies.

Initial history and physical examination

1. Establish rapport. It is going to be a prolonged relationship.
2. General past medical history. Try to understand if there were already any signs of HIV-related illness in the past. Ask for STDs, TB., Herpes zoster.
3. HIV- related history. Identify risk factors. Assess awareness of HIV serostatus, any past treatment etc.

4. History of previous medications, allergies, reasons for discontinuation, alternative therapies, self medications.
5. Personal history related to sexual behaviour, substance abuse (smoking, alcohol, injection drug use etc.).
6. Social history: Education-employment, financial status, family and social support systems, patient's and family's beliefs, values and specific wishes regarding level of aggressiveness of medical care.
7. Family history : Other diseases that may influence the HIV management (malignancies, drug allergies, etc.).
8. Symptoms:

Systemic:

Skin: rash, discoloration, itch, scars, herpes zoster.

Oropharynx: ulcers, plaques, exudates, gum disease.

Lymph nodes: swelling, tenderness.

Pulmonary: cough, expectoration, dyspnoea, exercise intolerance.

Gastrointestinal: nausea/vomiting, diarrhoea, abdominal pain.

Neurologic: headaches, weakness, tremors, gait imbalance, neuropathic pain.

Psychiatric: difficulty in concentrating, memory loss, personality changes, depression.

Eyes: Blurring of vision, floaters, diplopia.

Musculoskeletal : myalgia, arthralgia/arthritis.

Genitourinary: dysuria, vaginal or penile discharge or ulcers, sexual dysfunction.

Hematologic: Abnormal bleeding, bruising.

Constitutional :

Fatigue/malaise,

Night sweats,

Weight loss/anorexia

Fever

9. General appearance, gait, emotions, examination of vital signs : weight, temperature, respiratory rate, pulse and blood pressure.
10. Systemic examination. Thorough examination of skin, oropharynx, lymph nodes, cardiopulmonary system, abdomen, genital and rectal examination, gynaecologic examination, musculoskeletal examination, neurologic examination, fundoscopy.
11. Regular follow-up examination : Ask the patients to report any illness immediately, if asymptomatic ask them to report every 3 to 6 monthly. Patients with advanced HIV disease need to be followed up more frequently.

Initial laboratory tests:

1. Hemogram (with ESR and platelet counts),
2. Urine examination,
3. Serum electrolytes,
4. Renal functions (urea nitrogen and creatinine),
5. Liver function tests,
6. Hepatitis serology,
7. Serum lactose dehydrogenase,
8. Syphilis serology,
9. Chest X-ray,
10. Ultrasonography abdomen,
11. Toxoplasma serology,
12. If-possible: CD4 /CD8 counts.

(PPD- tuberculin test has little significance in Indian situation.)

Follow-up laboratory tests:

1. Complete blood counts:
Asymptomatic early HIV: every 6-12 months.
Symptomatic HIV: every 2-6 months.
Unstable counts: every 1-2 months.
2. CD4 counts: Every 6 months if asymptomatic and/or initial counts more than 500.
If symptoms appear and progress rapidly: every 3 months. If on antiretroviral treatment every 3 months.
3. Other investigations: As per symptomatology.

Remember in HIV-disease and associated immunodeficiency

1. Common infections occur with common presentations.
2. Common diseases occur with uncommon presentations.
3. Unusual organisms and sites of infection may occur.
4. Previously treated infections may recur.
5. 'Standard' treatment regimens may not be effective.
6. Latent infections may get activated.
7. Opportunistic infections occur with increased frequency.
8. Multiple opportunistic infections may occur simultaneously.
9. Drug reactions occur more frequently.

12 SYSTEMIC MANIFESTATIONS

- 12.1 Pulmonary complications in HIV**
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- 12.2 Tuberculosis and HIV**
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12.1

PULMONARY COMPLICATIONS IN HIV

Dr. Nitin Abhyankar

INTRODUCTION

Lungs are involved as important target organs for opportunistic infections in HIV setting. The risk of respiratory infections increases progressively with dropping CD4+ counts and is maximal with counts below 200/c.mm. Tuberculosis, Pneumocystis carinii pneumonia(PCP), recurrent bacterial pneumonia and fungal pneumonia are the major infective problems encountered in HIV infected individuals.

Asthma, Bronchitis and Broncheactasis are diseases which at times co-exist with HIV. This co-existence is associated with more difficulties in managing both. Kaposi's sarcoma and Non Hodgkin's lymphoma can involve lungs with severe immunocompromized state. KS is more common with homosexual or bisexual men. Non-specific interstitial pneumonia and lymphoid interstitial pneumonia (especially in children) can occur early and may resolve spontaneously.

CLINICAL PATTERNS OF VARIOUS PULMONARY PROBLEMS

1. Patient is known HIV infected person and gets clinical symptoms and signs suggestive of pulmonary problems, which is fitting into a known disease pattern e.g. tuberculosis
2. In certain clinical setting with respiratory infections-HIV infection is suspected. E.g.-disseminated tuberculosis in a young individual
3. Patient who is known to be HIV infected also has another respiratory problem. E.g.-asthma or chronic bronchitis
4. Patient known to be HIV infected gets a respiratory problem that is persistent and difficult to diagnose on clinical grounds alone.

Groups 1 to 3 are relatively simple and a family physician can investigate and treat these conditions after necessary investigations. It must however be realized that Group 4 needs a sequence

of diagnostic tests and a co-ordinated effort between clinician, pulmonologist, radiologist, pathologist and a microbiologist. Early reference of such problems to an institution with adequate facilities is recommended.

Symptomatology

In one study 89% of patients with pulmonary problems in HIV setting- reported with cough, 64% had dyspnoea, 39% had productive cough, 20%- pleuritic pain and 3% had hemoptysis.

Acute symptoms are more common in patients with pyogenic bacterial pneumonias. Indolent slowly worsening symptoms-are more likely to be associated with opportunistic infections, mainly *Pneumocystis carinii* pneumonia. Productive cough indicates acute bronchitis, bacterial pneumonia and tuberculosis as likely differentials. Non productive cough suggests opportunistic infections (PCP), asthma (if patient is a known asthmatic and has wheeze), pleural effusion (tuberculous or Kaposi's sarcoma).

Signs

Certain signs can be helpful in identifying a particular disease process. Bilateral wheeze would logically be related to asthma or asthmatic bronchitis. A unilateral localized area of bronchial breathing and/or rales would be more in favour of bacterial pneumonia. A large area of dull note suggestive of pleural

effusion particularly with fever and weight loss is likely to be tubercular pleural effusion.

Presence of ancillary findings like oral thrush, lymphadenopathy, skin lesions, CNS involvement (in tubercular meningitis or cryptococcal meningitis) is of additional help in narrowing the differential diagnosis.

Baseline investigations

X-ray chest PA view, WBC counts - total and differential and ESR, Sputum-Gram, ZN stains and Aerobic culture with antimicrobial susceptibility (for patients with productive cough), and Mantoux test would be the baseline work up.

Sputum for fungal smears (*Candida* and *Cryptococci*), Sputum induction for ZN stain and Silver methenamine stain for PCP, S.LDH, may be needed at times. With the clinical data and baseline laboratory feedback treatment particularly for infective problems can and needs to be started. It is understood that large percentage of these unfortunate individuals belongs to low socio-economic strata and expensive investigations are not possible for many of them. Some empiricism is therefore inevitable.

Treatment considerations

- In any acute clinical setting- e.g.-a suspected bacterial pneumonia therapy must be started with

antibiotics based on current knowledge of prevalent organisms in the community and sensitivity patterns.

For example - with increasing penicillin resistance world over for pneumococcal infections - it is prudent to start with a molecule like cefuroxime or cefaclor.

- Pneumococci, H. influenza and Pseudomonas aeruginosa seem to be the commonest infective organisms causing acute bacterial pneumonia in HIV setting.

Treatment of bacterial pneumonia

- Antibiotic choice is based on sputum Gram stain and other considerations as discussed above.
- There is no need to use antibiotics for especially longer period of time.
- However it is observed that 25 to 50% of the patients get recurrent pneumonia despite adequate treatment.
- There must be adequate thought given however to the choice of antibiotic. For example fluoroquinolones like Ciprofloxacin are better avoided as they also have antimycobacterial activity. Inadvertent and partial coverage of tuberculosis makes diagnosis difficult and confusing and also increases the chance of MDR tuberculosis. Azithromycin and Clarithromycin are again to be reserved for Tuberculosis avium intracellulare.

- Similarly - Trimethoprim Sulphamethoxazole (TMP-SMX) combination which covers PCP pneumonia well is better avoided in presumed bacterial infections for similar reasons.

- Therapy for tuberculosis also has many pitfalls-particularly when started empirically-These problem areas are

1) more incidences of side effects associated with ATT in HIV

2) difficulty in diagnosis-viz, weight loss can be a part of HIV related cachexia as well as tuberculosis, tuberculin test (TT) can be false negative.

- Empirical therapy for a fungal pneumonia is another difficult problem:

1) many patients with HIV are on Fluconazole in a variable dose for prevention of cryptococcal infections and sometimes for oro-oesophageal candidiasis,

2) Amphotericin B is a toxic and expensive molecule demanding close monitoring and caution,

3) isolation of fungus from sputum can easily be a contaminant from oropharyngeal secretions.

- Empirical therapy for PCP however can be started if clinical picture is convincing and patient's general condition does not allow us time for specific diagnosis to be made.

PNEUMOCYSTIS CARINII PNEUMONIA

Clinical presentation of PCP

Non-productive cough and progressively worsening dyspnoea on exertion are dominant symptoms along with some fever which is often mild.

Fatigability is another important pointer. Near complete absence of foreign sounds on auscultation is a useful clue. Few basal rales at times may be audible.

Increased breath rate is a common feature and goes on increasing as hypoxia worsens.

For *Pneumocystis carinii* pneumonia impaired cellular immunity is the key predisposing factor. These organisms which normally colonize respiratory tract of almost all human beings by 3 years of age without causing any clinical disease interact with type 1 pneumocytes of patients with impaired cell mediated immunity and fill alveoli with foamy vacuolated exudate. There is a very mild and non specific host inflammatory response. PCP was the index disease-in-65% cases among the first 1000 cases. Lifetime incidence is believed to be 85% in all HIV +ve individuals.

- PCP therefore is one of the most important differentials in Group 4 cases and invasive and expensive investigations are needed in these patients.

- Investigations-In patients with pulmonary infiltrates-suspected to be having PCP-Sputum induction is done and tested for with Silver methenamine stain-if confirmed they are started on TMP-SMX.
- If not confirmed then they are subjected to fiberoptic bronchoscopy with bronchoalveolar lavage (which has a reported sensitivity of 89-90% for PCP detection by SM stain). In some cases transbronchial lung biopsy is needed (particularly when other differential diagnosis is being considered)
- In patients with no pulmonary infiltrates but a strong clinical suspicion-DLCO (not widely available in India) or High resolution CT Scan thorax (HRCT) (available in most of cities across the country) - are advised. If HRCT is able to demonstrate ground glass appearance-sputum induction and/or bronchoscopy are considered (HRCT has a sensitivity of 100% and a specificity of 86%).
- Bronchoscopy however remains the most effective (gold standard) diagnostic tool as a bronchoalveolar lavage-processed correctly can diagnose tuberculosis, fungal and bacterial pneumonia and PCP with accuracy and transbronchial lung biopsy can diagnose rare entities like non Hodgkin's lymphoma, Kaposi's sarcoma, non-specific interstitial pneumonia and lymphoid interstitial pneumonia.

Treatment for PCP

In cases where diagnostic tests are not possible due to severe hypoxia, treatment can be started on the basis of strong clinical suspicion. Raised serum LDH can be a useful but a non-specific marker for PCP.

For moderate to severe PCP

TMP-SMX combination is the treatment of choice. The recommended dose is-TMP-20mg/kg/day, SMX-100mg/kg/day, in four divided doses.

(Adverse reactions-rash, fever, liver dysfunction, renal dysfunction, leucopenia, thrombocytopenia, hyponatremia, anemia, upper gastro intestinal upsets, severe mucocutaneous reactions.) Despite high incidence of rash many times treatment can be continued under steroid coverage and every case does not develop into a Steven-Johnson syndrome.

Clinical response takes about 4-5 days to become apparent and supportive therapy with oxygen and steroids is important to pursue alongwith mechanical ventilation if needed.

Pentamidine isethionate is considered equally effective and can be given by intravenous infusions or by aerosols (IV dose-4mg/kg-od-diluted in 250cc 5% Dextrose / for 14 days.)

(Adverse effects include-fever, rash, renal dysfunction, neutropenia, thrombocytopenia, hyponatremia,

hypotension, hypohyperglycemia, ventricular arrhythmia, pancreatitis).

Pentamidine aerosols-5mg/kg/day-OD recommended for same duration.

Trimetrexate-with Leucovorin and Dapsone is another alternative for patients not tolerant to both regimens. Dosage is Timetraxate 45mg/m²/day, Leucovorin 20mg/m²/q6H, Dapsone-100mg/day.

For mild to moderate PCP

Dapsone-TMP-Regimen-in a dose of 100mg OD of Dapsone and 20mg/kg/day in 4 divided doses of Trimethoprim is considered adequate.

(Adverse reactions-hemolytic anaemia, Methhemoglobinaemia, thrombocytopenia, neutropenia, liver dysfunction, pancreatitis, rash, upper gastrointestinal upsets)

Alternative regimens

1. Clindamycin-Primaquine-1800mg/day divided into 3-4 doses-for Clindamycin and 30mg/day of base p/o of Primaquine.
 2. Atovaquone-750mg BID by mouth has fewer side effects but is associated with much higher therapeutic failure rate.
- Steroids are advised as important adjuvant therapy particularly if there is hypoxia $paO_2 < 70$. Recommended dose for adjuvant usage of Prednisolone is 40mg BID-for 7 days,

followed by 40mg OD for 7 days,
followed 20mg OD for 7 days.

Despite many available treatment options PCP remains important cause of mortality and morbidity.

Treated cases have <10% mortality. In patients needing ventilation mortality is as high as 80% without steroids, which reduces to <50% in steroid treated individuals.

Management of asthma and airway hyperactivity

There is increase in symptoms related to asthma in known asthmatics, after getting infected with HIV. Similarly HIV infected individuals seem to be suffering from airway hyperactivity more often than normal population. Treatment is with inhaled bronchodilators and in some cases with inhaled steroids. Pentamidine aerosols induce bronchospasm in some patients. These individuals are treated with inhaled bronchodilators before Pentamidine. Some PCP infected individuals seem to have dry cough and bronchospasm in the early days and are therefore pre-treated with bronchodilators before further work up. Studies are underway to define incidence of asthma like sequelae after an episode of PCP.

Bronchitis and emphysema in HIV

There seems to be an association between HIV and increased tendency to get repeated acute bronchitis episodes and this is more marked after PCP infections and also more prevalent with very low CD4+ counts. Smoking and Intravenous drug abuse are associated with emphysema and these often coexist in HIV setting.

Prevention of pulmonary problems in HIV

- Avoidance of smoking and injecting drug use should be encouraged.
- Chemoprophylaxis for tuberculosis is discussed separately.
- Inhaled steroids can be used for symptomatic asthmatics to control airway inflammation and prevent exacerbation.
- Antivirals do work as best prophylactic agents as they improve cell mediated immunity by reducing viral load.
- Pneumococcal vaccine: 0.5 ml IM single dose, possible revaccination after 6 years.

PCP PROPHYLAXIS

Adults with a prior history of PCP have a relapse rate of approximately 60% within 1 year if prophylaxis is not given.

PCP prophylaxis is recommended to:

1. To all with prior history of PCP
2. CD4 cell count $< 200/\text{mm}^3$
3. If other symptoms suggest advanced immunodeficiency.

Recommended regimen:

TMP-SMX 1 DS/day or 1 DS 3 times a week.

Alternatives:

Aerosolized Pentamidine 300mg given by nebulizer.

Dapsone 50mg/day, 100mg/day or 100mg twice a week.

Dapsone 50mg/day plus Pyrimethamine 50mg/week and folinic acid 25mg/week.

DIFFERENTIAL DIAGNOSIS OF CHEST X-RAY FINDINGS

HILAR ADENOPATHY

M. tuberculosis
Lymphoma
Cryptococcosis
M. avium
Kaposi's sarcoma

PLEURAL EFFUSION

M. tuberculosis
Pyogenic bacteria
P. carinii
Cryptococcosis
Hypoalbuminemia
Septic emboli (IDU)
Heart failure
Kaposi's sarcoma

CAVITARY DISEASE

M. tuberculosis
P. aeruginosa
S. pneumoniae
Klebsiella sp
Anaerobic bacteria
M. kansasii
Cryptococcosis
S. aureus (IDU)
Histoplasmosis
Coccidioidomycosis

CONSOLIDATION

Pyogenic bacteria
Cryptococcosis
Kaposi's sarcoma

NODULES

M. tuberculosis
Cryptococcosis
Kaposi's sarcoma

DIFFUSE RETICULO-NODULAR INFILTRATES

Pneumocystis carinii
P. carinii + CMV
Military tuberculosis
Lymphocytic interstitial pneumonia
Toxoplasma gondii
Histoplasmosis
Coccidioidomycosis
Kaposi's sarcoma

NORMAL

P. carinii
M. tuberculosis

12.2

TUBERCULOSIS AND HIV

Dr. Soumya Swaminathan,
Dr. P. R. Narayanan

Tuberculosis (TB) is a bacterial disease caused by *Mycobacterium tuberculosis*. TB is spread primarily through airborne droplets produced by coughing and sneezing in patients with pulmonary or laryngeal disease. Tubercle bacilli enter the alveoli, multiply and establish infection. Later, these organisms spread through lymphatic channels to regional lymph nodes and then to distant organs via the blood stream. Primary or progressive primary disease is the clinical presentation of tuberculosis in a person infected for the first time and usually manifests in childhood in endemic countries like India. Reactivation TB occurs many years after the initial infection when some unknown factor (? suppression of host immune response) makes the dormant TB bacilli multiply. The tuberculin skin test is used to identify individuals infected with *M. tuberculosis*. About 60% of adult Indians are infected with the tubercle bacillus of which about 10% will develop active disease over their lifetime.

INCIDENCE OF TB IN HIV

Tuberculosis is the commonest opportunistic infection in HIV/AIDS patients. Various studies in India have estimated that nearly 60-80% of HIV positive patients develop TB during their lifetime, i.e. an attack rate of 8-10% per year. Most cases of TB in HIV infected patients are due to reactivation of previous infection. However, the presence of HIV infection also greatly increases the risk of clinical TB in those recently exposed to a TB contact.

TB may occur at any time during HIV infection, and is often seen early in the course of HIV disease. The clinical presentation of TB is dependent on the degree of immune suppression. Patients with relatively preserved immune function with CD4+ cell counts above 200/cu.mm are more likely to have typical symptoms, upper lobe disease and positive sputum smears for AFB. Patients who are more severely

immunosuppressed are more likely to have atypical clinical and radiographic features and negative sputum smears. Extrapulmonary disease including TB meningitis and miliary TB are also more common in the later stages of the disease. At this stage, the symptoms of TB overlap with those of many other opportunistic infections and a thorough work-up may be required.

As in adults, in children with early HIV disease the signs of TB are similar to those in children without HIV, but with declining immunity disseminated TB (meningitis, miliary TB and widespread TB lymphadenopathy) occurs frequently.

DIAGNOSIS

An HIV positive patient with any of the following symptoms should be suspected of having TB and investigated further.

Cough more than 2 weeks duration.

Sputum production

Fever : lasting more than 2-3 weeks

Weight loss

Fatigue, listlessness, night sweats

Unexplained dyspnea

Chest pain

Hemoptysis

Lymph node enlargement

Abdominal swelling (due to ascites)

Headache, vomiting, alteration of sensorium or convulsions.

Physical examination should include a search for pallor, enlarged lymph nodes, localized respiratory signs, hepatosplenomegaly, ascites and neurological signs.

INVESTIGATIONS

Initial investigations should include :

1. **Chest X-ray:** Radiographic abnormalities include parenchymal infiltrates, cavitation, hilar or mediastinal lymph node enlargement pleural effusion and miliary mottling. The lesions may be bilateral and extensive or very minimal.

2. **Sputum smear examination for AFB:** 3 specimens, preferably overnight collections of sputa, should be obtained for AFB smear and culture. Smear examination by Z-N or auramine-rhodamine (fluorescent) stain is the simplest test to perform. About 50% of patients with HIV-TB have positive AFB smears.

If a sputum smear is unexpectedly negative (e.g. a patient with upper lobe cavities on chest x-ray), think of the possibility of a false negative result and repeat the sputum microscopy.

Mycobacterial culture increases the yield of isolating *M. tuberculosis* from specimens but takes a long time (6-8 weeks), requires special microbiological facilities and is not widely available. The

HIV is the most powerful factor known to increase the risk of TB

BACTEC radiometric method reduces the time required for culture significantly (10 to 14 days) but is expensive.

3. Tuberculin skin test (Mantoux test): This test does not play a major role in diagnosis of TB in India as 60% of HIV infected adults in India are tuberculin positive. The cut-off for a positive Mantoux test in HIV positive persons is a 5mm reaction after 1 TU of PPE RD 23 is administered and read after 48-72 hours. A positive Mantoux test only indicates infection with M. tuberculosis and not necessarily active disease. Similarly, TB may occur in the absence of a positive reaction. In the late stages of HIV disease, the tuberculin test may be negative because of anergy.

ADDITIONAL INVESTIGATIONS

Depending on the clinical manifestations, one or more of the following investigations may be required in order to make a diagnosis:

1. **Clinical specimens** from non-pulmonary sites e.g. blood, urine, CSF, stool and bone marrow should be examined for AFB if extrapulmonary TB is suspected.

2. **Fine needle aspiration of enlarged lymph nodes (FNAC)** gives a good yield (65-70%) in TB lymphadenitis.

3. **CT scan** of the chest may reveal enlarged lymph nodes or parenchymal lesions that are not visible on plain X-rays.

4. **Induced sputum/gastric lavage :** The patient can be given an inhalation of nebulised hypertonic saline or alternatively, Salbutamol 2mg three times daily for a week in order to induce sputum. Gastric lavage can be performed in patients unable to expectorate. These specimens can then be sent for AFB smear and culture.

5. **Flexible fiberoptic bronchoscopy with lavage (BAL) and transbronchial biopsy :** Though BAL by itself does not increase the yield of AFB over sputum, it may help to rule out other infections like Pneumocystis carinii.

Newer diagnostic techniques

1. **BACTEC:** This is a radiometric culture system using an enriched liquid medium that shortens the time required for culture and sensitivity testing to 2 weeks. However, it is expensive as the culture medium has to be imported and the facility is only available in major cities.

2. **PCR (polymerase chain reaction):** This is a rapid and sensitive technique to detect the nucleic acid of tubercle

Impact of TB on HIV

In an individual infected with HIV, the presence of other infections, including TB, allow HIV to multiply more quickly resulting in more rapid progression to AIDS

bacilli in clinical specimens. However, this technique is still under evaluation and its role in the clinical management of HIV-TB has not yet been determined.

3. Serologic assays for antimycobacterial antibodies are not promising at this time either in HIV infected or non infected population.

If the results of investigations are not conclusive and TB is a diagnostic possibility, a trial of broad spectrum antibiotics (e.g. co-trimoxazole) may be given for 2 weeks and the patient reviewed and an X-ray obtained. If the X-ray lesion is persistent or has deteriorated, then TB is a strong possibility. In addition, sputum smears may become positive for AFB after a few weeks and should be repeated.

TREATMENT

The principles of treatment for HIV-TB are the same as for the general population. Standard anti-tuberculosis drug regimens are extremely effective in treating most HIV-infected patients with TB. A recent report has confirmed that

short course regimens of 6 or 9 months duration using four drugs in the initial phase are equally effective in HIV-TB. The response to treatment is good initially, though relapse rates may be higher as seen in some studies from Africa.

Effective therapy for TB is divided into 2 phases: an initial 2-month **bactericidal phase** and a **sterilizing phase** which is 4 months or longer. The initial phase should consist of 4 drugs - INH, Rifampicin, Pyrazinamide and Streptomycin or Ethambutol given either daily or 3 times a week. The continuation phase usually consists of INH & Rifampicin given daily or intermittently (See Table 1).

The Revised National TB Control Program (RNTCP) of the Government of India advocates treating new sputum positive TB patients with a 6-month supervised intermittent short course regimen (2EHRZ₅/4RH₃). Patients who have relapsed or failed or have taken more than 1 month of previous chemotherapy are to be treated with an

Table 1:
Recommended drugs for the initial treatment of TB in children and adults

Drug	Daily dose in mg/kg	Intermittent dose 3 times/wk in mg/kg
Isoniazid	5 (4-6)	10 (8-12)
Rifampicin	10 (8-12)	10 (8-12)
Pyrazinamide	25 (20-30)	35 (30-40)
Ethambutol	15 (15-20)	30 (25-35)
Streptomycin	15 (12-18)	15 (12-18)

8 month intermittent regimen (2SEHRZ₃/1EHRZ₃/5EHR₃). There is no reason to believe that these regimens will not be effective in HIV-TB patients also and hence no separate recommendations have been made, in the program. These regimens should be given under supervision at least in the initial intensive phase by DOTS (Directly observed treatment, short course). DOTS provider can be either health workers or volunteers from the community.

Treatment of patients with drug resistance

Drug resistance to single and multiple drugs is increasing in the community mainly due to wrong prescriptions given by doctors and poor compliance by

patients. The incidence of drug resistant tuberculosis in HIV infected patients is no greater than in the general population, in developing countries. If the patient is infected with INH resistant Mycobacterium tuberculosis, the response to standard short course regimens is usually good. The presence of INH & Rifampicin resistance (MDRTB) is associated with treatment failure rates upto 70% and a high mortality rate. Hence, for MDRTB, at least 3 effective drugs should be used (preferably 4 or 5) based on drug susceptibilities or past treatment history. Table 2 lists some of the second line agents used for drug resistant cases. The duration of therapy is 18-24 months or at least 6 months after sputum conversion. The drug regimen and

Table 2:
Second-line drugs used in the treatment of multi-drug resistant TB

Drug	Dosage in adult (Daily)	Dosage in children (Daily)
Capreomycin	15 mg/kg im	15-30 mg/kg
Kanamycin	15 mg/kg im, iv	15-30 mg/kg
Amikacin	15 mg/kg im, iv	15-30 mg/kg
Ethionamide	500-1000 mg PO	15-20 mg/kg
Para-amino salicylic acid (PAS)	8-12 gm PO	150 mg/kg
Cycloserine	500-1000 mg PO	10-20 mg/kg
Ciprofloxacin	1 gm - 1.5 gm PO	Not recommended
Ofloxacin	600 - 800 mg PO	Not recommended
Clofazimine	100 - 200 mg PO	1 mg/kg

duration of therapy in cases of MDR TB should be determined by a physician experienced in the treatment of TB.

Evaluation of response to treatment

The most effective means of assessing therapeutic response in patients with pulmonary TB is through monthly sputum for AFB smears and cultures. More than 85% of patients will convert their sputum from positive to negative after 2 months of therapy that includes INH and Rifampicin. Persistently positive smears after 2 to 3 months of therapy suggest the possibility of disease due to drug resistant organisms or non-compliance with therapy. Patients who convert should have at least one

additional smear and culture by completion of therapy. A follow up chest radiograph can also be obtained at completion of treatment.

In patients who were treated presumptively for TB with negative sputum smears and cultures, response to therapy should be guided by clinical examinations and a follow up chest X-ray at 3 months. Failure of radiographic abnormalities to improve after three months of therapy should lead to re-examination of the diagnosis. Evaluation of response to treatment of extrapulmonary TB will have to be individualized according to the site and extent of disease.

Table 3:	
Major adverse reactions to anti-tuberculosis drugs	
Drug	Adverse reactions
Isoniazid	Hepatitis, peripheral neuropathy, skin rashes, neurologic disturbances
Rifampicin	Hepatitis, skin rashes, flu-like syndrome, renal failure, thrombocytopenia
Pyrazinamide	Hepatitis, skin rashes, hyperuricemia, arthralgia
Ethambutol	Optic neuritis,
Streptomycin/Kanamycin	Vestibular and auditory toxicity, nephrotoxicity, skin rashes
Amikacin	
Ciprofloxacin, Ofloxacin	Nausea, abdominal pain, skin rashes
Ethionamide	GI disturbances, hepatitis, skin rashes, arthralgia, photosensitivity, peripheral neuropathy
Cycloserine	Psychiatric symptoms, seizures
PAS	Nausea, vomiting, diarrhea, hepatitis, skin rashes, high sodium load

Drug toxicity and monitoring (Table 3)

Adverse events are more frequently reported with anti-TB agents in HIV infected patients. This is partly due to the multiple medications these patients may be taking. Only serious or life threatening side effects warrant the discontinuation of therapy and most cases can be managed symptomatically. **Thiacetazone should not be given to HIV positive patients as there is a high incidence of severe skin reactions including Stevens-Johnson syndrome that may be fatal.** Drug interactions between anti-TB drugs and other medications can also occur e.g. concomitant use of protease inhibitors result in high serum levels of Rifampicin and lower levels of protease inhibitors. Similarly, serum levels of antifungal agents like fluconazole and ketoconazole are lower when given along with Rifampicin.

Course and prognosis

Though patients with HIV and TB respond well to anti-TB treatment, the mortality in this group has been observed to be 4 to 5 times higher than in HIV positive patients who do not develop TB. Tuberculosis accelerates the clinical course of HIV infection probably by activating viral replication and predisposing to other opportunistic infections. Hence, early diagnosis and treatment of TB in HIV positive patients can not only prevent transmission to

others but also improve survival and outcome in this group.

Screening and preventive therapy for tuberculosis infection

All HIV infected patients should be screened for TB at least annually by Mantoux testing and Chest X-ray. A skin induration of 5mm or greater is considered significant when I TU PPDRT23 is used for the Mantoux test. A negative reaction may be due to the patients being truly uninfected or due to anergy which generally occurs when the CD4 + count is less than 100/cu.mm.

Preventive treatment for TB is useful both in the PPD positive as well as the anergic subgroups of patients. Isoniazid 300mg (for adults) given orally daily for one year has been the standard preventive regimen used. Shorter regimens have been tried using two or more drugs but, in general, regimens shorter than six months are not as effective. Though preventive treatment for TB is recommended routinely for HIV positive patients in developed countries, the feasibility and cost effectiveness of such an approach in developing countries like India needs to be studied. It is essential that active TB be ruled out before any patient is started on a preventive regimen.

TB and HIV

Selected bibliography:

1. **Tuberculosis and HIV infection.** In AIDS/HIV Reference Guide for medical Professionals, 4th Edition, Editors JL Fahey and DS Flemming, Williams and Wilkins, 1997, USA.
2. **Treatment regimens in HIV-infected tuberculosis patients.** An official statement of the IUATLD. Int J Tuberc Lung Dis 1998;2(2); 175-178.
3. **Tuberculosis and human immunodeficiency virus infection.** Barnes PF, Block AB, Davidson PT et al. NEJM 1991; 324:1644-1650.
4. **Clinical presentation of tuberculosis in patients with AIDS: An Indian experience.** S.K. Sharma, A. Mohan, R. Gupta et al. Indian J Chest Dis Allied Sci 1997; 39: 213-228.
5. **Tuberculosis guide for low income countries.** DA Enarson, HL Rieder, T Arnadottir, A Trebucq. IUATLD, Fourth Edition, 1996.

12.3

ORAL MANIFESTATIONS

Dr. Vinay Kulkarni

Since ancient times the mouth has been regarded as a mirror reflecting the health of the rest of the body. This remains true even in case of HIV infection. Oral lesions can lead to initial diagnosis, can inform about the progression of the disease and the prognosis.

The lesions could be classified as those strongly associated, less commonly associated and occasionally associated.

Lesions strongly associated:

Candidiasis,
Oral hairy leukoplakia,
Kaposi's sarcoma,
Non-Hodgkin's lymphoma,
Periodontal disease.

Lesions less commonly associated

Bacterial infection (typical and atypical mycobacteria),
Melanotic hyperpigmentation,
Necrotising (ulcerative) stomatitis,
Salivary gland disease (dryness due to

decreased salivary secretion, swelling),
Thrombocytopenic purpura,

Viral infections (Herpes simplex, Human papilloma virus (warts), Varicella - Zoster virus).

Lesions occasionally associated :

Bacterial infections (Actinomycosis),
Drug reactions (ulcerative, erythema multiforme, toxic epidermolysis, lichenoid),
Bacillary angiomatosis,
Fungal infections (mucormycosis, Histoplasmosis etc.),
Recurrent aphthous stomatitis,
Viral infections (Molluscum contagiosum, Cytomegalovirus).

For the purpose of this chapter those occurring more frequently are described.

CANDIDIASIS

It is by far the commonest lesion seen in HIV disease. There are four types of

lesions seen. The most identifiable is Pseudomembranous candidiasis. In this there are white creamy plaques on inflamed base. These could be rubbed off easily. They involve the palate, buccal mucosa or tongue. In the Erythematous (atrophic) type spotty or red confluent patches are seen. This is usually underdiagnosed. In the Hyperplastic type also called the “Candidial leukoplakia” we see white lesions that do not easily wipe off but respond to antifungal treatment. In Angular cheilitis there are erythema and fissures at the corner of mouth. All these forms are associated with esophagitis. The diagnosis is usually clinical. Oral swab or scraping for KOH wet mount or culture can assist in the diagnosis.

It is essential that all patients maintain good oral hygiene. In mild cases topical antifungal agents may be useful. Clotrimazole mouth paints, nystatin oral pastes may be used. Good old gentian violet may be used for the consideration of the cost of other therapies but it is messy and not very effective. However recurrences are frequent and compliance is poor. Ketoconazole (200-400 mg) daily for 2 weeks, Fluconazole (50-100 mg) daily for 2 weeks, Itraconazole (200 mg) daily for 2 weeks are other drugs that are used systemically. The drugs should be used until all signs and symptoms have resolved. There is evidence that prophylactic use of these drugs reduces the number of episodes. Fluconazole (100-200 mg) per day is recommended but once a week use has

also been found to be effective.

ORAL HAIRY LEUKOPLAKIA

Initially thought to be pathognomonic of HIV infection has now been shown to occur in other immunocompromised patients. They usually occur on the lateral borders of the tongue appearing as white plaques with vertical folds. It may affect the dorsum of the tongue. The diagnosis is usually clinical. A biopsy will show epithelial hyperplasia with “hairs”. Electron microscopy will demonstrate Epstein-Barr virus. No treatment is required, as it is asymptomatic. Acyclovir (800 mg) four times a day for 14 days will lead to remission but there are recurrences as soon as the treatment is stopped. Sometimes there could be spontaneous resolution.

HERPES SIMPLEX

Crops of small painful vesicles on an erythematous base seen most commonly on the palate and gingiva are characteristic. Usually the first exposure to Herpes simplex virus (HSV) leads to severe lesions and recurrences are milder but in immunocompromised persons the attacks of recurrent herpes are more frequent and could be more severe. Cervical lymphadenopathy, pyrexia, malaise and anorexia could be present. Diagnosis is mainly clinical. Smears may show multinucleate giant cells. Serology showing rising titres is significant. Oral hygiene is important. Acyclovir 200-800 mg 4 times a day orally or 5-10 mg/kg intravenous 8 hourly is treatment of

choice. If the lesions involve the pharynx and there is difficulty in deglutition the patients may need supportive care for oral feeding e.g. 2% viscous lidocaine, or diphenhydramine HCl (Benadryl).

HERPES ZOSTER

The varicella zoster virus is also latent in the trigeminal ganglion and is reactivated in immunocompromised patients. Pain may occur before, during and after the rash and will be in the distribution of the trigeminal nerve. Unilateral vesicles appear both on the skin and in the mouth. The distribution is extremely important in diagnosis. Smears will show multinucleate giant cells. Acyclovir (800 mg) 4-5 times a day or 5-10 mg/kg IV every 8 hourly in severely immunocompromised patients is needed. Major complications are ocular involvement and severe post-herpetic neuralgia.

RECURRENT APHTHOUS STOMATITIS

The aetiology of this disorder is unknown. Typically the ulcers are preceded by a prodromal irritation. Then there are crops of ulcers (1-10 mm diameter). The ulcers are shallow with a yellow sloughing base. They last from a week to a month. At times there could be ulcers greater than 1 cm in diameter especially on the soft palate. They are extremely painful and may take upto 3 months to heal. The diagnosis is clinical. There may be underlying deficiency such as iron, vitamin B 12 and folate. There

could be neutropenia. It is crucial to maintain good oral hygiene. Chlorhexidine (0.2%) mouthwashes are invaluable. Topical steroids preferably in ora-base, a mouthwash prepared from tetracycline 250mg capsule 4 times a day, mouth rinse with local anaesthetics and in very severe cases oral prednisolone, starting at 40 mg/day with taper over one month is recommended.

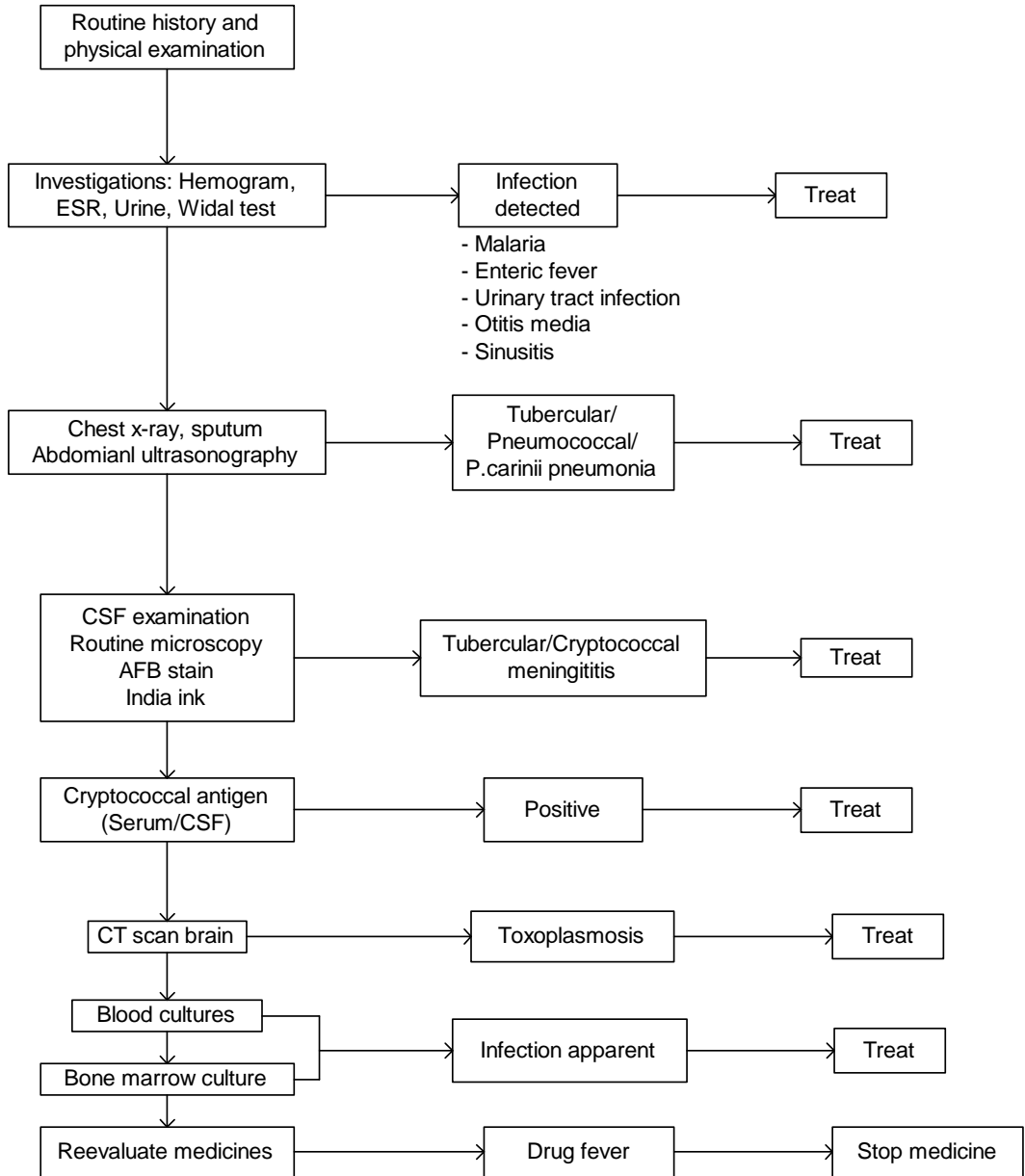
NECROTISING ULCERATIVE PERIODONTITIS AND GINGIVITIS

This condition is thought to be due to anaerobic fusiform bacteria and spirochetes. There is ulceration at the tips the interdental papillae leading to there loss. There is gingival bleeding, soreness and fetor. Diagnosis is clinical. Topical antiseptics like povidone iodine, chlorhexidine in the form of rinses, antibiotics (Amoxicillin, Clindamycin), Metronidazole (400 mg tid) can be used.

DISORDERS OF PIGMENTATION

Platelet deficiency can lead to purpura. Areas of black or brown pigmentation can also be found in all parts of the oral cavity as part of the HIV disease. Treatment with zidovudine has also been recorded as causing brown patches. Kaposi's sarcoma is a neoplasm of the endothelial cells. It is very rarely seen in India. The early lesions may present as red, purple or brown patches, which can later become nodular, enlarged and ulcerated.

Fever



12.4

GASTROINTESTINAL COMPLICATIONS

Dr. Parimal Lawate

Virtually all patients with HIV infection develop gastrointestinal complications during the course of their illness. Such patients can be divided into 2 groups at presentation.

- a. Patients who have already been diagnosed as having HIV infection (and) who develop a gastroenterologic complaint.
- b. Patients who have not been diagnosed as having HIV infection, who present with gastrointestinal (GI) symptoms. GI symptoms, which should raise a suspicion of HIV infection are painful swallowing (odynophagia), wasting, oral candida or hairy leukoplakia.

The following discussion is based on a symptom oriented approach to patients who have HIV infection and GI symptoms.

DYSPHAGIA:

Patients present with difficulty in swallowing (dysphagia), painful swallowing (odynophagia) or substernal

pain while swallowing.

Causes:

Symptoms described above are almost always related to oesophageal ulcers that could be due to

- a. Candida oesophagitis : white curdy patches and ulcers.
- b. CMV oesophagitis : large ulcers in the oesophagus.
- c. Herpetic oesophagitis : multiple small ulcers in the oesophagus
- d. Tubercular ulcers : large often circumferential ulcers often with narrowing.
- e. Idiopathic ulcers : large ulcers lower end esophagus that can mimic malignancy.

Diagnosis:

Although some idea can be obtained from radiographs (barium swallow)-endoscopy and biopsy remain the mainstay of diagnosis of esophageal ulcers. Tissue culture facilities when

available are helpful because the yield of biopsies can be low due to sampling errors. A repeat biopsy is often required for tissue diagnosis.

Care has to be taken during and after endoscopy with regards to cleansing and sterilisation of endoscope. Immersion in glutaraldehyde solution (3%) is recommended for endoscopes as well as accessories, for minimum 10 minutes. It is often helpful to schedule endoscopies on such patients at the end of the list. A dedicated endoscope and accessories for HIV+ve patients might be desirable but is not a very practical idea in developing countries due to high costs of endoscopes and accessories. It is important to remember that the above mentioned cleaning and disinfecting procedures should be meticulously followed after **each and every** endoscopy irrespective of the patient's HIV status.

Treatment:

- a) Candida esophagitis:- Fluconazole 100-150mg po/day for 10-14 days.
- b) Herpes esophagitis:- Acyclovir 200-800mg po 5 times per day for 7 days (for active treatment) and 400mg po bid for secondary prophylaxis
- c) CMV esophagitis:- Ganciclovir 5mg/kg body weight IV every 12 hours for 14-21 days. Maintenance therapy is recommended for patients with CMV retinitis only (5mg/kg/day IV or 6 mg/kg IV 5 times a week or 1gm po tid)

d) Tubercular esophagitis :- standard antituberculosis treatment.

e) Idiopathic ulcers :- Corticosteroids, oral intravenous or occasionally intralesional. Prednisolone 40mg/day po tapering 10mg/week. IV steroids may be initially required if severe odynophagia exists.

Intensive and aggressive treatment of esophageal lesions is important as these preclude reduced oral intake and can contribute significantly to wasting and weight loss. Supportive treatment with prokinetics (domperidone 10mg /po/tds, cisapride 10mg po/tds or metoclopramide 10mg /tds) and acid inhibiting agents (ranitidine, omeprazole in standard doses) should also be given. Use of cisapride may aggravate diarrhea and should be used with caution.

DIARRHEA:

Diarrhea is the commonest GI symptom in patients with HIV infection. The basic approach to a patient with diarrhea remains the same as that for a patient without HIV infection. A useful starting point may be to try and distinguish if the patient's diarrhea is small bowel origin or large bowel origin. (See table 1).

In practice most patients with HIV have a small bowel type diarrhea. In the few patients with large bowel diarrhea-colonoscopy would be the test of choice. A colonoscopy is useful in patients with small bowel diarrhea to evaluate the ileocecal junction that is involved in patients with tuberculosis.

Table 1. : Differential diagnosis of diarrhea

	Small bowel diarrhea	Large bowel diarrhea
Site of pathology	Small intestine	ileocecal junction Colon
Diarrhea volume	Large	Small
Tenesmus	Absent	Present
Blood and mucus	Absent	Present
Borborygmi	Present	Absent
Pain	+/-	+
Stool exam	Absent RBCs and pus cells	RBCs and pus cells present

Common causes of diarrhea in HIV disease:

Infections	Protozoa:	Giardia lamblia Cryptosporidium Microsporidium Cyclospora Entameba histolytica
	Viruses :	CMV Herpes simplex ?HIV
	Bacteria :	Salmonella Shigella Campylobacter M. tuberculosis, MAI, Clostridium difficile
	Fungi:	Histoplasma Coccidioidosis Candida
	Neoplasms:	Lymphoma Kaposi's sarcoma.
	Pancreatic insufficiency	Pancreatitis, CMV/MAC Drug induced pancreatitis (Pentamidine, ddI,)
	Idiopathic:	AIDS enteropathy

Evaluation of diarrhea :

In all patients:-

Stool smear: Fecal leukocytes, RBCs
Ova and parasites (3-6 fresh specimens)

AFB stain

Special stains for cryptosporidium (if available)

Sudan III stain for fat

Bacterial culture: Salmonella
Shigella
Campylobacter

In patients with large bowel diarrhea

Flexible sigmoidoscopy or colonoscopy with

- a) Tissue biopsy
- b) Culture of rectal mucosa

In unexplained persisting diarrhea :

Upper GI endoscopy with (aspiration of secretions for) ova/cysts/parasites

Bacterial culture

Biopsy for : parasites, culture

Treatment :

1. Symptomatic treatment :

- a) Antidiarrheals : Loperamide, (Immodium.)
- b) Rehydration : Oral rehydration solution
Intravenous fluids.

2. Specific treatment :

Depends on the organism causing diarrhea. Many patients would tend to have transient improvement with a course of tetracycline (500 mg BD) along with folic acid (5 mg BD) and injectable Vit. B₁₂ (1mg intramuscular once/twice per week) for a total of 2 weeks.

Causes of diarrhea which are treatable and drugs used for them are shown below :

- a) Isospora belli : Trimethoprim (160mg) sulamethoxazole (800mg) po QID for 10 days and then bid x 5 weeks
- b) Giardiasis : Metronidazole 400mg tid 5 days.
- c) E. histolytica : Metronidazole 400mg tid 10 days.
- d) MAC: Clarithromycin 500mg bid. + Ethambutol 15-25mg/kg OD or Clofazimine 100-200mg/day or Ciprofloxacin 750mg bid.
- e) M. tuberculosis : same as for pulmonary disease.
- f) Cytomegalovirus : Ganciclovir, foscarnet as for esophagitis

For some of the agents causing diarrhea definitive curative treatment is unavailable. Drugs have been tried with variable success.

- a) Cryptosporidium : Paromomycin 500-750mg QID variable duration.
- b) Microsporidia : Albendazole 400mg bid. variable duration.

Table 2:		
Symptoms	Suspected cause and pathogenesis	Tests of choice
Mild diffuse or colicky with diarrhoea	Infectious enteritis	Stool exam
Colicky mild/severe with distension	Subacute obstruction Lymphoma Tuberculosis KS.	Plain X-rays abdomen for fluid levels Barium contrast studies, colono-ileoscopy
Rt. Upper quadrant pain	Cholecystitis (CMV, crypto) Cholangitis (CMV, crypto, microspori) Granulomatous hepatitis (TB)	Liver function tests Ultrasonography ERCP liver biopsy
Sudden severe pain	Perforation Pancreatitis	Plain abdominal films, Ultrasonography Surgical consultation Paracentesis of ascites

ABDOMINAL PAIN

Abdominal pain in an HIV infected patient may be due to an unrelated/existing lesion such as duodenal ulcer or due to relatively specific diseases associated with AIDS and HIV infection. The patterns of pain may be helpful in assessing the pathogenesis and consequently the cause for pain (table 2).

Management:

Management options depend on the underlying cause and include medical treatment or surgery. Indications for surgery are same as those for non-HIV infected individuals. Morbidity and mortality (post operative) are high in patients with advanced disease and surgery only for palliation may be a

logical goal in such patients. Lesions such as Kaposi's sarcoma and lymphoma can respond to chemotherapy. Supportive treatment, antispasmodics, analgesics, antibiotics and acid reducing agents.

HEPATOBIILIARY PROBLEMS:

These can present as

- a) Asymptomatic/incidentally detected abnormalities in liver function tests. These include : raised billirubin and/or raised transaminases or alk. PO₄ase
- b) Hepatomegaly
- c) Jaundice with or without cholestatic features
- d) Acute presentation due to cholangitis, biliary obstruction

Table 3

Clinical syndrome	Possible (common) causes	Tests of choice or management course
A] Asymptomatic liver function abnormalities.		
↑ s Billirubin only	May have no significance	Clinical observation and follow up.
↑ s Billirubin and transaminases	Hepatocellular injury due to viruses (ABCDE) CMV, drugs	Serological markers for hepatitis viruses, Liver biopsy Withdrawal of hepatotoxic drugs
↑ s Billirubin and alk PO ₄ ase	granulomatous hepatitis (Tuberculosis) or Infiltrative disorders	Liver biopsy
B] Hepatomegaly		
	Hepatitis	Ultrasound, liver function tests
	Infiltrative disorders	Liver biopsy
C] Jaundice		
With cholestasis	Infiltrative disorders	Ultrasound (no biliary dilatation), Liver biopsy
	Extrahepatic biliary obstruction	Ultrasound (biliary dilatation) ERCP+papillotomy and Stenting LFTs
Without cholestasis	Hepatitis	Viral markers Withdrawal of drugs.

ANORECTAL PROBLEMS

Anorectal problems are generally seen in male homosexuals. Pain, fissures, and proctitis are nonspecific effects of receptive anal intercourse.

Proctitis can also be due to gonorrhoeal infection, herpes or CMV infection. Anal carcinomas and lymphomas occur with increased frequency.

Diagnosis is made after careful history taking of sexual practices. Rectal examination with proctoscopy or sigmoidoscopy is the most important diagnostic test.

GASTROINTESTINAL BLEEDING

GI Bleeding in patients with HIV and AIDS most commonly originates from lesions unrelated to HIV/AIDS, such as ulcers, diverticuli etc.

A combination of alcoholic liver disease with bleeding varices and HIV infection is not uncommon and is managed on the same lines as in an uninfected patient. If endoscopic variceal injections are planned a dedicated needle or preferably disposable needle is mandatory for the procedure.

Kaposi's sarcoma is one lesion specific for HIV infection that can bleed. It can arise from in the stomach or small/large bowel.

SPLENOMEGALY

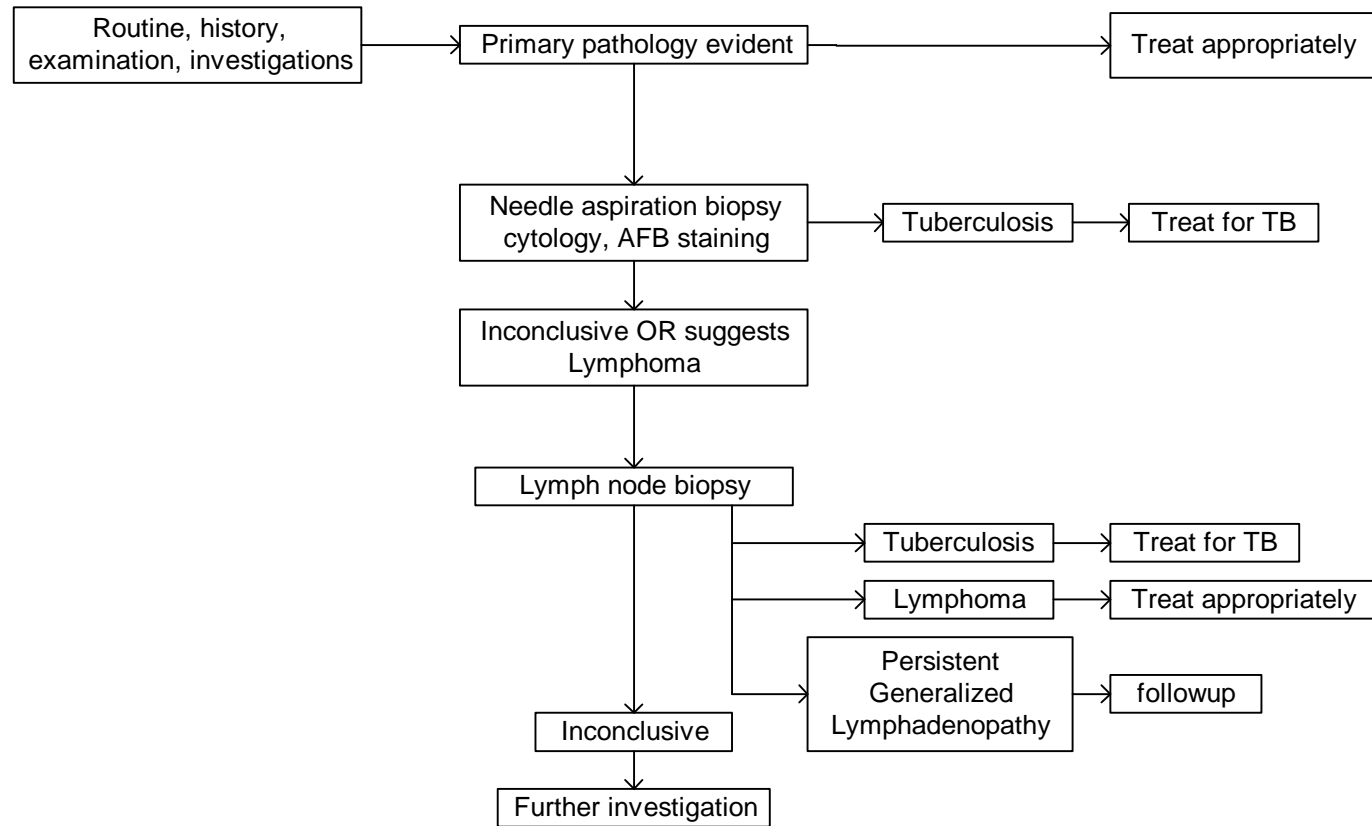
Splenomegaly, can be caused by disseminated infections such as M. tuberculosis, MAC, disseminated fungal infections including hepatosplenic candidiasis or can result from lymphomas. Patients with associated alcoholic liver disease can have splenomegaly related to portal hypertension. Ultrasonography and CT scanning are helpful.

Treatment is dictated by the clinical diagnosis.

GASTROINTESTINAL SIDE EFFECTS OF ANTIRETROVIRAL AGENTS

Zidovudine	Hepatomegaly Steatosis Hepatitis	Uncommon
Didanosine	Pancreatitis	Rare but can be fatal
Stavudine	Pancreatitis	Rare
Lamivudine	Pancreatitis	Rare (more often seen in paediatric age group)
Nevirapine	Asymptomatic, increased GTP and ALT/AST	Often
Saquinavir	Nausea, diarrhea Abd. discomfort Asymptomatic increase in liver enzymes	Rare
Ritonavir	Altered taste, Elevated liver enzymes	Caution with many drugs
Indinavir	Unconjugated hyperbilirubinemia Aphthous ulcers	At doses > 2.4 g/day
Nelfinavir	Diarrhea	Often

Lymphadenopathy



12.5

WASTING SYNDROME

Dr. Parag Pandit

It is a common observation, both amongst clinicians as well as paramedical staff involved in AIDS management, that patients infected with HIV, at varying stages during their illness, show signs of wasting. They lose body weight and tissue substance. It is probably for this reason that Africans through several generations termed this as 'slim disease' - an observation that a person afflicted with this disease steadily loses weight and becomes emaciated. In India too we are coming across this situation quite commonly to the extent that many clinicians when confronted with a young but emaciated patient strongly suspect HIV as an underlying cause.

Physically, the patients look underweight, malnourished and have a look of being ill about them. Though this condition can occur per se, as part of the HIV-AIDS complex, there are some underlying causes that can either cause or potentiate it.

HIV related weight loss is so common and the variety of causes so great that it is difficult to ascribe it to a single

opportunistic infection or neoplasm. It may be due to impaired caloric intake, excess caloric loss, or increased caloric utilization.

HIV infected patients, who lose more than about 4.5kg (or more than 10%) of their usual body weight with no obvious explanation, are diagnosed as having AIDS. Often the weight loss is even more striking. Mean weight loss may vary from 10 to 15kgs. Associated anorexia is the rule.

There could be several reasons for loss of appetite that results in decreased oral intake and is a common cause. Several patients have gastrointestinal malabsorption that may lead to diarrhea and weight loss. Wasting may result from metabolic changes and increased catabolism. This in turn could be caused by the production of cytokines such as Tumour Necrosis Factor-(TNF) and Interleukin 6. Apart from these, factors which may not necessarily cause weight loss themselves but can potentiate it include side effects of medications and endocrinopathies such as

Addison's disease.

Several conditions have to be considered when dealing with an HIV positive patient with weight loss and three things have to be remembered.

1. Diarrhea and weight loss are common problems in AIDS patients accounting for as many as 80% of cases in some series.
2. Altered bowel habits are common in HIV infected persons without AIDS and may even be present in patients referred to as asymptomatic.
3. In AIDS patients with diarrhea, an infectious agent can be found in most comprehensively evaluated cases, in contrast diarrhea is unexplained in most HIV infected patients without AIDS.

Causes of diarrhea leading to weight loss can be divided into two broad groups:

I. Malabsorptive diseases:

Nutrient malabsorption is an extremely common occurrence in AIDS. In many cases it is clinically occult and involves fat and vitamin B12 malabsorption. A subset of AIDS patients has severe malabsorption associated with histologic evidence of small intestinal injury.

(1) Cryptosporidiosis : *Cryptosporidium parvum* is a common contaminant parasite of drinking water. Diarrhea due to this parasite is very common in AIDS patients. In immunocompetent patients it may cause a short self-limiting illness.

In immunocompromised patients the effects can be catastrophic. After ingestion and excystation of the oocysts, the sporozoite invades the epithelial cell, possibly by specific receptor binding and occupies an extracytoplasmic site, beneath the brush border. Cycles of asexual division with autoinfection occur as well as sexual division with production and faecal excretion of thick walled oocysts. Destruction of epithelial cells with villous atrophy and inflammation results the infection. Disease can vary from diffuse intestinal & mild colonic involvement causing diarrhea to biliary and pancreatic infection resulting in pancreatitis, sclerosing cholangitis or (acalculous) cholecystitis. Diagnosis can be done with stool concentrating methods, failing which by intestinal biopsies.

No treatment has been found to be uniformly successful but Spiramycin, Paramomycin and Azithromycin have been tried with varying results. Most patients need symptomatic treatment.

(2) Microsporidiosis : Two species cause diarrhoea : *E. bienewisi* and *septata intestinalis*. Infection is most likely via the oral route and at severe levels of immunosuppression. Clinically infection resembles cryptosporidiosis, other diffuse small intestinal diseases or short bowel syndrome. Diagnosis is possible using light microscopy. Albendazole is being tried for *E. bienewisi* but seems to be effective for *septata intestinalis*. Supportive therapy is essential.

(3) *Isospora belli* : is closely related to cryptosporidium. Disease is very similar as well though occasionally it can be associated with cholecystitis and cholangiopathy. Co-trimoxazole can be tried. Since the infection is chronic, therapy has to be long term.

(4) Giardiasis : More common in homosexuals, can be diagnosed by routine stool examination. Symptoms are similar to amoebiasis and treatment is with metronidazole.

(5) *Mycobacterium avium* complex (MAC) infection : Acquired either orally or through aerosol infection, occurs late in AIDS. Though diarrhoea may be the main symptom, MAC is a systemic infection involving liver, spleen, lymph nodes and bone marrow. Cellular infiltration in intestinal wall blocks lymphatic flow and produces fat malabsorption with exudative enteropathy. Histology and culture are used for diagnosis. Antitubercular treatment can be tried though response is usually poor.

II Enterocolitis:

1. Cytomegalovirus infection (CMV) : May be associated with generalised CMV infection including retinitis, esophageal ulcers, gastritis, hepatitis, pancreatitis etc. Diagnosis is made by biopsy and histologic analysis (basophilic inclusion bodies). PCR can be used as well. Treatment is with ganciclovir or foscarnet.

2. MAC complex.

3. *Mycobacterium tuberculosis* : diagnosed by histological demonstration of AFB in biopsy samples and culture. Treatment is by standard anti-tubercular drugs.

4. Cryptosporidiosis.

5. Bacterial enteritides like shigella, salmonella and campylobacter all cause illnesses which can be very severe and more importantly can relapse. Treatment has to be very aggressive.

6. Fungal infections : Most common is candidiasis though *Torulopsis glabrata* can be the causative agent as well. Systemic and deep fungal infections are rapidly progressive and can involve the GIT. Treatment for candidiasis is by systemic fluconazole or itraconazole but for deep fungal infections IV Amphotericin B is the drug of choice.

In addition many approaches have been used to reverse symptoms of weight loss, including appetite stimulants such as megestrol acetate and marijuana derivatives (taken in pill form) & hormone replacement.

POSSIBLE CAUSES OF MALNUTRITION IN HIV DISEASE:

Impaired oral intake :

- Odynophagia, dysphagia
- Dysgeusia
- Depression, Neurologic impairment
- Fear of worsening diarrhea

- Poor supportive care

Impaired deglutition :

- Oropharyngeal infection or tumor
- CNS disease

Malabsorption :

- Intestinal mucosal disease (MAC, cryptosporidiosis)
- Small bowel overgrowth, achlorhydria
- Diarrhea
- Lactose intolerance
- Biliary obstruction (tumor or infection)
- Pancreatic insufficiency
- Mucosal atrophy secondary to protein - calorie malnutrition.

Metabolic alterations :

- Hypermetabolic state.
- Protein wasting
- Cytokine factors (esp. Tumor Necrotizing factor)

Treatment:

Apart from prompt and proper treatment of infections,

1. Provide adequate nutrients, reduce malabsorptive symptoms.
2. Educate patients and their relatives.
3. Identify and treat treatable causes of malnutrition.
4. Avoid drugs that induce anorexia, nausea, vomiting.
5. Use oral or enteral routes (nasogastric tube) unless contraindicated before parenteral route.
6. Consider ethical and clinical issues before making decisions regarding nutritional support.

Give consideration to the costs and needs of the patient as well as the family members.

12.6

NEUROLOGIC DYSFUNCTION

Dr. Vinay Kulkarni

OVERVIEW:

HIV is a lentivirus. One of the characteristics of these viruses is to cause chronic neurological disease in their hosts. It is not surprising then, that neurologic complications are common in HIV disease. These are not restricted to opportunistic infections. The brain, meninges, spinal cord, nerve and muscle all levels be involved. Neurologic disease is the first manifestation of symptomatic HIV infection in roughly 10-20 percent of persons, while about 30 to 40 percent of patients with advanced HIV disease will have clinically evident neurologic dysfunction during the course of illness. The incidence of sub-clinical neurologic involvement is even higher.

HIV crosses the blood-brain barrier and enters the nervous system early, probably at the time of initial systemic infection. This is usually asymptomatic but meningitis, encephalitis and inflammatory polyneuropathy may be seen. Virus infected macrophages maintain the latent HIV infection in the

central nervous system (CNS). Despite early infection of the CNS, however, symptoms of cognitive impairment occur, usually, late.

Neurologic manifestations are usually described according to their occurrence in different stages of HIV disease. (Table 1).

In situations where diagnostic facilities do not exist or are beyond the means of most patients it is difficult for a clinician to follow a classification like this. We will discuss these conditions according to clinical syndromes.

COMMON MODES OF PRESENTATION OF AIDS RELATED NEUROLOGICAL PROBLEMS

- 1) Focal deficits
- 2) Changes in mental state
- 3) Seizures
- 4) Headache

Table 1.

A. During Seroconversion :

Mononucleosis like syndrome
Aseptic meningitis

B. Less Common (Seroconversion or early latency)

Diffuse encephalopathy
Myelopathy
Cranial neuropathy
Brachial plexopathy
Angitis
Rhabdomyolysis

Clinically Latent Phase

Guillain-Barre syndrome
CIDP syndrome
Mononeuritis multiplex
Multiple sclerosis like disorder
Asymptomatic CSF abnormality
Anxiety and Psychoses
Headaches
Intellectual decline
Opportunistic TB and Herpes roster
Disorders from group B above.

Late HIV Disease

1. Due to HIV

HIV Dementia (HIV Encephalitis)
Vacuolar myelopathy
Predominantly sensory neuropathy
Late sensory motor neuropathy
HIV headache

2. Opportunistic Infections

Toxoplasmosis
Tuberculosis
Cryptococcosis
CMV
HSV
HTLV (Human T Lymphotropic virus)
PML (Progressive multifocal leukoencephalopathy, JC virus)

3. Tumours

Lymphoma

4. Drug induced and metabolic.

- 5) Impaired level of consciousness
- 6) Difficulty with walking
- 7) Peripheral tingling pain/numbness
- 8) Impaired visual ability

The different pathologies leading to these presentations can be listed as follows.

I) **Focal deficits :**

Space occupying lesions caused by :

- 1) Toxoplasma gondii abscess
- 2) Tuberculoma (also atypical mycobacteria like mycobacterium avium)
- 3) Primary CNS lymphoma
- 4) Fungal abscess (Candida, Cryptococcus)
- 5) Focal encephalitis/cerebritis (CMV,HSV,HIV)
- 6) Kaposi's sarcoma (KS)

Vascular lesions caused by :

- 1) Haemorrhage secondary to lymphoma or thrombocytopenia
- 2) Infarction secondary to embolism from marantic endocarditis, VZV vasculitis, meningovascular syphilis, or lupus anticoagulant.

Demyelination caused by :

- 1) Progressive multifocal leuko-encephalopathy

II) **Changes in mental state**

- 1) HIV associated dementia complex
- 2) Depression
- 3) Subacute encephalopathy plus depression or toxic effects
- 4) Cerebral lymphoma
- 5) HSV encephalitis
- 6) CMV encephalitis
- 7) Metabolic and toxic encephalopathy

III) **Seizures**

- 1) Space occupying lesions (abscesses or lymphoma)
- 2) Cryptococcal meningitis
- 3) HIV associated dementia complex
- 4) HSV encephalitis
- 5) CMV encephalitis

IV) **Headache**

- 1) Tension headache/migraine
- 2) Space occupying lesions
- 3) Meningitis (Cryptococcal/HIV/lymphomatous /TB)

V) **Impairment of level of consciousness**

- 1) Mass lesions
- 2) Cryptococcal meningitis
- 3) Metabolic encephalopathy, (e.g., respiratory, renal or hepatic failure, septicaemia, or drug effect)

- 4) Encephalitis (HIV, CMV, HSV, VZV)
- 5) Postictal or partial status epilepticus.

VI) **Difficulty with walking**

- 1) Focal cerebral lesions
- 2) Encephalitis
- 3) Myelitis due to HIV, CMV, HSV
- 4) Spinal lymphoma
- 5) Spinal abscess
- 6) Radiculopathy (CMV, VZV)
- 7) Mononeuritis multiplex (HIV)
- 8) Acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome)
- 9) Distal symmetric neuropathy
- 10) Myopathy
- 11) General debility, pain etc.

VII) **Peripheral pain, tingling or numbness**

- 1) Peripheral neuropathy due to HIV, drugs, dietary deficiencies
- 2) Myelitis (HIV, CMV, HSV)
- 3) Early Cord Compression from lymphoma
- 4) Radiculopathy due to CMV/VZV.

VIII) **Impaired visual acuity**

- 1) Retinitis : CMV, Toxoplasma gondii, Candida albicans.

This list of differential diagnosis is very extensive. We shall concentrate only the salient disorders.

CNS DISORDERS

There are four general categories :

1. Primary HIV infection of the brain,
2. Opportunistic infections by parasitic, fungal, viral and bacterial organisms,
3. CNS neoplasms,
4. Complications of systemic disorders.

Primary HIV Infection of the brain :

Also called AIDS Dementia Complex (ADC), Cognitive and Motor deficit, HIV encephalitis, Multinucleated giant cell encephalitis.

There is no focal lesion clinically or on the scan and there is no clouding of consciousness. Approximately 30% AIDS cases coming to post-mortem show this. Pathologically, the findings are highly variable and severity does not always correlate with the degree of clinical dementia. Microscopically multinucleated giant cells within foci of macrophages and microglia, and multifocal perivascular infiltration are pathognomonic. Careful post-mortem studies have revealed that the virus is in the microglial cells and macrophages and only rarely in the astrocytes. The neuronal cells are not involved. Neuronal and cognitive dysfunction is believed to be due to elaboration of neurotoxic products, by the infection.

Clinically there is impaired concentration and attention, forgetfulness, slowed reaction times, dysphoria, and social withdrawal. It may be impossible to distinguish early dementia from depression. Motor dysfunction with gait unsteadiness, loss of rapid limb movements and eye movements, progressing to frank quadriparesis may be seen. Signs of corticospinal tract involvement, prominent primitive reflexes (hand grasps) may be seen.

CSF examination is helpful to exclude other infections or neoplastic causes of dementia.

CT/MRI may show diffuse atrophy and enlarged ventricles and, on MRI, patchy or diffuse abnormal signal in the white matter on T₂-weighted images.

There is no proven therapy. Stabilisation or partial clinical improvement is seen

in patients treated with zidovudine.

The AIDS dementia complex is often associated with vacuolar myelopathy, another syndrome directly related to HIV disease.

Differential diagnosis cognitive disturbance associated with clouding of consciousness and absence of focal lesion on CT/MRI includes metabolic encephalopathy, drug effect, encephalitic disorders like CMV, HSV and diffuse Toxoplasma encephalitis.

CMV Encephalitis:

It causes subacute dementia. There is evidence of systemic CMV infection in most cases : adrenal, retinal, gastrointestinal or pulmonary. CSF may show polymorphonuclear pleocytosis. The efficacy of antiviral (ganciclovir) is not well established.

Simplified version of 1991 American Academy of Neurology definitions of levels of dysfunction :

Levels of cognitive dysfunction :

Mild : Decline in work and home activities noticeable to others, but person not totally dependent on others. Incapable of more complicated daily tasks. Self-care intact.

Moderate : Unable to work, including in the home. Requires assistance in activities of daily living.

Severe : Unable to perform any activities of daily living without assistance. Requires continual supervision.

Levels of myelopathic dysfunction :

Mild : Ambulatory, but requires constant unilateral support.

Moderate : Requires constant bilateral support for walking.

Severe : Unable to walk even with support.

Intracranial Opportunistic Infections:

HIV disease with focal brain disorder may appear acutely as in stroke.

It must be considered in all cases of strokes in young individuals.

In subacutely evolving focal defects we must consider

- 1) Toxoplasmosis
- 2) Tuberculosis
- 2) CNS Lymphoma
- 3) Progressive Multifocal Leukoencephalopathy, (PML)

Toxoplasma gondii:

CNS Toxoplasmosis is so common a cause of intracerebral mass lesion in HIV infected persons that it is universally recommended that we give a trial with

antitoxoplasma treatment. A toxoplasma lesion should resolve in 2 weeks. On CT, toxoplasma infection usually shows multiple ring enhancing lesions. toxoplasmosis in HIV is usually reactivation of infection acquired long ago. Thus toxoplasma IgM is usually not elevated and toxoplasma IgG only means past infection and its presence is of no diagnostic value.

Absence of toxoplasma IgG excludes the diagnosis. A very high titre greater than 1000 is supportive of the diagnosis.

Treatment :

Sulphadiazine (4gm/day) and pyrimethamine (75mg/day) plus folinic acid (10mg/day). Alternatively clindamycin (1200mg intravenously every 6 hours for 3 weeks followed by 300mg orally every 6 hours) may be used.

Table 2

Multiple Nodular Brain Lesions

	Toxoplasmosis	CNS Lymphoma	PML	Tuberculoma
Time	Days	Days-weeks	Weeks	Weeks
Alertness	Reduced	Variable	Normal	Reduced
Fever	Common	Nil	Nil	YES
Number	Many	One or 2	Many	Many
Lesion	Ring	Irregular	Irregular	Ring
Enhancement	+++	+	Nil	++
Site	Basal ganglia	Cortex	Periventricular White matter	Disseminated

Rarer causes of focal lesions include cryptococcoma (always with meningitis), CMV disease, VZV and HSV.

Cryptococcus neoformans:

Cryptococcus neoformans is the most common fungal infection of the CNS. The usual manifestation is subacute meningitis or meningoencephalitis. It is as common as tubercular meningitis. Cryptococcal meningitis in HIV is atypical. Fever and headache are infrequent. An India ink examination of CSF is a must, as the cells in CSF may not be increased. If India ink staining is negative and diagnosis is still in doubt cryptococcal antigen test is necessary.

Treatment: It is dictated by cost and availability of drugs.

Amphotericin B for 2-3 weeks followed by either fluconazole or itraconazole (400mg) per day for further 8-10 weeks is preferred mode of treatment. Toxicity of Amphotericin B is an important consideration. Dose needs to be increased gradually & there should be strict monitoring of renal function. Liposomal Amphotericin B may be used to circumvent the problem but the cost is extremely prohibitive. Flucytocin may be added.

After the acute attack is treated the person has to be on chronic (lifelong) suppressive therapy.

Fluconazole is the drug of choice (200mg per day).

Tuberculosis:

Tuberculomas are common in India. CSF studies and drug trial may clinch the issue.

Tubercular Meningitis

Mycobacterium tuberculosis frequently causes meningitis in India, in HIV infected patients, apart from causing tuberculomas and abscesses.

The most common clinical manifestations are seizures, altered mental status and fever with meningismus. On rare occasions CSF may be normal and negative microbiological studies of CSF are also not unusual. The response of AIDS patients to the standard antitubercular treatment is generally gratifying.

Aseptic Meningitis:

Patients usually present with headache, occasionally with altered mental status & cranial neuropathies. Because of extremely high incidence of CSF abnormalities in HIV infected patients, regardless of symptoms, interpretation can be difficult and diagnosis of aseptic meningitis is only by exclusion.

Table 3 : CSF Examination in HIV disease

Infection	Cerebrospinal fluid
CMV (Cytomegalovirus)	Protein: 100-1000ml WBC: 10-1000 (monos)/ml Glucose usually decreased CMV PCR positive
PML (Progressive multifocal leukoencephalopathy)	Normal or changes associated with HIV infection
HIV associated dementia	Normal: 30-50% Protein: increased in 60% WBC: increased in 5-10% (monocytes) Beta-2 microglobulin elevated (>3mg/L)
Neurosyphilis	Protein: 45-200/ml WBC: 5-100 (monos) VDRL positive: sensitivity-65%, specificity-100%
Tuberculosis	(Normal: 5-10%) Protein: Normal (40%) – 500/ml WBC: 5-2000 lymphocytes Glucose: 4-40/ml AFB smear positive: 20%

HIV Headache: It is a distinct entity. A continuous headache in the absence of any other cause of infection/abnormality. It is usually seen with very low CD4 counts. It is linked to production of cytokines and disturbed serotonin metabolism.

Progressive Multifocal Leukoencephalopathy (PML)

It is caused by JC virus. It is a subacute or chronic progressive illness most often characterised by focal neurologic findings: hemiparesis, gait abnormalities,

visual field cuts, altered mental status and personality changes. CT/MRI usually reveal focal or diffuse lesions in the white matter, particularly in the parieto-occipital region, CSF is nondiagnostic.

Prognosis & treatment: Usually there is progressive decline over the course of 4 to 5 months until death. With antiretroviral treatment in patients with CD4 > 200, it may be arrested. Intrathecal cytosine arabinoside was tried in some patients.

Neurosyphilis :

We are seeing neurosyphilis more frequently now, is associated with HIV. It is both more fulminant and more difficult to eradicate.

Common manifestation are meningitis, cerebral arteritis & cerebritis, as well as optic neuropathy and deafness.

Any HIV infected person with positive serology for syphilis should undergo lumbar puncture. A positive CSF-VDRL would establish diagnosis of latent neurosyphilis. A negative CSF-VDRL but CSF pleocytosis, mildly elevated protein should also be treated for at least 10 days with IV aqueous penicillin G 4 million units 4 hourly.

CNS Neoplasms :

Non-Hodgkin's Lymphoma:

Among systemic cancers non-Hodgkin's lymphoma is the most common cause of neurologic dysfunction in HIV disease. It invades CNS by spreading along the leptomeninges. Cranial nerve palsies, polyradiculopathy, myelopathy due to epidermal metastases with spinal cord compression are usual signs. Cytological examination of CSF, often requiring multiple large volume (10-20ml/tap), is essential for diagnosis.

Primary CNS Lymphoma :

Most common signs are confusion, lethargy and personality changes (can mime ADC), focal deficits (hemiparesis,

hemisensory loss, ataxia & aphasia), seizures may be seen.

CT/MRI can show single or multiple enhancing lesions which are irregular. It may be indistinguishable from toxoplasmosis - radiologically but a single lesion favours lymphoma. One may try 2 weeks antitoxoplasma drug trial and in absence of response should consider brain biopsy.

It is radiosensitive and whole brain radiation prolongs survival.

SPINAL CORD DISORDERS

These are less common than intracranial and peripheral nervous system disease, but severe myelopathies may occur.

Common presenting complaints are:

Clumsiness,
Weakness,
Sensory disturbances of legs leading to gait difficulty.
Urinary and fecal urgency or incontinence

Common signs are:

Relatively symmetric leg weakness and sensory loss,
Spasticity
Hyperreflexia of both legs,
Babinski signs.

Subacute myelopathy: Vacuolar Myelopathy

It is often seen associated with AIDS dementia complex.

Paresthesias, spastic ataxic syndrome, and brisk tendon reflexes are the hallmarks.

Acute myelopathy - like transverse myelitis :

This could be due to VZV or CMV infection. Rarely HTLV-I can cause myelopathy. Other causes like spinal cord compression from lymphomatous metastases, tuberculous spinal abscess must be ruled out.

Vitamin B₁₂/ folate deficiency:

In cachexic patients may lead to subacute myelopathy.

A possibility of syphilitic meningomyelitis must always be kept in mind. Very rarely an autoimmune disorder like multiple sclerosis is seen in HIV patients. This responds to steroids.

NEUROMUSCULAR DISORDERS

A wide range of peripheral nervous system disorders develop in patients with HIV leading to pain, sensory symptoms and muscle weakness.

Neuromuscular complications associated with HIV infection

1) Neuropathies due to identifiable systemic complications of HIV infection:

- a) Polyneuropathy associated with therapeutic drugs
- b) Vitamin B₁₂ deficiency

2) Neuropathies of uncertain cause

- a) “Idiopathic” distal symmetrical polyneuropathy
- b) Chronic inflammatory polyneuropathy
- c) Acute inflammatory polyneuropathy
- d) Mononeuropathy multiplex
- e) Progressive lumbosacral polyradiculopathy.
- f) Autonomic neuropathy
- g) Sensory ganglionitis

3) Myopathies

- a) “Idiopathic” myopathy/ myositis
- b) Zidovudine myopathy.

4) Miscellaneous

- a) Motor neuron disease.

Drugs causing polyneuropathy

Vincristine,
Isoniazid
Dapsone,
ddI,
ddC.

Distal symmetric polyneuropathy (DSPN)

By far the most common neuropathy in HIV disease. Tingling, numbness and burning pain in toes or over the plantar surface of feet are typical symptoms.

Bilateral depressed ankle jerks and elevated vibrator threshold in the toes. Weakness is mild.

Differential diagnosis includes chronic alcoholism, neurotoxicity of drugs, uraemia, diabetes mellitus. EMG and nerve conduction studies typically show a length-dependent sensorymotor polyneuropathy. They help confirm the diagnosis and assess the severity but generally cannot differentiate between DSPN and other causes of polyneuropathy.

Treatment is directed towards the neuropathic pain. Desipramin (25-150mg at bedtime) or amitriptyline (25-250mg at bedtime); start at low dosages, increase gradually. Topical capsaicin and other analgesics may be used.

Progressive lumbosacral radiculopathy:

It is a devastating condition; occurs in patients of HIV disease with very low CD4 Counts. It is an uncommon disorder, probable cause is CMV infection. It has a remarkable predilection for lumbosacral roots.

Neurologic deficit is limited to the legs. Bilateral leg weakness and difficulty in walking progresses rapidly to flaccid paraplegia. Urinary retention, constipation or obstipation may be seen. Sensory deficit is rarely severe. Sensory loss over the perineal or perianal areas, if present, is characteristic.

Loss of tendon reflexes and sensory symptoms differentiate it from myopathy/wasting syndrome. CSF studies are diagnostic. WBC in excess of 500 cells/mm³ with polymorphonuclear cells about 50%. Mononuclear pleocytosis may also be seen in some.

CT/MRI will exclude compressive/space occupying lesions in cauda equina/lower thoracic spinal cord. EMG/Nerve conduction may help localization. There is no evidence of usefulness of ganciclovir.

Mononeuritis multiplex :

It is often proved to be due to CMV infection. It typically presents as subacute multifocal or asymmetric sensory motor deficits in the distribution of peripheral nerves or spinal roots. Deep tendon reflexes mediated by affected nerves are diminished, but diffuse areflexia is not seen.

Patients with CD4 >200 usually have benign disease. There is only anecdotal data regarding efficacy of ganciclovir or foscarnet.

Inflammatory demyelinating polyneuropathies:

HIV patients may develop either Guillain-Barre syndrome (GBS) or Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). They occur in early latent phase of HIV disease.

Patients present with progressive, usually symmetric weakness in upper and

lower extremities. There is usually generalised areflexia. If the illness is monophasic with maximum neurologic dysfunction reached within the first month, it is by definition GBS. If the disease progresses beyond 4-6 weeks it's CIDP.

Nerve conduction studies show multifocal conduction slowing and block. EMG shows signs of denervation in clinically weak muscles. CSF protein is increased and (unlike in general population) mononuclear pleocytosis is sometimes seen.

Treatment :

IV Immune globulin (400mg/kg/day for 5 days) or plasmapheresis (5-6

exchanges over 2 weeks). Repeated treatment may be required. Zidovudine treatment has doubtful role.

Myopathy :

Symptomatic primary muscular disease is uncommon. Two types are seen a) a polymyositis like syndrome and b) secondary myopathy attributable to zidovudine.

HIV wasting disease is a common HIV induced manifestation.

A pyomyositis with multiple staphylococcal abscesses has been reported.

Lastly rhabdomyolysis may occur with HIV disease.

Further reading :

1. AIDS and Neurology. Harrison M.J.G., McAuthur J.C., Churchill Livingstone, 1995
2. The Neurologic Complications of HIV infection. Berger. J.R., Levy R.M., Medical Clinics of North America. Vol. 77,1,1993, 1-23.
3. Neurologic Manifestations of HIV infection. Wadia R.S., Pujari S, Ichaporia N.R. Proceedings and abstracts, National Conference on HIV/AIDS Medicine, 1996, Pune.

12.7

HIV AND MENTAL HEALTH

Dr. Shailesh Chougule

Incurable illnesses with poor prognosis and inevitable fatal outcome are not new to medical science. In spite of intense research and development of new treatment modalities, the number of such incurable, untreatable conditions is significant.

Whenever one becomes aware that s/he is suffering from a terminal/ incurable fatal illness-one undergoes a state of profound emotional turmoil. This is well documented and even seen in psychiatric practice. Several stages, which come in succession, are,

1. Shock and numbness
2. Denial
3. Anger
4. Depression
5. Acceptance

Similar stages are seen in HIV infected individuals too. Then, is HIV infection and subsequent development of AIDS, just another addition to the list of incurable illnesses?

The answer is, 'NO'.

Various studies have reported that, the psychological upsets seen in HIV seropositive and AIDS patients are qualitatively and quantitatively different from that seen in other incurable illnesses. This is because of several reasons.

1. Social stigma: patient suffering from other terminal illness usually gets a lot of emotional support, empathy from family members and close relatives. HIV/AIDS patient is afraid of social criticism, social rejection, isolation, etc. So s/he tries to hide the illness from society. Such person feels trapped - while in need of emotional support, lacks the same, and may even get rejected by the family.
2. Guilt feeling: people who become infected with HIV because of their high risk life style, develop guilt feeling and blame themselves. This may precipitate depressive episodes.
3. Young age: majority of the HIV infected individuals are in their

young age or early adulthood. So worries about their jobs, anticipated financial problems, future of the dependents, illness of the spouse and/or children, multiple losses add to their emotional turmoil.

Several mood and anxiety disorders, as well as organic mental disorders, such as delirium and dementia are seen during the spectrum of HIV disease. HIV associated cognitive and motor impairment and its advanced manifestation, dementia, are discussed in the chapter on neurologic manifestations in HIV disease.

The disorders associated with HIV could be organic or functional. It could be difficult to differentiate between the two. In addition, substance abuse, e.g. Alcohol, cocaine, etc. may complicate the symptomatology. In general it could be said that psychiatric symptoms in HIV infected persons who are asymptomatic and have CD4 counts above 300 cells/mm³ are likely functional, organic causes become progressively more likely with advanced HIV disease.

ORGANIC MENTAL DISORDERS:

Various symptoms seen are-

1. Delirium
2. HIV associated cognitive and motor impairment, dementia
3. Manic syndromes
4. Psychosis
5. Side effects of medication

6. Metabolic abnormalities
7. Opportunistic infections
8. C.N.S.malignancies
9. Substance abuse

MOOD AND ANXIETY DISORDERS

The most commonly seen syndromes are:

1. Depression
2. Bereavement
3. Suicidality
4. Anxiety
5. Insomnia

There are various hypotheses proposed to explain the origin of psychiatric symptoms - seen in an HIV infected person.

1. Transitional model: according to this, the origin of psychiatric symptoms can be viewed as a reaction /manifestation of stress, which the patient undergoes. Right from detection of seropositive status to the development of terminal stages patient undergoes various stressful situations and each of such stress adds to cumulative stressors experienced earlier, e.g. detection of HIV positive state, confirmation of the same, decline in CD4 cell count, hospitalization, diagnosis of AIDS, death of another known AIDS patient, etc.
2. Background model: According to

this, psychiatric symptoms are seen in patients who are already vulnerable or predisposed to psychiatric illness because of their family history, past history, other concurrent stressors, etc. the new stress of seropositive status acts as precipitating factor.

3. **Biological model:** According to this, the psychiatric symptoms are manifestation of altered central nervous system functioning. Thus the structural or functional damage to nervous system caused directly or indirectly by opportunistic infections, medication and direct involvement of central nervous system by HIV are responsible for psychiatric manifestations.

Although, theoretically any psychiatric syndrome can be seen in seropositive individuals. The more commonly observed are:

I] **Anxiety disorders** - Symptoms like excess worry, fear, restlessness, poor concentration, decreased confidence, are seen. Commonly reported anxiety disorder is 'Generalized Anxiety Disorder' where the patient is anxious about almost everything. 15-20 % seropositive patients exhibit anxiety disorder.

II] **Depression** - Symptoms like depressed mood, lack of interest, easy fatigability, guilt feeling, crying spells, low appetite, disturbed sleep, are seen. The incidence of depression in HIV

disease is twice as that seen in general population.

Interestingly studies have reported that the incidence of depression in high-risk groups e.g., men having sex with men, drug users, is the same as that seen in the HIV infected individuals. So it is the life style pattern of these individuals which makes them more vulnerable for depression or the contamination with the virus is not yet very clear.

The high suicide rates, which were predicted earlier - in anticipation - have not been found in reality. Please note here that many a times health care providers do the testing without the patient's knowledge, as they fear that disclosure may lead to suicide. Proper pre-test counselling definitely helps and one need not unduly worry.

III] **Psychosis** - Behavioural abnormality, irrelevant talk, delusions, and hallucinations are common and the clinical picture is not different from that found in other patients. This usually responds to neuroleptics.

IV] **Delirium** - It is a symptom complex of disturbance of consciousness, i.e., reduced clarity of awareness of environment, disorientation, memory lapses, perceptual disturbances like, hallucinations, disturbed sleep-awake cycle, psychomotor hyperactivity, etc.

Usually delirious episode has multi-factorial aetiology. In HIV infected, the

common causes are systemic illness, opportunistic infection, and side effects of medicines.

V] **Cognitive disorders-** cognitive disturbances, which are seen in HIV infected individuals, have been divided into two types.

- a) Mild Neurocognitive Disorders, and
- b) HIV associated dementia.

The difference between the two categories is only of the intensity of symptoms. Qualitatively symptoms are more or less the same. Cognitive disturbances are seen in the form of,

- Impairment in recent memory
- Poor attention
- Ill sustained concentration
- Psychomotor slowing

- Delay and difficulty in understanding simple things.

About 30-66 % of symptomatic HIV disease patients show cognitive disturbances as compared to 5-10 % of otherwise asymptomatic seropositive patients.

Studies have shown that - mild neurocognitive disorder is not always a forerunner of impending dementia. Cognitive disorder may have a static course throughout, but worsening of cognitive state within a period of six months usually has its termination in HIV- associated dementia. For details of HIV- associated dementia see the chapter on neurologic manifestations in HIV disease.

A timely psychiatric intervention in such case will help the patient to minimize suffering and also facilitate ongoing medical care.

12.8

CUTANEOUS COMPLICATIONS OF HIV DISEASE

Dr. Sunil Tolat

INTRODUCTION:

A wide array of dermatological manifestations encompassing malignancies [e.g. Kaposi's Sarcoma], a variety of bacterial, fungal, viral infections and several non-infectious disorders may be evident in an HIV infected patient.

Immunosuppression due to HIV results in infective skin diseases with either known pathogens or with the unknown exotic organisms. Most infections with the known pathogens present with altered, aggressive or florid clinical patterns.

Immune dysregulation related to HIV infection maybe responsible for several inflammatory skin diseases and may pave the way for malignancies like Kaposi's sarcoma.

Most cutaneous complications appear and worsen as HIV induced immunosuppression advances.

However certain cutaneous complications occur early in the disease and may be the only clinical manifestation of HIV infection. Such disorders should alert physician to the diagnosis of HIV infection.

CUTANEOUS COMPLICATIONS :

These are of two types

- I. Infectious
- II. Non-infectious

I. **Infectious:**

- Viral infections
- Bacterial infections
- Fungal infections
- Bacillary angiomatosis
- Mycobacterial infections
- Arthropod infestations

II. **Non-infectious:**

- Psoriasis
- Seborrhoeic dermatitis

Xeroderma
Papulo-pruritic eruptions
Eosinophilic pustular folliculitis
Interface dermatitis
Nail and hair changes
Adverse cutaneous drug reactions
Malignancies

VIRAL INFECTIONS:

Herpes zoster:

Commonest cutaneous manifestation encountered in HIV disease, occurring in 15-30% of HIV patients. May erupt early in the disease and be a presenting feature of HIV or may herald the onset of immunosuppression when occurring later in disease.

Clinically, the eruption is classically “multidermatomal” with haemorrhagic vesicles that leave behind necrotic ulceration and scars.

It may run a chronic course and may rarely be complicated by systemic dissemination.

Treatment : Aggressive treatment is recommended.

In more severe, disseminated cases:
Acyclovir 800mg 5 times/day X 10 days.
I/V Acyclovir 10mg/kg thrice/day.

Complications: Meningitis or encephalitis if systemic dissemination. Chronic verrucous hyperkeratotic nodules. Granulomatous lesions at the

site of eruptions (but rare).
Recurrences.
Severe post-herpetic neuralgia.

Herpes simplex [HSV-1 and HSV-2]

Ulcers are chronic and painful in HIV patients (versus the non immune-compromised host wherein vesicular eruptions or superficial erosions are common.)

Anogenital as well as cutaneous lesions have been recorded.
Perianal lesions are more frequent in homosexuals.

Recurrences become more frequent and lesions turn persistent as immunodeficiency progresses.

Vesicles and erosions may become confluent resulting in deep ulcers with necrotic margins.

Rarely atypical ulceration of face and tips of fingers [herpetic whitlow] may occur. It is supposed that, “any chronic painful ulcer in an HIV infected individual is due to HSV unless otherwise proved.”

Treatment: Acyclovir 200mg 5 times/day

I/V Foscarnet 40mg/kg every 8 hourly.

Molluscum contagiosum:

Mollusci are commonly encountered in HIV patients. Incidence increases by 18

fold in HIV patients. Lesions tend to be larger and widespread. Face and genitals are frequently involved.

Several large molluscii can become confluent to give a “cluster of grapes” appearance. Sometimes innumerable tiny lesions which are flat and confluent can appear in the beard area to give a “cobble-stone appearance” Giant molluscii can simulate furuncles or abscesses.

Cutaneous nodular lesions of cryptococcosis may be mistaken for molluscii.

Treatment : is difficult. Cryofreezing gives only temporary regression, with rapid recurrence.

Electrocautery under local or general anaesthesia may be tried.

Antiretroviral therapy may cause disappearance of lesions.

Viral warts: In most patients in whom immunodeficiency is moderate viral warts are usual in size, number and respond to routine treatment. However warts tend to become more numerous, larger in size and refractory to treatments as immunodeficiency advances.

Malignant changes with intraepithelial carcinoma and frank invasive squamous cell carcinoma can also occur.

a. Condyloma acuminata [genital warts] are strikingly voluminous, huge, foul smelling with, a high chance of malignant

degeneration within them. Perianal condylomata are seen in males having sex with man.

b. Extensive verruca plana [flat warts] can closely mimic pityriasis versicolor.

c. Verruca vulgaris [common warts] may be akin to lesions of epidermodysplasia verruciformis.

Treatment : Most warts are recalcitrant to treatment with electrocautery, cryosurgery, chemical cautery. Rapid recurrence is known to occur

BACTERIAL INFECTIONS :

Staphylococcus aureus infections are common in HIV disease. Multiple recurrent furunculosis [boils] is common and may be presenting feature of HIV disease.

Streptococcus pyogenes is responsible for ecthyma, impetigo and folliculitis. Lesions of ecthyma may be unusually deep and necrotic.

Secondary infection of other dermatoses like scabies, eczema, HSV ulceration is more frequent in HIV patients and is more aggressive, resulting in necrotic ulcerative lesions or deep abscesses.

Staphylococcal and streptococcal bacteraemia may be a complication of IV catheterization in HIV patients.

1. Syphilis,
2. Mycobacterial infections,

3. Giant aphthous stomatitis are other important bacterial infections associated with HIV disease.

These are discussed elsewhere in this book.

FUNGAL INFECTIONS :

The spectrum of fungal infections encompasses

1. Dermatophytosis
2. Candidiasis
3. Pityrosporum infections
4. Deep (Systemic) Fungal Infections

In patients with symptomatic HIV disease: cryptococcosis, histoplasmosis, sporotrichosis, candidiasis, coccidioidomycosis, actinomycosis, phaeohyphomycosis are reported. Cryptococcal skin lesions are seen commonly on the head and neck as pearly 2-5 mm translucent papules resembling mollusci. Cutaneous Histoplasmosis lesions are non-specific erythematous macules, papules or eczematous lesions. Diagnosis is by biopsy. Multiple cutaneous ulcers and sub cutaneous nodules of sporotrichosis are occasionally encountered.

Dermatophytosis

Over 1/3 of HIV patients have superficial infections with the ringworm fungi. The lesions may be unusually widespread, with surprisingly diminished inflammatory component.

Nail involvement is quite common and characteristically all the nails are rapidly infected. A "proximal onychomycosis" with whitish discolouration of proximal parts of the toenails is characteristic of HIV disease.

Fungal infections of face may be diffuse, scaly and erythematous and mimic seborrhoeic dermatitis.

Palms and soles may show a widespread involvement and may resemble psoriatic keratoderma with thickening and scaling.

Candidiasis

Hallmark of HIV infection.

Presents in all stages of disease.

Sites affected are : oral mucosa, genitalia, inter-trigenous areas.

Oral mucosal lesions are : whitish plaques, erosive lesions, or hypertrophic areas (see the chapter on oral manifestation).

In advanced disease oesophageal involvement may lead to dysphagia and retrosternal pain.

Chronic angular stomatitis is frequent.

Candidial paronychia with frequent secondary bacterial infections (pyonychia) is also common.

Treatment : Ketoconazole 200mg once a day or Fluconazole 150mg once/week.

Pityrosporum infections:

Pityriasis versicolor may present with a florid hypo / hyperpigmented scaly

macular eruption that is recalcitrant to routine topical therapy (selenium sulphide).

Recurrence is frequent even after oral ketoconazole therapy.

Pityrosporum folliculitis is a frequent occurrence presenting with a widespread eruption of itchy follicular pustules over back and arms.

The fungus is also known to play an important role in the pathogenesis of seborrhoeic dermatitis, which in turn is frequent in HIV patients.

BACILLARY ANGIOMATOSIS :

Causative organism is *Rochalimaea henselae* and *R. quintana*.

Disorder is quite rare among Indian HIV patients.

Clinically angioma like lesions may affect the skin, mucosa and internal organs.

Larger lesions may closely mimic Kaposi's Sarcoma.

Lesions may bleed when injured.

Complications:- Laryngeal obstruction-death. Disseminated intravascular coagulopathy due to increased vascularity of lesions and sequestration of platelets.

Treatment :- Treatment of choice is erythromycin 500mg four times a day, for several weeks to months.

MYCOBACTERIAL INFECTIONS:

Though pulmonary tuberculosis appears to be the commonest opportunistic

infection in HIV infected patients, cutaneous tuberculosis paradoxically, is rarely encountered.

However cutaneous lesions have been encountered with *M. marinum*, *M. avium intracellulare*.

M. marinum leads to ulcerative ecthyma like lesions.

M. avium intracellulare infection is characterised by chronic matted lymphadenopathy with ulceration of overlying skin.

BCG vaccination given in HIV patients may cause chronic ulceration locally and systemic disease, it is thus contraindicated in children suspected to be HIV infected and showing signs of immunosuppression.

ARTHROPOD INFESTATIONS:

1. Scabies
2. *Demodex folliculorum*

Scabies:

It may present atypically with only generalised pruritus without a rash.

This is a common early complaint in HIV disease. However after immunosuppression advances keratotic or Norwegian scabies may occur. Herein the patient is infested with millions of mites and clinically presents with extensive erythema and scaling.

The clinical picture may be easily confused with extensive seborrhoeic

dermatitis or psoriatic erythroderma, both of which are common in HIV disease.

Demodex folliculorum :

This infestation may present with an itchy follicular, papular eruption distributed over the back, head and neck.

Diagnosis : Microscopic demonstration of mite clinches the diagnosis.

Treatment: Treatment of both infestations is with application of gamma benzyl hexacholride (1%) lotion or Permethrin (5%) cream.

**N O N - I N F E C T I O U S
COMPLICATIONS:**

Psoriasis:

Though psoriasis and HIV infection show a strong association, an overall increased incidence of psoriasis has not been documented in HIV infected patients.

Commonly, pre-existing psoriasis may worsen with widespread guttate or plaque type lesions occurring.

Complications: Patient may land into dreaded complications like.

Generalised pustular psoriasis.

Psoriatic erythroderma.

Treatment: Response is poor with topical therapy using steroids, tar or diathranol.

PUVA and methotrexate are contraindicated as they can induce emergence of Kaposi's sarcoma and other opportunistic infections like tuberculosis.

Etretinate remains an useful treatment option (but for the cost and availability). Psoriatic lesions have been known to resolve after starting antiretroviral drugs.

Seborhoec dermatitis:

This is supposed to be "the" commonest dermatitis observed in HIV disease.

It may be the only sign of HIV infection early in the disease, but extensive dermatitis is usually associated with low CD4 counts of below 400 cells/mm³.

The dermatitis involves all hairy regions like, scalp, face, axillae and pubic area. The lesions are florid, with intense erythema and greasy adherent scaling.

Pathogenesis :- Florid growth of Pityrosporum ovale due to immunosuppression and also an altered reactivity to it.

Treatment :- Topical steroids or salicylic acid and coal tar creams.

But lesions are recalcitrant to treatment and may only respond somewhat to systemic ketoconazole therapy.

Xeroderma / ichthyosiform dermatosis:

It is characterised by dry, scaly, hyperpigmented lesions especially on extremities and trunk.

Usually encountered in advanced disease and may be related to diverse factors like -

- : malnutrition,
- : chronic illness,
- : poor hygiene,
- : arthropod infestations.

Treatment :- is with liberal applications of emollients like- vaseline or sweet oil. or with topical steroids if inflamed and itchy lesions are present.

Papulopruritic eruption:

It is an eruption of tiny, flesh coloured, itchy papules on neck and trunk.

It is distinct from :Acneiform eruptions, :Pityrosporum folliculitis, Bacterial folliculitis.

Though the cause is unclear, it may be a reaction pattern to an internal focus of infection.

Treatment: Antibiotics, Anti-histaminics, Topical steroids. (All proved not very effective).

PUVA therapy may be given cautiously.

Eosinophilic pustular folliculitis:

This is a form of chronic, pruritic, pustular eruption. Lesions are sterile Urticarial lesions and papules may also be present.

Histopathology reveals an eosinophilic infiltrate around hair follicles.

Treatment : Treatment with antibiotic is futile. Lesions may somewhat respond to UVB therapy.

Interface dermatitis:

This is basically a histologic entity with varied clinical features.

The diagnostic pathological feature is degeneration and necrosis of basal keratinocytes with a dense infiltrate of inflammatory cells at the dermo-epidermal junction.

Clinically, it may present with a maculopapular rash, erythema with blisters, erythema multiforme type target lesions.

Treatment: Treatment with most modalities is unsatisfactory.

NAILS AND HAIR CHANGES:

Nails : A yellowish discoloration of nails especially in HIV patients with Pneumocystis carinii pneumonia has been observed.

Hairs : Thinning of scalp hairs with alopecia is very common in HIV infection. Interestingly, hypertrichosis with elongation of eyelashes has also been observed.

ADVERSE CUTANEOUS DRUG REACTION:

The incidence of adverse cutaneous drug reactions is very high in HIV disease. The multiplicity of drugs being used,

concomitant viral infections (EBV/CMV) and immune dysregulation may be major pathogenetic factors.

1. Antitubercular drugs.

Since pulmonary tuberculosis is commonest opportunistic infection in Indian HIV patients, reactions to ATT are commonly encountered. Severe reactions like, Steven-Johnson syndrome (SJ Syndrome), Toxic Epidermal Necrolysis may occur either to individual drug or their combinations.

A maculopapular rash and acneiform eruption are also commonly encountered in patients on ATT with HIV.

2. Trimethoprim and sulfamethoxazole (TMP-SMX) and other sulfonamides.

TMP-SMX and sulfadoxine-pyrimethamine remain the drugs of choice for prophylaxis. Reactions ranging from maculo-papular rashes to fixed drug eruptions and SJ syndrome have been frequently reported to these drugs.

3. Antiretroviral drugs:

Hyperpigmentation of skin and nails, hypertrichosis with increased length of eyelashes has been reported especially with zidovudine.

KAPOSI'S SARCOMA IN AIDS.

Overall incidence of Kaposi's sarcoma in AIDS is about 35%.

Usually it occurs in homosexual men. It is quite rare in Indian and Asian HIV patients.

Kaposi's sarcoma is a neoplasm of vascular endothelium.

The usual clinical presentation is with blue red or dark brown plaques and nodules especially on the lower extremities. Vascular lesions in the lymph nodes and other visceral organs may also occur.

The lesions of Kaposi's sarcoma in AIDS patient may differ from the classical picture in that they are smaller in size, extensive in distribution, rapid in progression, oral lesions are frequent and visceral involvement of gastrointestinal tract, lymph nodes and lungs is more common.

Treatment: Usually not curative, Indicated only for large troublesome lesions. Surgery, Radiotherapy, Chemotherapy with vincristine, vinblastin and bleomycin are the treatment options.

ACUTE RETROVIRAL SYNDROME [SERO-CONVERSION ILLNESS]

In majority of persons primary infection with HIV is asymptomatic and thus escapes diagnosis. However a constellation of signs and symptoms may occur in some patients soon after infection and herald seroconversion.

Symptoms of “seroconversion” illness include : fever, rigors, myalgia, sore throat, headache, neck stiffness etc. which are akin to influenza or other viral illnesses.

The cutaneous lesions may appear during this early phase and are akin to viral exanthema. They are coppery red, macular or papulosquamous lesions, mainly on the upper trunk, palms and soles. Oral lesions may also occur.

Only a high index of suspicion may alert the clinician to diagnosis. ELISA test maybe negative in this stage and diagnosis has to be confirmed either by HIV isolation from blood or CSF; or by tests for P24 antigenemia.

**DIFFERENTIAL DIAGNOSIS OF SKIN LESIONS OCCURRING
IN HIV DISEASE**

TYPE	DIAGNOSIS
Papules, Nodules	Staphylococcal abscess, furunculosis, verrucae, bacillary angiomatosis, molluscum contagiosum, Kaposi's sarcoma, cryptococcosis, squamous /basal cell carcinoma.
Crusted Papule, Nodule	Impetigo, ecthyma, herpes simplex ulcer, Kaposi's sarcoma.
Vesicles, bullae, pustules	Bullous impetigo, drug reactions, herpes simplex, herpes zoster, pustular psoriasis, erythema multiforme.
Acneiform	Acne vulgaris, drug rash (INH), rosacea, papular eruption of AIDS.
Folliculitis	Staph. aureus, Pityrosporum ovale, eosinophilic folliculitis, pustular eruption of AIDS, Demodex folliculitis.
Psoriasiform	Psoriasis, seborrhoeic dermatitis, drug rash, secondary syphilis, pityriasis versicolor, dermatophytosis, scabies.
Eczematous lesions Urticarial lesions	Seborrhoeic dermatitis, atopic dermatitis, scabies. Drug reaction.
Morbilliform eruption	Acute seroconversion illness, drug rash, CMV, histoplasmosis, etc and other exanthems.
Purpuric Erosions/Ulcers	Thrombocytopenic purpura, vasculitis, drug rash. HSV, herpes zoster, CMV, ecthyma, fixed drug eruption, malignant syphilis, lupus vulgaris.
Generalized Pruritus	Scabies, drug rash, atopic dermatitis, HIV associated pruritus, seroconversion illness.

12.9

SEXUALLY TRANSMITTED DISEASES

Dr. Rajiv Sule

INTRODUCTION:

These are diseases that are commonly acquired by sexual contact but this may not be the only route of transmission in all the cases.

The major STDs are :

- Syphilis
- Gonorrhoea
- Chancroid
- Donovanosis (Granuloma Inguinale)
- Lymphogranuloma venereum.

Other STDs are :

- Herpes simplex (herpes genitalis)
- Condyloma accuminata (warts)
- Gardnerella vaginalis vaginitis
- Chlamydia infection
- Mycoplasma infection
- Candidiasis
- Trichomoniasis
- Hepatitis B

Scabies

Pubic louse

Molluscum contagiosum

HIV infection.

Same risk behaviour pattern i.e. multi-partner unprotected sex, leads to acquisition of STDs and HIV. Additionally individuals having STDs have manifold increased risk of acquiring HIV infection. Presence of genital ulcerative diseases like syphilis, chancroid, herpes genitalis increases susceptibility to HIV infection by at least 10 times. Raw surface area and active lymphocytes at the base of ulcers are easy targets for HIV. STDs like gonorrhoea, causing genital discharge increase the risk by 4 times, due to inflamed mucosa. Considering these facts WHO has highlighted the importance of STD control in AIDS prevention programmes. Early diagnosis and prompt treatment of STDs can greatly help to prevent transmission of HIV infection. Presence of underlying HIV infection modifies clinical

presentation of STDs. In general, they tend to be more severe, invasive and recalcitrant to routine treatment.

STDs CAUSED BY BACTERIA

Gonorrhoea:

It is exclusively acquired by sexual contact and is caused by Gram negative intracellular diplococci *Neisseria gonorrhoeae*.

Clinical manifestations : Incubation period in males is 2 to 5 days. In females incubation period is difficult to calculate as they may get asymptomatic infection. In males gonorrhoea presents with thick, purulent profuse discharge from urethra due to urethritis. Complications like posterior urethritis, prostatitis, cystitis, epididymo-orchitis can occur if not treated. Urethral strictures and urethral fistulae may be seen. In females it leads to cervicitis and urethritis, which is asymptomatic most of the times. Complications like salphingo-oopheritis leading to tubo-ovarian mass and pelvic inflammatory disease(PID) are common.

Rarely gonorrhoea may present as pharyngitis or proctitis in both sexes. Complications like disseminated gonococcal infection are rarely seen. In infants ophthalmia neonatorum and in children vulvovaginitis can occur due to gonococcal infection.

Diagnosis: In males clinical picture is diagnostic. Gram staining of the smear of urethral discharge showing classical

Gram negative intracellular diplococci can confirm diagnosis. Culture on Thayer Martin medium or modified New York city medium and antibiotic sensitivity test is important if one is suspecting drug resistant strains like penicillinase producing *Neisseria gonorrhoeae* (PPNG).

Treatment for gonorrhoea: Single dose regimens are preferred because this ensures patient compliance.

- i) Inj. Procaine penicillin 4.8 mega units I/M (after skin testing), divided into two buttocks, along with 1 gm of probenesid orally.
- ii) Tab Norfloxacin 800gm orally (some prefer Norfloxacin 800mg/day X 3days or Ciprofloxacin 250mg bid for 2days).
- iii) Cap Azithromycin 1000 mg orally

Resistant gonorrhoea (PPNG strains)

- i) Inj Kanamycin 2gm I/M
- ii) Inj Ceftriaxone 0.25 or 0.5gm I/M
- iii) Inj Cefuroxime 1.5gm I/M
- iv) Rifampicin (900gm) orally

In case of complications like pharyngitis, proctitis, PID-give additionally Cap Ampicillin 2gm orally in 4 divided doses daily for 14 days.

Disseminated gonococcal infection is treated with crystalline penicillin 2-4 MU IV 6 hourly for 7 to 10 days.

Sometimes one has to treat concomitant non-gonococcal urethritis with tetracycline and metronidazole.

Non-gonococcal urethritis (NGU):

Any urethritis not caused by gonococci is NGU. Common causes are Chlamydia trachomatis and mycoplasma (ureaplasma urealyticum). Other organisms like herpes simplex virus and E. coli, Proteus, Klebsiella, trichomonas, candida occasionally cause urethritis.

Clinically the symptoms of burning micturition are associated with scanty mucoid or mucopurulent urethral discharge. Urine examination would show increased pus cells. Treatment consists of oral tetracycline 500mg QID or erythromycin (500) QID. Addition of metronidazole (200mg TDS X 7 days) will provide additional coverage.

Syphilis:

Syphilis is caused by very slender spiral organisms (spirochetes) called Treponema pallidum. Once a wide-spread disease, it was gradually eliminated with the advent of antibiotics. With HIV epidemic syphilis has recurred and is also seen occasionally in with severe, destructive forms.

Clinical manifestations : -

Primary stage: After incubation period of approximately three weeks (range : 9 to 90 days) the classical primary chancre develops. It's a clean ulcer with punched out edges and indurated base. Primary chancre is non tender and is associated with bilateral firm, shotty, discrete non-tender inguinal lymph nodes. Usually a single ulcer is seen but occasionally there could be multiple ulcers. It could be present at extragenital sites like oral cavity, anus, fingers tips. Rarely primary chancre can be very superficial and erosive. Left untreated primary chancre heals on its own leaving papery scar.

Secondary stage: After 6 to 12 weeks the secondary stage ensues. In this stage erythematous or coppery red, macular, papular, papulosquamous, pustular, annular rash erupts on body. There is generalised lymphadenopathy associated with mild fever, malaise and arthralgia. The rash is symmetrical, non-pruritic with a tendency to affect flexor aspects of the body. Palms/soles, flexures, mucosae are preferentially affected. Papular lesions on palms that are tender on pressure are diagnostic. The enlarged lymph nodes are non-tender, discrete and firm. Flat topped, moist papules appear around anus and vulva, called condyloma lata, and are diagnostic. On buccal mucosa whitish patches are seen leading to serpiginous ulcers. Rarely cranial nerve palsies may be associated. If associated with HIV infection severe nodulo-ulcerative form of secondary

syphilis, known as malignant syphilide, can be seen.

Left untreated secondary syphilis lesions heal without scarring, after a variable interval of 2-6 weeks.

Latent stage: In this stage patient is asymptomatic and can be diagnosed only by serological tests. According to whether the infection was acquired two years or before, it is called early latent or later latent syphilis.

Tertiary stage: Benign tertiary syphilis presents as mucocutaneous gummata involving skin and bones in about $\frac{1}{3}$ rd of patients. In the remaining serious complications like cardiovascular syphilis and neurosyphilis are seen. They had become a rarity with the advent of antibiotics, but now in association with HIV infection neurosyphilis can occur at earlier age, with atypical forms.

Congenital syphilis: Syphilis in mother can cause second trimester abortion, still born child or child with congenital syphilis in subsequent pregnancies. Congenital syphilitic infants have nasal snuffles (rhinorrhoea like discharge), bullous rash on palms, all surfaces, soles and also on mucous and body tenderness. There may be generalised lymphadeno-pathy, hepatosplenomegaly, fever. It may cause lifelong Syphilitic stigmata (Hutchinson's teeth, mulberry molars, rhagades etc.).

Diagnosis: At primary stage classical ulcer is clinically diagnostic. Diagnosis

can be confirmed by a microscopy test called dark ground illumination (DGI) to detect treponemes. In fact DGI test should be done in all genital ulcers irrespective of diagnosis but is not very readily available. Tests like VDRL become positive one to two weeks after appearance of chancre. VDRL titres 1:16 and above are always indicative of active syphilitic infection. In secondary stage, VDRL is always reactive with 1:16 or more dilution. In latent and tertiary syphilis VDRL may become non-reactive but specific tests like TPHA (Treponema pallidum haemagglutination assay) and FTA-ABS test (fluorescent treponemal antibody absorption test) remain reactive. CSF examination is required to diagnose neurosyphilis and should be performed in all HIV infected individuals having syphilis.

Treatment of Syphilis: Penicillin remains the drug of choice.

A) In the first 2 years of infection, (i.e.- in early syphilis or in early latent syphilis)

- Procaine penicillin 8 lac IU MOD (after test dose) for 10 days.

OR

- A single dose of benzathine penicillin 2.4 MU IM (after test dose) divided, half in each buttock.

In HIV positive cases, especially in those with immunodeficiency - Inj. Procaine penicillin 24 lac IU IM OD (after test dose) for 14 days. OR crystalline penicillin 3g QID IV for

10 days may be used. Benzathine penicillin is not advisable, but if compliance is not assured then 2.4 MU IM after test dose, once every week for 3 weeks.

In late syphilis (late latent, benign tertiary, cardio- and neurosyphilis): Whenever possible crystalline penicillin 40 lac IU IV for 14 days, every 4 hours. Alternatively procaine penicillin 8 lac IU OD X 14-21 days. If CSF examination is normal Inj. Benzathine penicillin 2.4 MU IM every week for 3 consecutive weeks may be used.

In HIV positive cases crystalline penicillin 20-40 lac IU IV 4 hourly, preferably with probenecid, for 14 days is necessary.

Alternatively, Inj. Procaine penicillin 24 lac IU IM OD for 14 days.

Antibiotics other than penicillin should only be used for patients with proven penicillin hypersensitivity. Erythromycin or tetracycline (500mg) QDS for 30 days, Ceftriaxone 500mg IM OD for 10-14 days or Cephalexin 500mg QID orally for 2-4 weeks can also be used.

Therapy of syphilis during pregnancy: Drugs other than penicillin are either contraindicated or poorly penetrate the placenta (erythromycin). Benzathine penicillin, too, does not cross placenta very well. So if these drugs are used, one must treat the baby at birth.

Chancroid (soft sore, soft chancre):

Chancroid or soft sore is caused by gram negative bacillus *Hemophilus ducreyi*.

Clinical manifestations: After an incubation period of 2 to 7 days patient develops multiple, superficial ulcers that are extremely tender. Their floor shows dirty granulation tissue, with foul smelling discharge and is associated with red, tender inguinal bubo. If left untreated bubo will burst open forming giant chancroid. Phimosis is a known complication. Destructive phagedenic ulcers occur because of secondary infection.

Diagnosis: Gram staining shows classical rail track arrangement of *Hemophilus ducreyi*. Culture is very difficult to obtain. Diagnosis depends on clinical picture and exclusion of other pathologies like syphilis and herpes.

Treatment : Azithromycin 1 gm orally as a single dose has been recommended. Erythromycin 2 gm daily orally in divided doses for 7 to 14 days can be given. Cotrimoxazole 2 tablets twice daily for or tetracycline 500mg QDS 1-2 weeks may be used. It is important to note that bubo should never be incised but should be aspirated (when fluctuant) from a non-dependant site. Ensuring good hygiene by frequent washes with a mild antiseptic solution is a must.

Gardnerella vaginalis vaginitis :

The main symptom of Gardnerella vaginalis vaginitis is a smelly vaginal discharge that is grey coloured and has the consistency of thin flour paste. Little inflammation occurs, so few women complain of itchiness or soreness. The fishy smell increases when semen is mixed with the discharge.

Gardnerella vaginalis (previously known as Hemophilus vaginalis and Corynebacterium vaginale) are small rod-shaped bacteria which, when present in large numbers, cause symptoms. They can be present for long periods without causing symptoms and in small numbers are considered part of the normal vaginal flora. They probably interact with other anaerobic bacteria to create the infection.

The incubation period is about 5-10 days during which the Gardnerella bacteria replace the normal Lactobacillus bacteria in the vagina.

Under the microscope the secretions contain few Lactobacilli but many "clue cells" these are vaginal cells with bacteria clinging to them. Gardnerella vaginalis can also be seen on a Gram stain and cultured in the laboratory.

Treatment: Treatment is instituted only if the woman finds the discharge unpleasant. The recommended treatment is metronidazole 500 mg twice a day for 7 days. Recently single dose treatment with 2 gram metronidazole has been

found almost as successful. An alternative treatment is ampicillin 500 mg 4 times a day for 5-7 days.

Donovanosis (Grunuloma inguinale)

This is caused by a Gram negative coccobacillus called *Calymmatobacterium granulomatis*.

Clinical manifestations: Incubation period varies between 3 weeks to 3 months. It is followed by an indurated papule which bursts open to form a typical ulcer with elevated edges and a beefy red, exuberant granulation tissue. If left untreated this ulcer goes on spreading by contiguity but lymphatics are not involved. Fibrosis and destruction of local tissue leads to oedema and complications like esthiomene in females and chancre in males. Long standing ulcers may undergo malignant transformation.

Diagnosis: Most of the times clinical presentation is diagnostic. Tissue smear from ulcer and staining with Giemsa or Wright's stain shows intracellular organisms with classical safety pin appearance.

Treatment: Inj. Streptomycin 1 gm IM daily for 20 days is drug of choice. Tab cotrimoxazole (double strength) given twice a day orally for 14 days, Erythromycin (500mg) QDS, Tetracycline (500) QDS given for 2-3 weeks are also useful. Clindamycin, minocycline, pefloxacin and azithromycin are also effective.

DISEASES CAUSED BY CHLAMYDIA :

Lymphogranuloma venereum (LGV):

This is caused by organism *Chlamydia trachomatis*. Urethritis caused by chlamydia has already been discussed.

Clinical manifestations: After 5 to 10 days of incubation period the patient develops a very superficial, transient ulcer on genitals. After about a month patient develops inguinal swelling on both sides of inguinal ligament that forms the classical 'groove sign.' This bubo bursts open giving rise to multiple sinuses. It is associated with fever, anorexia, weight loss. Late complication is proctitis leading to perianal and urethral fistulae.

Diagnosis: Usually clinical.

Treatment: Tetracycline 2gm orally daily in divided doses for 2 to 4 weeks is recommended. Cotrimoxazole orally can also be given. Pregnant women may be treated with erythromycin. Bubs need to be aspirated with wide bore needles and from non-dependent site.

DISEASES CAUSED BY VIRUSES

Apart from HIV infection other sexually transmitted diseases caused by viruses are genital warts, molluscum contagiosum, genital herpes, hepatitis B.

Genital warts (condyloma accuminata)

The causative organism is human papilloma virus (HPV).

Clinical manifestations: Incubation period on an average is 3 weeks but can be as long as 1 year. This is followed by fleshy, papular lesions on genitals that grow to become cauliflower like. Perianal area may be involved. In females vulva, vagina, cervix are involved and condylomata may become exuberant during pregnancy. Infected mother can transmit HPV to new born child during labour causing laryngeal papillomatosis.

Treatment: Podophylline 25% in tincture of benzoin is applied locally every week till lesions disappear. Cryosurgery is done in extensive lesions and in pregnant women.

Recurrences are common.

Molluscum contagiosum:

This is caused by a pox virus.

Clinical manifestations : Small pearly white, umbilicated papules appear on genitals 2 weeks to 3 months after skin to skin contact. In case of HIV infection numerous widespread papules may be found all over body. They may be much larger in size.

Treatment : Molluscum is treated by removing the molluscum body by sterile needle and cauterising the lesion by

carbolic acid. Cryosurgery, electrosurgery may be needed sometimes.

Herpes Genitalis:

This is caused by herpes simplex virus, HSV-2 most often and occasionally by HSV-1.

Clinical manifestations: In primary infection, 2 to 5 days after sexual contact group of vesicles appear on genitals. They readily break forming superficial ulcers. Tender inguinal lymphadenopathy, malaise, low-grade fever is common. Though lesions heal within 2 to 3 weeks recurrent lesions do appear. Sexual intercourse, sun exposure, menstruation, physical and mental stress are precipitating factors for such recurrences. Because of recurrent nature of disease patients may develop psychological problems like depression, impotence etc. Immunodeficiency due to HIV is an important cause of increased frequency of recurrences. Also, then the lesions tend to be more chronic and more destructive.

Treatment: In primary attack and in immunocompromised patients acyclovir 200mg, 5 times a day, orally for 5 days is the treatment of choice. Recurrent attacks need counselling and psychological support along with early treatment with acyclovir. This helps to reduce morbidity. Oral acyclovir 200 gm three times a day can be given indefinitely to prevent relapses.

DISEASES TRANSMITTED BY FUNGI AND PROTOZOA:

Candidiasis:

This is an opportunistic infection caused by *Candida albicans* and other candida species. In females thick, white, curd like discharge is seen. Predisposing factors are pregnancy, oral contraceptives, treatment with broad-spectrum antibiotics, diabetes mellitus. In males candidiasis leads to balanoposthitis. Extensive oral candidiasis is an important marker of HIV disease, as is recurrent candidial vaginitis.

Treatment: Fluconazole 150mg single dose orally gives better compliance. Vaginal clotrimazole pessaries inserted for 6 days is also a good alternative. Both partners need to be treated. Oral candidiasis in AIDS requires long-term prophylaxis.

Trichomoniasis:

Causative organism is protozoon *Trichomonas vaginalis*.

Clinical manifestations: It commonly causes pruritic discharge per vagina. In males can cause urethritis. Trichomoniasis can be confirmed by observation of hanging drop preparation of the discharge under microscope.

Treatment : Both partners are treated simultaneously with Metronidazole 200mg three times a day for 7 days. Secnidazole 2gm orally as a single dose is also effective.

DISEASES TRANSMITTED BY ECTOPARASITES

Scabies:

It can also be transmitted sexually and is caused by a mite *Sarcoptes scabiei*.

Clinical manifestations: Incubation period is variable. Extremely pruritic lesions appear on genitals, thighs, lower abdomen, gluteal folds. Interdigital webspaces are commonly involved where burrows are seen. Pruritus is more at night. Scabies is very commonly secondarily infected. In AIDS patients severe generalised form of scabies called Norwegian scabies can occur.

Treatment: Gamma benzene hexachloride 1% lotion is applied all over the body below neck and kept for 12 hrs. Application is repeated after one week.

Maintaining good hygiene is important, as is treating all family members simultaneously. Permethrin 5% in cream base is also effective, as is 25% benzyl benzoate.

Pediculosis:

Causative organism is body louse called *Pediculus corporis (hominis)* and pubic louse called *Pthirus pubis*.

Clinical manifestations : Involves hairy areas of genitals and spreads to other hairy areas. Pruritus is common and secondary infection occurs frequently.

Treatment: Gamma benzene hexachloride 1% lotion applied overnight on hairy areas and repeated after one week or Permethrin 1% shampoo is also effective in treating pediculosis.

HEALTH EDUCATION-ESSENTIAL FOR THE PREVENTION OF STD

INTRODUCTION

Now it has become more than ever important to explore the strategies for the prevention of STDs. A patient with a STD may have already acquired HIV infection, or may get infected in the future if the risk behaviour continues. Therefore, treatment alone is not sufficient, and health education to prevent sexually transmitted infections is of paramount importance. This will entail discussions on sex and sexuality between doctor and patient, between

parents and children and between teachers and students.

Communicating about STDs is extremely difficult. It involves discussing sexual practices, a topic many people in many cultures would rather prefer to be left alone, and bringing communication to a very personal level. In order to prevent STDs and the spread of HIV infection, it is necessary for individuals to change their behaviour, which many mean choosing not to have many partners, or to use condoms.

Social aspects

STDs have been in existence for centuries. The most important risk factor for contracting a STD is having many sexual partners, or having as partner who has many sexual partners. Although anyone can get a STD, certain groups of individuals are more prone, due to their lifestyle and social or economic circumstances. These people might include :

- Migrant workers who live away from their families;
- Men who travel frequently as a part of their work;
- Those who have to resort to commercial sex as a means of livelihood;
- Armed forces or police personnel who are posted away from their families.

The living conditions of many people expose them to behaviour options that place them at increased risk of contracting a STD.

Although abstinence or mutually faithful relationship with one lifelong partner are very effective in preventing STDs. It is obvious that the sexual networking of our society is very complex. Multiple partner sex is not at all uncommon in our society. For health education approaches to work, the approach must be more practical. Behaviour change is not at all a very easy process and sustained educational efforts are urgently required. As the behaviour of adults is more difficult to modify, we must

concentrate on the adolescents and the youth that form the highest risk group as far as STDs are concerned. However, they may be convinced to use condoms and seek proper treatment for their STDs. In the era of AIDS, practical messages and approaches are essential.

Health education and counselling to STD patients

Every time a physician sees a patient with a STD, or with a suspected STD, it is an opportunity for health education and individual counselling. Health education and counselling should focus on the following messages:

- a. Treatment compliance.** For the treatment to be successful it is important that the complete course of treatment is taken, even if the patient feels improvement after a few days. Incomplete treatment might lead to chronic infection, with potential serious long-term consequences. It will also lead to emergence of resistant strains of the pathogens.
- b. Partner notification.** The patient was infected by a sexual partner and/or may have infected another partner. These people are at a risk of being infected. Partners of STD patients should therefore be medically examined and treated if found infected, simultaneously.
- c. Prevention of future infection.** Advice should be given to prevent future infections. This

includes recommendations on reduction of the number of sexual partners and on the consistent use of condoms. Wherever possible condoms should be dispensed to the patient. Clear and simple instructions on condom use should be provided. A condom demonstration might be required.

d. Health care seeking behaviour.

The patient should be advised to return if the symptoms do not disappear, and to seek adequate health care for any future episodes of STD.

It is often necessary to include basic information on the facts that STDs are spread through sexual contact, many STDs are asymptomatic (so it is often not possible to know whether a sex partner is infected), and most STDs are curable, with the exception of HIV infection and other viral infections. The long-term health consequences of chronic STDs should be emphasised.

It will often not be possible for the treating physician to spend adequate time with each patient for health education and counselling. Health education and counselling can be done by properly trained counsellors. Still, the treating physician usually commands respect from the individual and the community. Their message has often great impact. So, even if little time is available, the physician should try to reinforce the health education and counselling messages.

One of the most important aspects of management of patients with STDs, and of health education and counselling for STDs patients, is a sympathetic and non-judgmental attitude. Moralistic messages and a condemning attitude of health care workers are counterproductive, and will drive patients away. Essential are privacy and confidentiality, and an atmosphere of professionalism, where STDs are treated as any other disease. This will in turn contribute to controlling STDs, including HIV.

CONDOM INSTRUCTIONS

1. Carefully open the package so the condom does not tear. Do not unroll condom before putting it on. The condom should be put on the erect penis right from the beginning.
2. If not circumcised, pull foreskin back. Squeeze the tip of the condom and put it on the end of the erect penis.
3. Continue unrolling the condom till it covers the entire penis.
4. Always put the condom on before entering partner.
5. After ejaculation (coming), hold rim of condom and pull penis out before it loses the erection.
6. Throw away or bury the condom after tying a knot on the condom.

Remember :

- Do not use grease, oils, lotions or petroleum jelly (Vaseline)

lubricate the condom. These make the latex condoms break. Only use a water-based jelly or cream that does not have oil in it.

- Use a new condom each time you have sex.
- Use a condom only once.
- Store condoms in a cool, dry place.

- Do not use condoms that may be old or damaged.

Do not use a condom if :

- the package is broken and past the expiry date
- the condom is brittle or dried out
- the colour is uneven or changed
- it is unusually sticky.

SIMPLIFIED STDs TREATMENT GUIDELINES

INTRODUCTION:

The treatment regimens recommended are all deemed to be effective in the Indian context. However, in view of studies conducted in the country, some of the recommended treatments might be less effective in some situations and careful monitoring of treatment efficiency should be done wherever possible.

A choice has been made for the most simple and shortest treatment, while still being highly effective. For instance, a single dose oral treatment is preferable over a multi-day treatment; and oral treatment is preferable over intramuscular treatment.

The order in which the treatment regimens are placed indicates an order of preference: the first listed treatment is the treatment of choice.

SYNDROMIC APPROACH

Most STD patients consult a doctor or health care provider with complaints related to one of the following syndromes :

1. urethral discharge
2. vaginal discharge
3. genital ulcer
4. inguinal swelling
5. lower abdominal pain

Different pathogens can cause the same syndrome, while there is often co-infection by more than one organism. It is usually impossible to make a reliable etiological diagnosis on clinical grounds only, but laboratory support to confirm a clinical diagnosis is not available for the majority of the STD patients in the country.

Following the syndromic approach, combined treatment is prescribed for all

pathogens that are commonly found to be causing a syndrome. For instance, as urethral discharge is most commonly caused by either *N. gonorrhoeae*, *C. trachomatis*, or *U. urealyticum*, treatment for male patients with this complaint would be for both gonococcal and non-gonococcal urethritis.

The flowcharts will assist in the decision making process, by showing which steps are taken to arrive at a treatment recommendation.

Recurrent or persistent symptoms

Recurrent or persistent symptoms can be due to poor compliance with treatment, to infection with resistant strains of pathogens, or to reinfection. Where symptoms persist or recur after adequate treatment of both the patient and his/her partner, they should be referred for laboratory investigations.

S Y N D R O M E - B A S E D TREATMENT GUIDELINES

1. Urethral discharge

Male patients complaining of urethral discharge and/or dysuria should be examined for evidence of discharge. If none is seen, the urethra should be gently massaged from the ventral part of the penis towards the meatus.

Urethral discharge is usually due to gonococcal or non-gonococcal urethritis. Unless gonorrhoea can be definitely excluded by laboratory test (negative Gram-stain), the treatment should be for

both causes.

Recommended treatment :

Norfloxacin 800 mgm in a single dose orally

and

Doxycycline 100 mgm orally twice daily for 10 days

In case of treatment failure, re-treat with:

Spectinomycin 2 gm I. M. stat

Persistent and recurrent symptoms

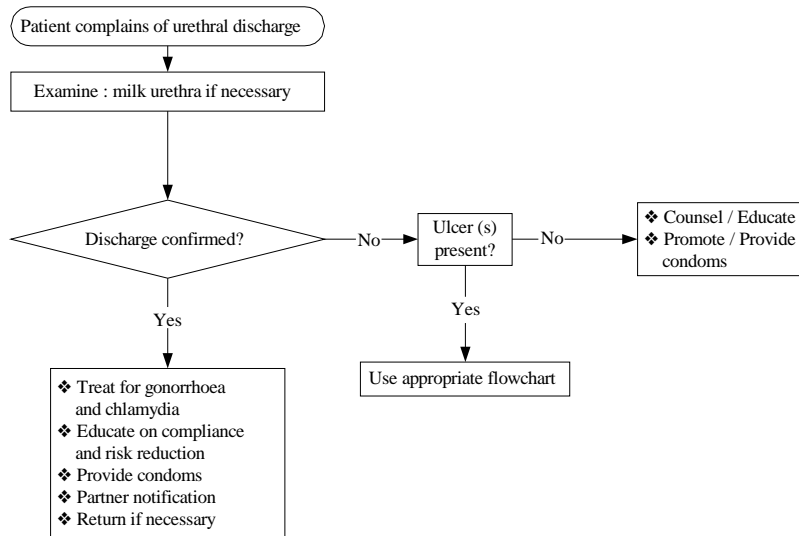
Recurrent or persistent symptoms may be due to poor compliance, reinfection or infection with a resistant strain of *N. gonorrhoeae*, or infection with *T. vaginalis*. Where symptoms persist or recur after adequate treatment of both patient and partner(s), they should be referred for laboratory investigation.

Investigation should include a Gram stain to confirm the presence of urethritis and to look for *N. gonorrhoeae*. Urethritis is defined as the presence of >5 polymorphonuclear leukocytes/1000x field in areas of maximum cellular concentration. *T. vaginalis* may be identified by microscopy of first-voided urine sample, although the sensitivity of this test is fairly low as compared to culture. If presence of *T. vaginalis* is confirmed, metronidazole 2 gm should be given as a single oral dose.

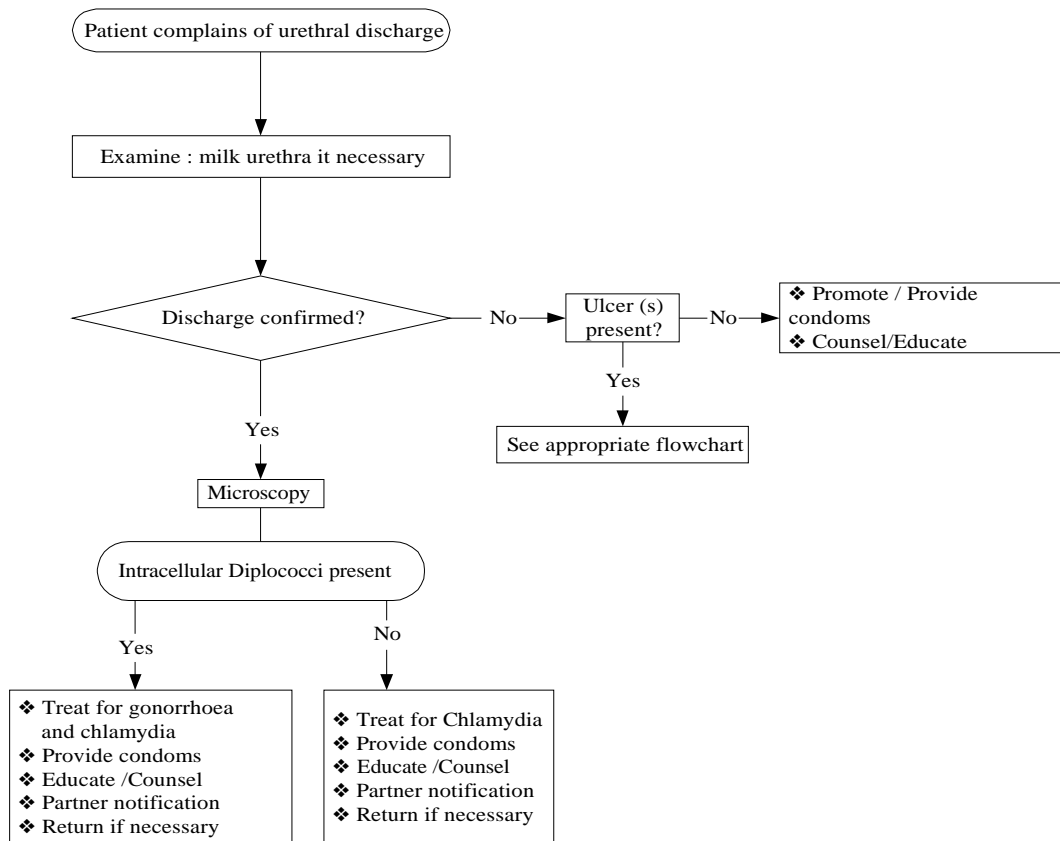
2. Vaginal discharge

Vaginal discharge can be due to either a cervical discharge, such as caused by

Flow Chart for Urethral Discharge



Flow Chart for Urethral Discharge with Microscope



gonococcal or non-gonococcal cervicitis, or can be due to a vaginitis. The latter can be due to Trichomoniasis, Candidiasis or Bacterial Vaginosis. Cervicitis and vaginitis can occur together, and a speculum examination is essential to distinguish between these two. Where no speculum examination is possible, the patient should at least be asked if her partner is symptomatic. If so, then treatment should be given for both cervicitis and vaginitis. If he is not symptomatic, then treatment for only vaginitis should be given.

2a. Cervical discharge on speculum examination

Recommended treatment (non-pregnant women):

Norfloxacin 800 mgm in a single dose orally

and

Doxycycline 100 mgm orally twice daily for 10 days

In case of pregnancy :

Norfloxacin 800 mgm in a single dose orally

and

Erythromycin stearate 500 mgm orally four times day for 7 days

2b. Vaginal discharge on speculum examination

Recommended treatment :

Metronidazole 200 mgm three times a day for 7 days

and

Miconazole 100 mgm intravaginally once daily for 6 days

During the first trimester of pregnancy no Metronidazole must be given, and treatment is by Miconazole only.

The flowcharts can be used, depending on the availability of speculum examination :

3. Genital ulcer

Genital ulcer can be caused by syphilis, chancroid, lymphogranuloma venereum or granuloma inguinale. In addition to these genital ulcers can be caused by genital herpes infections. The treatment recommended below will cure all ulcers, except those caused by herpes.

Recommended treatment (non-pregnant patients) :

Benzathine benzyl penicillin 2.4 Mega Units I. M. in a single dose

and

Doxycycline 100 mgm orally twice daily for 15 days

Pregnant patients :

Benzathine benzyl penicillin 2.4 Mega Units I. M. in a single dose

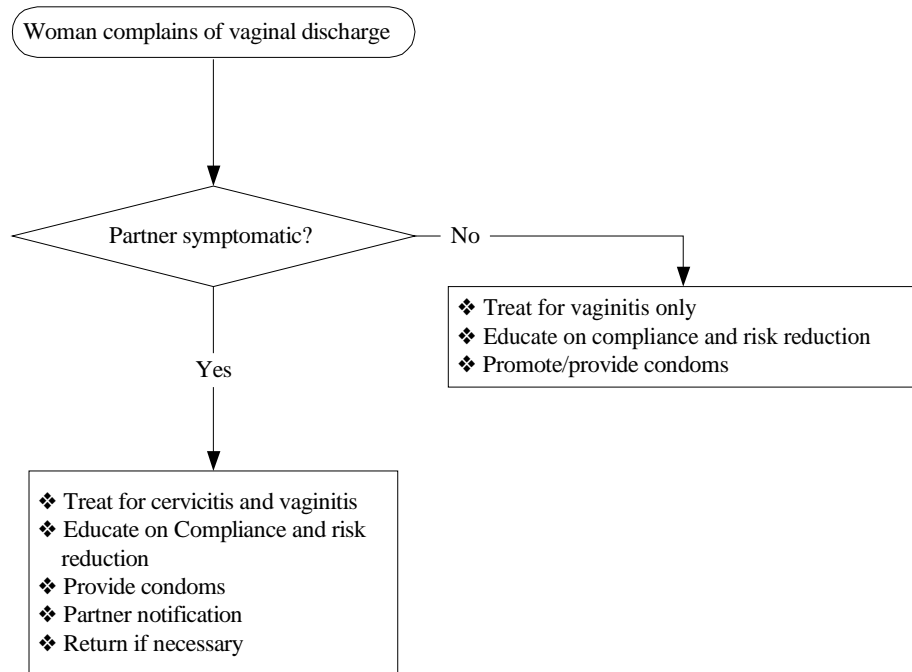
and

Trimethoprim (80 mgm)/ Sulphamethoxazole (400 mgm) 2 tabs twice daily for 15 days

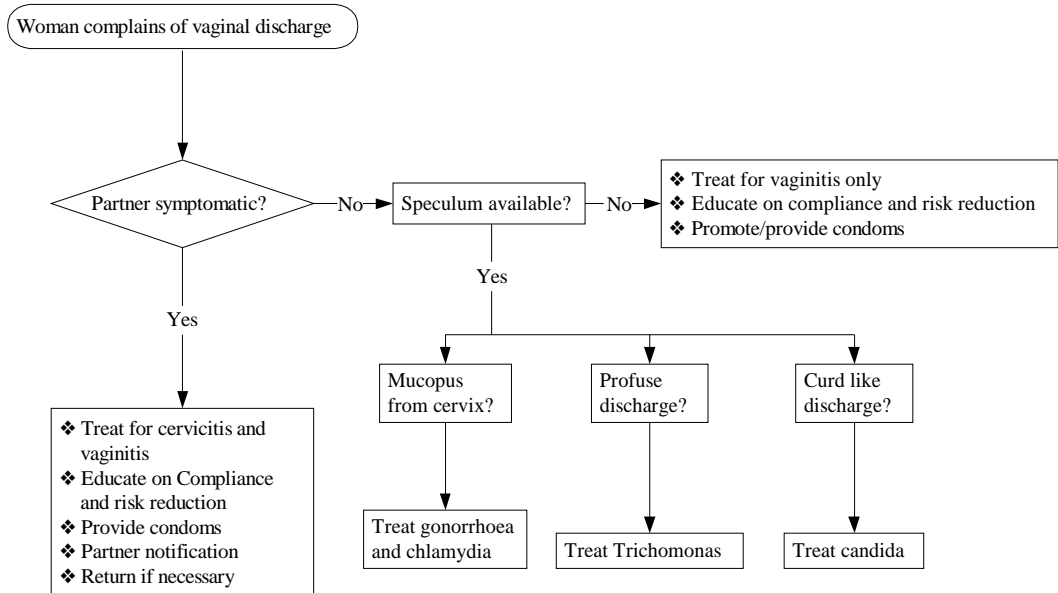
4. Inguinal swelling (bubo)

The most common cause for inguinal swelling, without the presence of genital

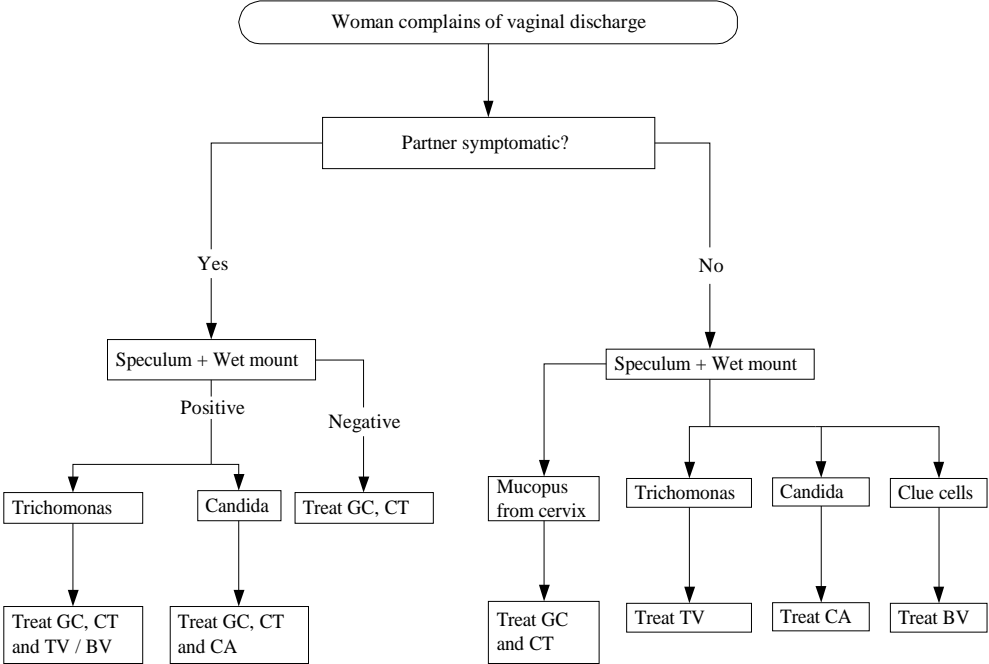
Flow Chart for Vaginal Discharge



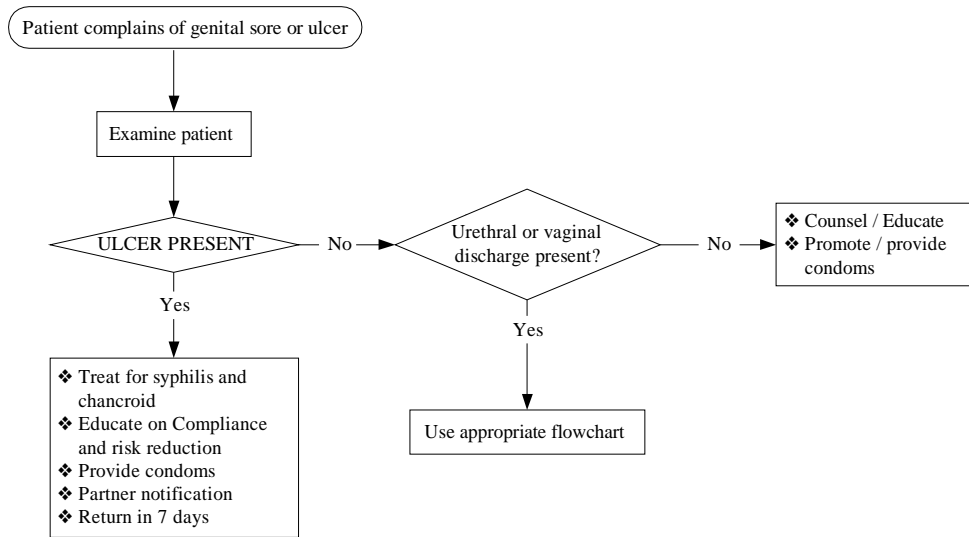
Flow Chart for Vaginal Discharge with Speculum



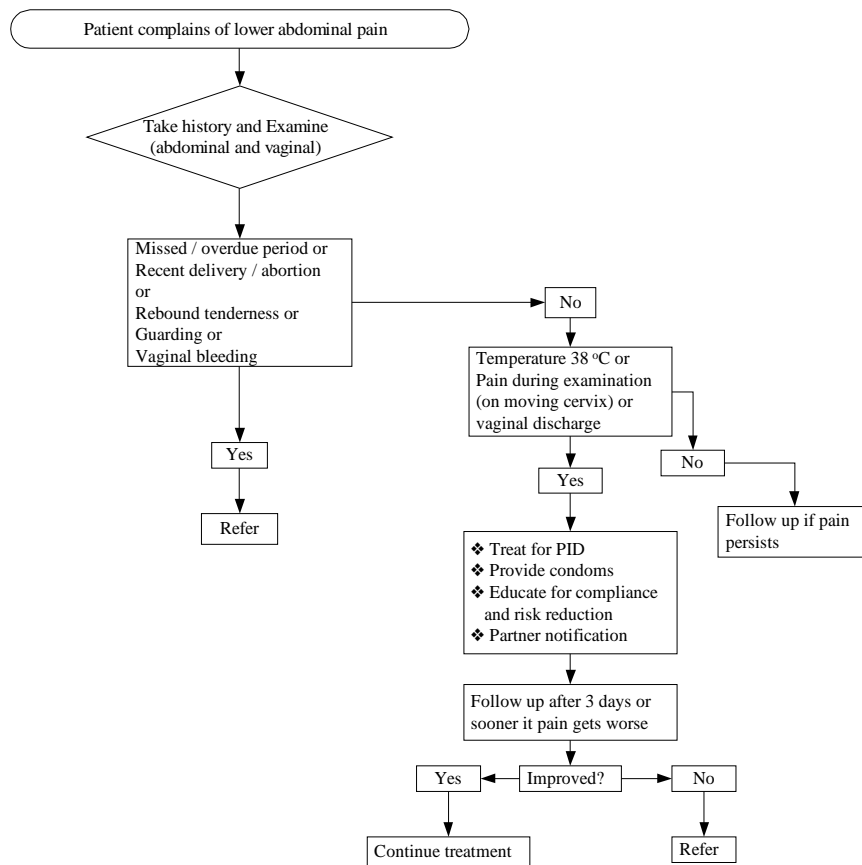
Flow Chart for Vaginal Discharge with Speculum and Microscope



Flow Chart for Genital Ulcers



Flow Chart for Lower Abdominal Pain



ulcers, is Lymphogranuloma Venereum (LGV).

Recommended treatment :

Doxycycline 100 mgm orally twice daily for 15 days

5. Lower abdominal pain - pelvic inflammatory disease (PID)

All sexually active women presenting with lower abdominal pain should be carefully evaluated for the presence of salpingitis and/or endometritis. In addition, routine bimanual examination should be done on all women with a presumptive STD since some women with PID or endometritis will not complain of lower abdominal pain. Women with endometritis may present with complaints of vaginal discharge, and/or bleeding and/or have uterine tenderness on pelvic examination. Symptoms suggestive of PID include abdominal pain, dyspareunia, vaginal discharge, menometrorrhagia, dysuria, onset of pain in association with menses, fever, and sometimes nausea and vomiting.

PID is difficult to diagnose. However, PID becomes highly probable when one or more of the above symptoms are seen in a woman with adnexal tenderness, evidence of lower genital tract infection, and cervical motion tenderness.

Hospitalisation of patients with acute pelvic inflammatory disease should be

considered when (a) the diagnosis is uncertain; (b) surgical emergencies such as appendicitis and ectopic pregnancy need to be excluded; (c) a pelvic abscess is suspected; (d) severe illness makes outpatient management impossible; (e) the patient is pregnant; (f) the patient is unable to follow or tolerate an outpatient regimen; (g) the patient has failed to respond to outpatient therapy; or (h) if clinical follow-up 72 hours after the start of the antibiotic treatment can not be guaranteed.

Because of the fact that many organisms can cause PID, and because it is difficult to establish an etiology for individual infections, it is recommended that PID is treated with concurrent treatments for gonorrhoea, non-gonococcal infection and anaerobic infection.

Recommended treatments are:

Kanamycin 2 gm I. M. in a single dose
or

Spectinomycin 2 gm I. M. in a single dose

and

Doxycycline 100 mgm orally twice daily for 2 weeks

and

Metronidazole 400 mgm orally twice daily for 10 days

All patients treated on an outpatient basis should be followed up after 72 hours, and admitted if not improved.

From: Simplified STD Treatment Guidelines National AIDS control organization, New Delhi.

12.10

GYNAECOLOGIC AND OBSTETRIC CONSIDERATIONS

Dr. Vinay Kulkarni

The demographic pattern of the HIV epidemic has changed over the years. During the early phase, in the U.S. and Western Europe the epidemic was, by and large restricted to men having sex with men and injection drug users. The experience of the African continent was that the epidemic was more heterosexual and the proportion of women infected with HIV was substantially high.

In India, in the early years the epidemic was mainly noticed among women in prostitution and immediately among their male clients. For a long time the proportion of men suffering from HIV infection remained substantially high. Gradually the infection spread from these men to their spouses - and the number of women infected with HIV started rising. The next step in the demographic shift was the vertical transmission from pregnant women to their infants. We are already at this stage of the epidemic, as we, now see children having signs of HIV disease, and so often are these children the index cases in the family, the parents being still unaware about their own infection. Women with HIV, thus,

are emerging, as an important group unique in their epidemiology, clinical course, and response to treatment and psychosocial needs.

Seroprevalance studies:

These are difficult to interpret, but certain studies among women in prostitution, women with sexually transmitted diseases, (STDs), spouses of male STD patients (apparently monogamous married women), data from the surveillance studies done at a certain antenatal care clinics (ANC clinics) - all point to increasing rates of incidence and prevalence of HIV infection in women.

Demographics

Eighty percent of women infected with HIV are of childbearing age (15-44 years). The fastest rate of new HIV infection has been reported to be in women between age 15-20.

Modes of transmission

The two major modes of transmission

of HIV infection to women in India remain unsafe sex and unsafe blood transfusion. Though injection drug use has infected quite a few women in North-East India - the overall proportion remains the relatively low. The proportion of infection through unsterile injection needles is difficult to substantiate. Transmission via unsafe blood transfusion has largely been controlled.

Factors believed to increase the risk of HIV transmission heterosexual partners are:

Presence of genital ulcerative disease, anal sex, advanced clinical HIV disease in the index partner, lack of condom use, sex during menses, oral contraceptives, IUDs, number of sexual contacts, etc. These are important to note during counselling of both seropositive and seronegative patients.

INDICATIONS FOR HIV TESTING IN WOMEN:

Screening for women is important because:

1. As is in the case of men - it helps in obtaining timely interventions like-chemoprophylaxis against opportunistic infections, institution antiretroviral therapy, counselling on behavioural change for positive change in quality of life;
2. Counselling for prevention of

transmission to sex partners can be provided; and

3. Informed choices regarding child bearing could be taken.

Women with known risk factors like multiple sex partners, present or past history of STD, unsafe sex with a partner having multiple partners and /or history of STDs, history of blood or blood product transfusion or injection drug use etc. need to be screened on priority. However, as has been seen quite often, presence of HIV infection among apparently monogamous spouses of HIV infected men being detected during anonymous unlinked surveillance studies at ANC clinics - point to the fact that HIV infection is much more wide-spread than apparent from screening only those women with high risk factors. In fact it could be said that just being sexually active, when one has hardly any knowledge of, or the empowerment to discuss sexual behaviour of one's spouse, may be considered as a risk factor. With increasing prevalence and incidence among women it could be suggested that all women attending ANC clinics be screened: provided the test is performed ONLY after an informed consent is taken and a positive result is not used as a criteria for exclusion of these women from the 'care' and 'support' system.

In addition to this, women just like men,

Studies of HIV discordant partners show that the risk of transmission from men to women is consistently higher than that from women to men.

showing symptoms and signs suggestive of HIV infection need to be screened.

CLINICAL SPECTRUM OF HIV DISEASE IN WOMEN

The natural history and clinical spectrum, evaluation and clinical management of HIV disease in women generally remain the same as in the case of men. Kaposi's sarcoma (KS) which, as it is, has been reported less frequently in HIV patients in India, is less common in women than in men. There are certain gynaecologic manifestations that need attention in women with HIV infection. All those infections that occur in immune-competent women occur with greater frequency and often greater severity in HIV-infected women.

Menstrual disorders :

Menstrual irregularities have been anecdotally reported but there is hardly any specific data of effect of HIV infection on the reproductive hormone axis.

Candidial vulvovaginitis :

It is the most common gynaecological infection in HIV positive women. More than 4 attacks in a year or doubling of the frequency of attacks in a woman with past history of candidial vaginitis should alert the physician about the possibility of underlying immunodeficiency due to HIV.

Treatment: For uncomplicated vaginitis - topical antifungals (clotrimazole 1% cream or 2% miconazole cream every night for 7 days) are effective. If resistant or recalcitrant treat with oral ketoconazole (400 mg) each day or fluconazole (200mg) each day for 14 days. To prevent recurrences: fluconazole (200 mg) once a week or ketoconazole (100mg) each day may be used.

Herpes simplex virus (HSV):

As in men, HSV (type II) infection may be more fulminant and recalcitrant.

Treatment: Acyclovir (200 mg) 5 times a day for 5-7 days. Occasionally higher doses may be required. Chronic suppressive treatment with acyclovir (400 mg) twice a day may be considered for very frequent recurrences.

Syphilis and other STDs :

It is important to note their presence, as ulcerative genitourinary diseases are known to facilitate transmission of HIV. The clinical manifestations and management essentially remain the same as in men. (See chapter on sexually transmitted diseases).

Pelvic inflammatory disease (PID) :

Mostly being a consequence of STDs, PID is more common in women with HIV infection. (See chapter on sexually transmitted diseases).

Condyloma accuminata :

Human papilloma virus (HPV) infection can cause anogenital condylomata. In HIV infected women the warts could be more florid. A pap-smear needs to be studied before treating warts. A biopsy from atypical or resistant lesions be obtained.

Treatment: Trichloroacetic acid (85%) or 25% podophyllum in tincture of benzoin are used for chemo-cauterization of small lesions. Larger lesions need surgical excision or cryosurgery or LASER surgery. In case of pregnant women the treatment may be deferred until after delivery, depending upon the symptoms the woman has.

Cervical intra-epithelial neoplasia:

There is a strong association between HIV, HPV and cervical neoplasia. Because HIV and HPV are both associated with high-risk sexual behaviour, the precise relationship between each of these two and CIN is not entirely clear. Invasive cervical cancer has now been included as an AIDS defining criterion in HIV infected women.

A pap- smear study, done repeatedly, every 6-12 months should be an essential screening test for all HIV infected women. If there are any abnormalities on pap-smear, colposcopy is recommended. If cervical dysplasia or neoplasia is noted the same treatment options as HIV- negative woman should be offered.

HIV DISEASE IN PREGNANCY

With increasing incidence and prevalence of HIV infection in women, especially during the childbearing age, this has evolved as a major issue recently.

It has been shown that HIV infection has no effect on the fertility of the woman (as well as that of a man).

Reproductive choice :

A proper counselling , so that the woman, with the help of her family members - if required, makes an informed choice regarding becoming pregnant or continuing pregnancy is of utmost importance. The facts that need to be considered are :

- A) Nearly one-third chance that the offspring will be HIV infected,
- B) Her own disease and health status,
- C) Her spouse's disease and health status,
- D) Her social support systems and other factors.

The knowledge that one is pregnant and HIV positive can cause extreme psychological stresses and needs extremely careful and expert handling.

Whatever clear decision the woman makes, it should be respected and supported.

Monitoring of pregnant woman's health:

It has not been shown that pregnancy accelerates the progression of HIV disease. CD4 test may be done so to understand the immune status. It should be remembered that advanced HIV disease increases the chances of vertical transmission. Also if the CD4 counts are low (> 200), (or if there is history of PCP), one may start PCP prophylaxis. TMP-SMX (trimethoprim-sulphamethoxazole) remains the mainstay- one double strength tablet 3 times per week. Alternatively dapsone (100 mg) per day may be used.

Antiretroviral treatment:

The effects on the foetus, the pregnancy and on the transmission are not completely understood. In general, the pregnant women have tolerated zidovudin (AZT) well and our experience has largely been limited to this drug. Some recommendations regarding use of multiple drugs have been made but it is difficult to comment on them. In general it may be said that the decision regarding antiretroviral treatment for the woman must be made by taking into account all the cost-benefit factors.

Treatment of other opportunistic infections (OIs):

The decisions need to be taken on an individual basis and taking into account the risks and benefits. In general, one needs to treat OIs promptly and aggressively for the benefit of the mother's health.

VERTICAL TRANSMISSION OF HIV:

The exact rate is difficult to define. It generally varies between 20 to 40 percent in different studies.

As there is passive transfer of maternal antibodies to the neonate, which may persist for 18 months, complicates the matter further. So a positive antibody test at birth does not mean that the child is definitely infected, neither does a negative antibody test rule out infection. The best diagnostic test would be an antigen based test (e.g. PCR) done about 2 weeks after birth. This test being costly and at the same time not very readily available, we follow the following protocol:

1. To test an asymptomatic child at the end of 6 months. If the antibody test is still negative - we assume the child is not infected.
2. A positive result is repeated at the end of 18 months. If still positive, it is assumed that the child is infected.
3. If the child gets any symptoms suggestive of HIV induced immunodeficiency before 18 months

a PCR is advised if available, or presumptive treatment is given - and test is repeated at the end of 18 months. A presumptive diagnosis of HIV infection is made till that time.

Timing of vertical transmission of HIV:

This could be intrapartum, peripartum, and postpartum. However the available data suggest more than 50% of all vertical transmission occurs intrapartum.

Isolation of HIV from tissues of foetuses aborted at 15 to 20 weeks' gestation, immunologic abnormalities in some neonates, rapidly progressing HIV disease in some infants after birth; suggest intrauterine infection.

Isolation of HIV from cervical and vaginal secretions, higher risk of HIV infection in the first - born among twins, injury to delicate skin of the advantages of caesarian section in reducing the rates of transmission, increased chances of the mother's blood mixing with that of the fetus at the time of separation of the placenta all support intrapartum transmission.

Isolation of HIV from colostrum and breast milk suggests postpartum infection. Recent evidence suggests that the risk HIV transmission through breast milk is substantial among women who become infected during the period of breast-feeding (due to very high levels of viremia).

(Regarding the discussion on "recommendations about breast feeding by HIV positive women" see the chapter 'Children and AIDS')

Risk factors for vertical transmission:

HIV infected women with a history of delivering a previous HIV infected baby may have an increased risk of vertical transmission. Recent or acute HIV infection is accompanied with high levels of viremia, as are women with advanced HIV disease-with increased viral load. Premature infants have higher rates of seropositivity. Chorioamnionitis, trauma to placenta, invasive procedures (like amniocentesis) during pregnancy increase the chances of vertical transmission.

Prevention of vertical transmission:

While there is no way in which one can assure complete prevention of vertical transmission-there are several options that may help decrease such transmission. These are:

1. To counsel women with advanced HIV disease or history of previous HIV infected child to reconsider getting pregnant or continuing the pregnancy (considering the option of termination of pregnancy).
2. To avoid invasive monitoring (such as scalp monitors); invasive procedures like amniocentesis, fetal skin biopsies, etc.
3. To consider option of AZT chemoprophylaxis (discussed below).

4. To decide regarding caesarian section.
5. To decide regarding breast feeding, considering other options to it.
6. Avoiding high-risk sexual activity during breast-feeding.

Zidovudin (AZT) chemoprophylaxis:

A number of trials were done through the National Institute of Health-sponsored AIDS Clinical Trials Group (ACTG).

The most famous of these trials is: ACTG 076. In this protocol Zidovudin was given orally starting between 14 and 34 weeks of gestation, at a dose of 100 mg five times a day, was continued as intravenous infusion during labour. Infants were treated with AZT 2 mg/kg orally 4 times daily beginning within 8 to 12 hours after birth until 6 weeks of age. It was observed that the rate of vertical transmission was reduced to 8.3% in the AZT treated group as compared to 25.5% in the placebo group. No significant health hazards to the mother or new-born babies were noted during 18 months follow up.

We offer the following protocol to women who decide to continue their pregnancy:

1. AZT (100 mg) 6 hourly started as early as possible after 14th week of pregnancy.
2. Stepping up of the dose of oral AZT (as intravenous infusion is not available) during labour or before

caseseian section (for about 24 hours).

3. Caesarian section, preferably,
4. Avoidance of breast feeding, and,
5. AZT 2 mg/kg/4 hourly to the new-born for 6 weeks.

Depending upon various social factors there are several combinations seen e.g. starting AZT later during pregnancy, going in for natural delivery, continuation of breast feeding etc. The data need to be analysed, but the numbers are not large enough to make any comments.

Recently some studies from Thailand have shown that AZT given after 34 weeks of gestation also has been effective in preventing vertical transmission to a significant extent. This study could definitely be a good alternative in resource poor countries.

For prevention of transmission through breast milk we ask the women to manually express breast milk heat it and them give it to the child. The details of the debate regarding controversies around breast feeding are discussed elsewhere in the book, but we feel that this is the best strategy to ensure the well being of babies in resource poor situations.

12.11

HIV AND OPHTHALMIC DISORDERS

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Ophthalmic diseases occur in 40 - 90 % of patients with AIDS. At least 20 % of AIDS patients develop cytomegalovirus retinitis (CMV retinitis). Most of these will be known to be HIV infected at the time of ophthalmologic consultation, but in at least 5 % CMV retinitis is the AIDS defining illness.

Ocular findings of HIV disease

Lids and conjunctiva

- Blepharitis
- Molluscum contagiosum
- Herpes zoster ophthalmicus
- Conjunctival vascular changes
- Kaposi's Sarcoma (KS)

Cornea

- Ulcers (candidial)
- Microsporidial keratitis
- Herpetic keratitis (VZV,HSV)
- Keratoconjunctivitis sicca

Optic nerve

- Papilloedema secondary to meningitis
- CMV papillitis

Cranial nerves

- Palsies secondary to CNS Lymphoma
- Herpes zoster ophthalmicus

Retina

- Non infectious HIV retinopathy
- Cotton-wool spots
- Retinal haemorrhages
- White-centred haemorrhages
- Microvascular abnormalities
- Capillary non-perfusion
- CMV retinitis
- Toxoplasma choroidoretinitis
- Syphilitic retinitis and vitritis
- HSV retinitis
- VZV retinitis
- Acute retinal necrosis
- Candidial choroidoretinitis and vitritis
- Endogenous bacterial retinitis
- M. tuberculosis
- MAI in retinal and choroidal granulomas
- Histoplasmosis

Choroidoretinitis, choroiditis

- Pneumocystis choroiditis
- Cryptococcal choroidoretinitis.

Most common of this exhaustive list are:

- HIV microvasculopathy
- CMV retinopathy
- Other intraocular opportunistic infections: HSV, VZV, toxoplasmosis, syphilis or metastatic bacterial infection
- External eye syndromes : blepharitis, sicca, molluscum contagiosum, HSV keratitis, herpes zoster ophthalmicus
- Neuro-ophthalmic syndromes: papilloedema, chronic papilloedema, 'pseudo-benign intracranial hypertension syndrome', optic neuritis or focal brainstem syndromes.

HIV microvasculopathy:

It is the commonest ocular manifestation of HIV infection. Seen anytime during the course of the disease, is seen in more than 50 % patients at some time. Cotton-wool spots are accompanied by retinal haemorrhages, microaneurisms and other microvascular abnormalities.

Cytomegalovirus retinopathy (CMV Retinitis)

This is the commonest manifestation to threaten vision in HIV infected person. It occurs in about 25 % of patients with AIDS and is an AIDS -defining illness in about 5 %. It occurs in patients with profound immunodeficiency. Patients complain of blurred vision, floaters, photopsia and field defects.

It is a necrotising retinitis characterised by creamy white, hemorrhagic, full thickness opacification. There is a predilection for the posterior pole and involvement of the optic nerve head and macular region is common. There is minimal or no accompanying uveitis.

Without treatment, the retinitis progresses relentlessly until the entire retina is destroyed. There is a significant risk of retinal detachment.

Treatment with the virostatic drugs ganciclovir or foscarnet arrests the rate of progression. The drugs are extremely costly.

It has been observed in patients on combination antiretroviral therapy that the progression is arrested once the HIV viral load reduces and the CD4 counts start picking up.

Toxoplasmosis

Toxoplasma retinochoroiditis is characterised by elevated whitish deep retinal and choroidal lesions. These may be multiple and bilateral. There is moderate to severe uveitis. It is often associated with CNS toxoplasmosis.

Treatment: Pyrimethamine and sulfadiazine.

Syphilis:

It may involve virtually any part of the eye, including the optic nerve with optic neuritis, optic papillitis, retinal lesions

appearing as yellow-white areas of retinal oedema, or more commonly with uveitis (iridocyclitis). There is blurring of vision, photophobia, and ocular pain. The diagnosis is confirmed by serology.

Treatment : Is the same as for CNS syphilis. (Penicillin G, 18-24 million units I.V. per day for 14 days in six divided doses.)

Other opportunistic infections

Rarely fungi like cryptococcus, histoplasma, candida etc. and mycobacteria (*M. tuberculosis*, *M. avium intracellulare*) may involve the eye. These often cause granulomatous uveitis, choroidoretinitis or panophthalmitis. These usually coexist with disseminated infection.

Herpes zoster ophthalmicus

It is common and requires systemic treatment with high dose acyclovir. Atypical features like multiple episodes, multiple dermatomal involvement or a poor treatment response are common. Since the ocular tissues are innervated by the nasociliary branch of the trigeminal nerve, lesions on the tip of the nose should alert the physician of ophthalmic involvement.

Treatment: Acyclovir (10 mg/kg/8 hourly I.V. or 800 mg orally five times a day for 10-14 days.)

Herpes simplex retinitis

It is rare. It causes fulminant retinal necrosis and visual loss. The efficacy of treatment is questionable, but undoubtedly acyclovir, 10 mg/kg/8 hourly I.V. should be initiated if the diagnosis appears likely.

Kaposi's sarcoma: (KS)

It is seen very rarely in India, but the diagnosis should be kept in mind. It involves the conjunctivae (especially the inferior cul-de-sac and the eyelids). The lesions usually appear as bright red subconjunctival masses or violaceous nodular lesions. They may be mistaken for subconjunctival haemorrhages. Visual problems are rare due to KS, but if they occur, radiation therapy or systemic chemotherapy would often cause the lesions to regress.

Apart from these, external ocular complaints are common. Itchy, burning, uncomfortable eyes, crusting, discharge or chalazia are common. Blepharitis related to seborrhoeic dermatitis, staphylococcal infection, dry eyes associated with sicca syndrome are frequently seen. Intensive treatment is required. Large molluscii on the eyelid would need removal.

12.12

PAEDIATRIC HIV/AIDS

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As the pandemic of HIV/ AIDS spreads its impact on children will definitely increase. HIV/AIDS is already a major health problem for children in many areas of the world, and unfortunately, the direct and indirect effects on children will become much more important in the years to come. HIV infections in children are closely linked with infections in women of childbearing ages. Over 90% of HIV infected children are exposed to HIV in utero, during childbirth or in the early post-natal period.

Apart from children with AIDS, several children are orphaned by AIDS. According to UNICEF, by the year 2000, from 6 to 11 percent of the children in 10 central and east African countries will have been orphaned by AIDS. In India the number of AIDS orphans is likely to reach about a million during next 5 years.

CLINICAL PICTURE OF PAEDIATRIC AIDS:

HIV does not lead to premature birth.

HIV, per se, does not lead to intrauterine

growth retardation (IUGR). Clinical signs are very rarely seen at birth.

Symptoms usually occur between ages 2 and 18 months, with an average age of 6 months. Hepatosplenomegaly and lymphadenopathy are common.

Infections involving common germs (staphylococci, streptococci, enterobacteria) or opportunistic organisms, are frequently seen. The opportunistic organisms are generally of the same types as described in adults. A rare exception is infection with the Calmette-Guerin bacteria (BCG) in children vaccinated before a diagnosis was made. Candidiasis, pneumocystis carinii and CMV infections are some of the most frequent ailments.

Lymphoid interstitial pneumopathy is much more frequent in children than in adults. Its aetiology is still debated. It is linked with the EBV virus or a direct response to the presence of the HIV in the pulmonary alveolar cells. If associated with moderate immunodeficiency, it is indicative of a

Factors Influencing Mother to Child Virus Transmission

Maternal factors

- Clinical and immunologic status
- Level and duration of viremia
- Immune response to HIV

Viral factors

- Virus phenotype and genotype

Placental factors

- Susceptibility
- Developmental stage
- Integrity

Foetal factors

- Gestational age at time of virus exposure
- Immune response
- Susceptibility
- Genetic factors (e.g., HLA type)

Obstetrical factors

- Skin and mucus membrane integrity
- Neonatal immune response

Breast milk factors

- Gastrointestinal maturity
- Level and duration of virus in the breast milk
- Non-specific antiviral defences
- Virus-specific local immunity

good prognosis, but it occasionally progresses towards chronic respiratory insufficiency. Diagnosis is based on histology and bronchoalveolar lavage. The main complication is intercurrent pneumococcal infection, which may be avoided or attenuated by routine treatment with oral penicillin and/or IV gamma globulin. Corticosteroid therapy occasionally produces spectacular

clinical and radiological improvement. Start with 1.5 to 2 mg/kg for 2 to 3 weeks, followed by a relatively rapid decrease over a 1 to 2 month period. Maintenance doses are taken on alternate days.

Encephalopathy is another important complication of HIV infections in children. The prevailing symptoms are

pyramidal hypertonicity, which is often severe, retardation followed by regression of psychomotor acquisitions. Bucofacial dyspraxia is often observed. The evolution seems to be closely correlated with the intensity of the immune deficiency. C.T. Scan may be normal or show signs of cortical atrophy. Calcification of the basal ganglia may develop subsequently.

CSF is usually normal.

Acute diarrhoea with dehydration and malnutrition is also a frequent presentation.

Repeated respiratory infections and otitis media seem to be frequent.

Immunological anomalies are much the same as in adults. The relative drop in CD₄ + lymphocytes is often masked by lymphocytic hyperplasia. Plasmocytosis is almost always seen. Biological parameters predictive of progression are still debated. All agree that the infection

is very serious: few children remain asymptomatic for long periods, and about 50% of infected children develop a severe form of disease within 3 years.

Diagnosis of HIV infection in infants is difficult.

Maternal antibodies (essentially anti-gp 120 antibodies) may persist for 12-13 months.

The p24 antigen assay is practically always negative at birth. Study of the gradual modification of the anti-HIV antibody profile using the Western Blot during the first months of life may be valuable if it shows the acquisition of antibodies not present at birth:

Isolation of the virus in the cord blood or PCR positivity are the only reliable means of early diagnosis, but such testing is difficult in practice, it is costly, not readily available, and there is still a strong possibility of false negative results.

CDC Classification System for HIV in Children

Class P-0. INDETERMINATE INFECTION

Infants < 15 months born to infected mothers but without definitive evidence of HIV infection or AIDS.

Class P-1. ASYMPTOMATIC INFECTION

Subclass A. Normal immune function

Subclass B. Abnormal immune function

Hypergammaglobulinemia, T4 lymphopenia, decreased T4-to T8 ratio, or absolute lymphopenia

Subclass C. Immune function not tested

(cont.)

Class P-2. SYMPTOMATIC INFECTION

Subclass A. Non-specific findings (at least two for > 2 months)

Fever failure to thrive, generalised lymphadenopathy, hepatomegaly, splenomegaly, enlarged parotid glands, persistent or recurrent diarrhea.

Subclass B. Progressive neurologic disease Loss of developmental milestones or intellectual ability, impaired brain growth, or progressive symmetrical motor deficits

Subclass C. Lymphoid interstitial pneumonitis

Subclass D. Secondary infectious diseases

Category D-1. Opportunistic infections in CDC case definition

Bacterial: mycobacterial infection (noncutaneous, extrapulmonary, or disseminated);

Nocardiosis

Fungal: Candidiasis (esophageal, bronchial, or pulmonary),

Coccidiomycosis, disseminated histoplasmosis,

Extrapulmonary cryptococcosis

Parasitic: P.carinii pneumonia, disseminated toxoplasmosis with onset > 1 month of age, chronic cryptosporidiosis, extraintestinal strongyloidiasis

Viral: Cytomegalovirus disease (onset > 1 month of age), chronic mucocutaneous/disseminated herpes (onset > 1 month age), progressive multifocal leukoencephalopathy

Category D-2. Unexplained, recurrent, serious bacterial infections (two or more in 2 years)

Category D-3. Other infectious diseases

Includes persistent oral candidiasis, recurrent herpes stomatitis (at least two episodes in 1 year), multidermatomal or disseminated herpes zoster.

Subclass E. Secondary cancers

Category E-1. Cancers in AIDS case definition

Kaposi's sarcoma, B cell non-Hodgkin's lymphoma, or primary lymphoma of brain

Category E-2. Other malignancies possibly associated with HIV

Subclass F. Other diseases possibly associated with HIV

Includes hepatitis, cardiopathy, nephropathy, hematologic disorders, dermatologic diseases

Onset of clinical symptoms

Among the perinatally infected children, the onset of symptomatic disease appears to occur in a bimodal fashion. Children who become symptomatic before 1 year of age frequently develop opportunistic infections and have HIV related encephalopathy. This pattern of disease presentation is associated with rapid progression and early mortality. In contrast, children who do not develop opportunistic infection or severe encephalopathy during this period follow a less rapid decline and are significantly more likely to survive beyond 5 years of age. The development of lymphocytic interstitial pneumonitis or recurrent bacterial infections as the primary manifestation of HIV infection is associated with a better prognosis than is the development of opportunistic infection or encephalopathy. Some perinatally infected children have remained symptom free for up to 10 years.

Another important distinction between vertically infected children and adults is that, whereas the development of serious opportunistic infection is associated with CD4 counts of less than 200 cell/mm³ in adults, children with counts manifold higher developed *Pneumocystis carinii* pneumonia.

General manifestations

The initial manifestations of disease may be subtle and insidious - failure to thrive, lymphadenopathy, slowly progressive

hepatosplenomegaly, an increased incidence of common infections (otitis, sinusitis, pneumonia) - or it may be dramatic; with the development of a usual infection such as *P. carinii* pneumonia. Symptomatic acute infection with mononucleosis - like syndrome is only rarely recognised in children. Its features include malaise, fever, lymphadenopathy (which may often regress in later stages of disease), hepatosplenomegaly, respiratory tract infections, chronic persistent or recurrent diarrhea, failure to thrive, and persistent mucocutaneous candidiasis. A variety of non-specific cutaneous manifestations have also been described, including seborrhoeic dermatitis and eczematoid eruptions.

Care of HIV infected children:

Most HIV-related illness is caused by common infections. These can be prevented or treated at home or in a clinic. They often last longer than in HIV-negative children and are more difficult to cure with standard treatments.

- Maintain good nutrition. This includes giving advice on both breast-feeding and other feeding, including feeding a child with poor appetite.
- Treat infections as early as possible.
- Immunise as usual,
- Emphasise early diagnosis and treatment of suspected TB for all family members.
- Give oral rehydration therapy (ORT) to prevent dehydration

during diarrhoea. Antibiotics for other infections can worsen diarrhoea.

- Monitor growth regularly.

- Treat the child as normal, ensuring for example that he or she plays with other children.

- Give comfort when in pain and distress.

Clinical features of HIV infection in children

Organ System	Signs and Symptoms
General	Fever, malaise, failure to thrive, lymphadenopathy
Respiratory	Otitis, sinusitis, lymphocytic interstitial pneumonitis; pneumonias (Bacterial, TB, viral (CMV), protozoal (PCP) and fungal)
Oropharyngeal	Candidiasis, oral hairy leukoplakia, aphthous ulceration, gingivitis, HSV Stomatitis.
Gastrointestinal	Esophagitis (candidal, CMV, HSV) hepatitis, cholecystitis, pancreatitis, enteropathy, colitis (bacterial, viral, protozoal, fungal)
Skin	Infectious: bacterial (<i>S. aureus</i>); viral (HSV, VZV, M. contagiosum, warts); fungal (<i>Candida</i> spp., tinea corporis, tinea capitis, <i>Malassezia</i> spp.); Infestations (scabies) Inflammatory: Seborrhoeic, eczematoid, and psoriatic eruptions, drug eruptions
Hematopoietic	Anaemia, leukopenia, thrombocytopenia
Central nervous	Loss of developmental milestones, impaired cognitive ability, acquired microcephaly, spastic paraparesis, extrapyramidal tract signs, aseptic meningitis, meningitis
Ocular	Choroidoretinitis (CMV, HSV, VZV, and toxoplasmosis), cotton wool spots
Endocrine	Short stature, adrenal insufficiency
Renal	Nephrotic syndrome, acute nephritis, renal tubular dysfunction
Locomotor	Peripheral neuropathy, myopathy
Malignancy	Lymphoma, Kaposi's sarcoma, leiomyoma, etc.

RECOGNITION OF SYMPTOMATIC HIV INFECTION IN CHILDREN

WHO has developed guidelines for recognising HIV infection in children. These may be used where a health worker suspects HIV infection and where testing is not available or affordable, or where the child is too young for the test to be accurate. These guidelines may be helpful for clinical management of the child and to alert the health worker to possible needs of the mother for counselling and care.

A diagnosis of symptomatic HIV infection is made if the following are present:

- any cardinal finding
- two or more characteristic findings
- one characteristic finding plus two or more associated findings
- three or more associated findings plus any epidemiological risk factors
- two associated findings plus laboratory evidence of HIV infections in the child.

Cardinal findings

- pneumocystis carinii pneumonia (PCP)
- lymphoid interstitial pneumonitis (an unusual form of viral pneumonia)
- fungal infection in throat and mouth (candidiasis or thrush)
- Kaposi's sarcoma (skin cancer, rare in children)

Characteristic findings

- recurrent bacterial and/or viral infections (such as respiratory and skin infections and meningitis)
- tuberculosis, of the lung or of other organs
- shingles (herpes zoster)
- cytomegalovirus infection
- neurological problems, such as slowness in developing skills in sitting, crawling and talking, fits, microcephaly (reduced head growth)

Associated findings

- oral thrush when the child is not being treated with antibiotics.
- failure to thrive (lack of weight gain)
- fever (continuous or intermittent for more than 1 month)
- diarrhoea (persistent or intermittent for more than 14 days)
- generalised lymphadenopathy (swollen lymph glands)
- skin rashes

(cont.)

Epidemiological risk factors

- mother has tested positive for HIV
- history of transfusion of unscreened blood or blood products
- sexual abuse involving penetrative sexual intercourse
- use of contaminated syringes and needles or a history of scarification, ear piercing or circumcision using non-sterile instruments.

From: AIDS Action, issue 27, April-June 1995.

LABORATORY DIAGNOSIS OF HIV INFECTION IN CHILDREN

WHO has published recommendations for the selection and use of HIV antibody tests (Wkly epidem rev 1992; 20: 145-9). The most common HIV antibody testing strategy for establishing seropositivity involves an initial test on a serum or plasma specimen. Specimens found reactive by the initial test are subjected to a supplemental test (sometimes referred to as a confirmatory test). The tests and the sequence in which they are used should be evaluated under field conditions in the region where they are to be used prior to implementation.

Enzyme-linked immunosorbent assay (ELISA) and particle agglutination are widely used as initial tests.

The alternative supplemental test should preferably be of a different test principle (indirect versus competitive) and/or use different antigen preparations (viral lysate versus recombinant polypeptides or synthetic polypeptides) to the initial test in order to minimise the occurrence of false positive results. Studies have shown that certain ELISAs and simple/rapid tests (e.g. immunodot and particle agglutination tests) are suitable

alternative supplemental tests.

A positive antibody test in an infant under 15 months of age may mean one of two things:

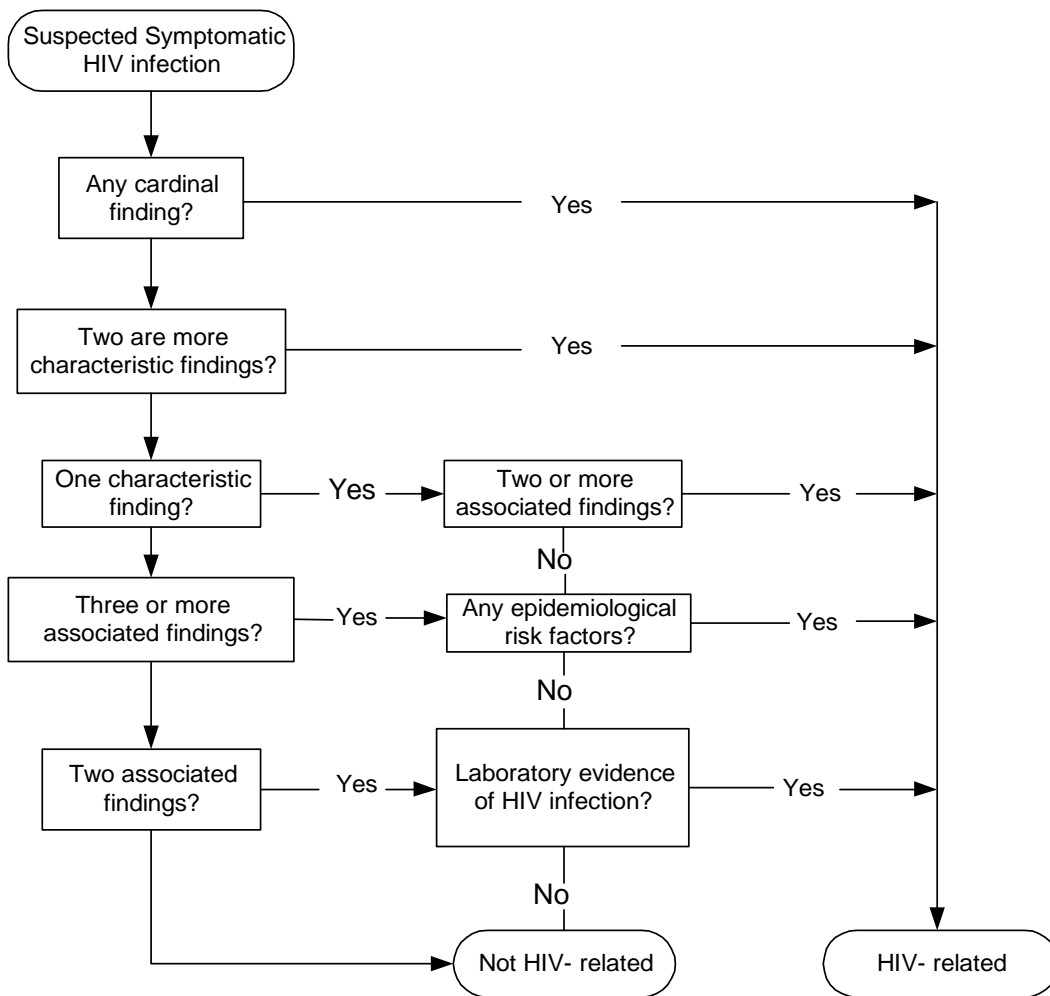
- i) the baby is carrying maternal HIV antibodies (i.e. persistence of maternal IgG antibodies following placental transfer); or
- ii) The baby is HIV infected and will continue to test positive.

The likelihood that a child is infected with HIV is greatly increased if one or more HIV - related clinical symptoms and/or biological abnormalities (CD4 <400 or hypergamma-globulinemia) are present. Hypogammaglobulinemia could be the first immune abnormality occurring in new-borns.

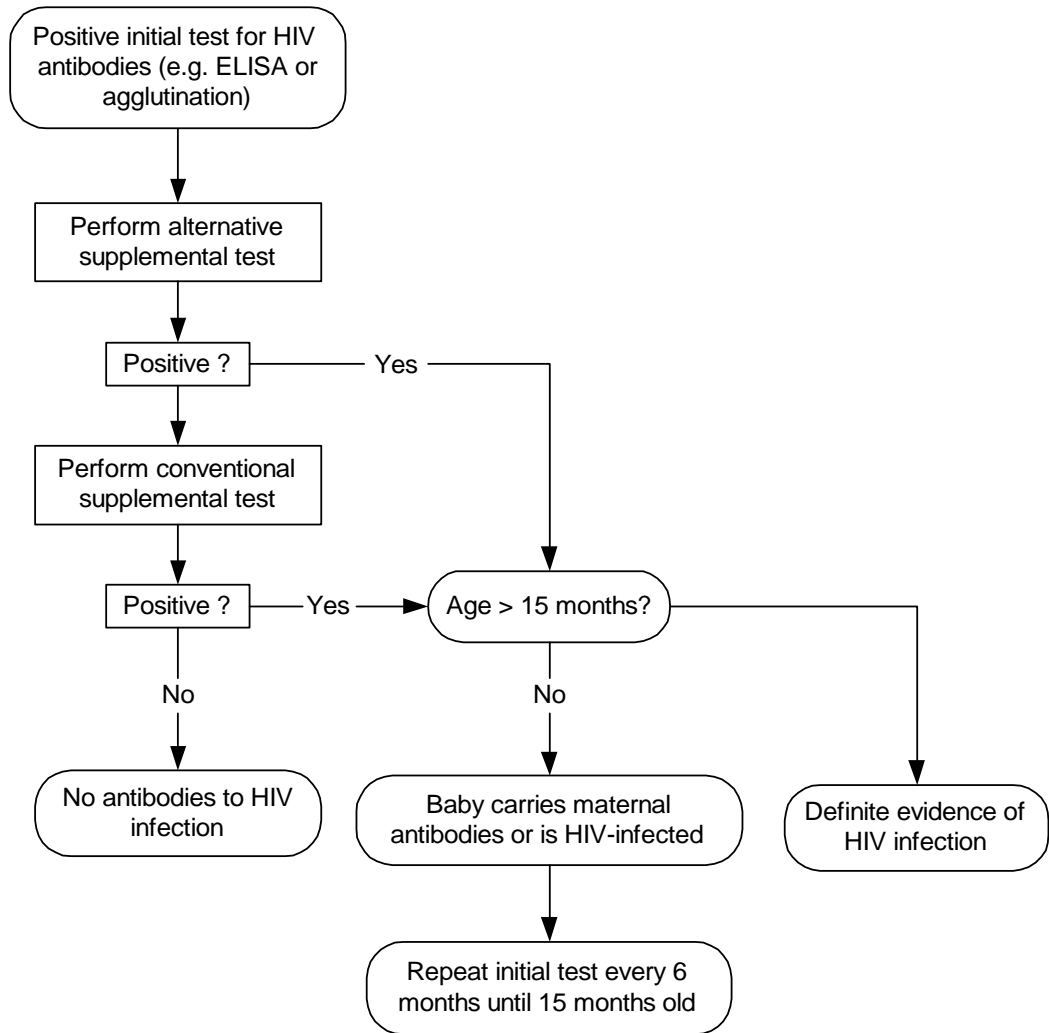
Repeat testing every 6 months until the child is 15 months old, by which time any circulating maternal antibodies should have disappeared and the HIV test will become negative. If the test continues to give a positive result the child is infected with HIV.

The following tests are presently under investigation to confirm HIV infection in children under the age of 15 months.

Recognition of Symptomatic HIV Infection in Children



Laboratory Evidence of HIV Infection



- detection of IgA antibodies (which do not cross the placenta)
- viral detection using the polymerase chain reaction (PCR) either by the standard technique or with dried blood spot specimens
- in-vitro antibody production assays
- p24 antigen assays.

Preliminary data show these tests to have a high specificity and sensitivity.

IMMUNISATION

The advantages of immunisation are obvious if it protects against serious infections. As regards specific vaccines we must ask two questions -

1. Do they work?
2. Are live vaccines safe?

Several studies suggest that many of the commonly used vaccines have adequate immunogenicity during the asymptomatic stage. Similarly, data on the safety of live vaccinations are sparse, but studies, which have been performed, have not demonstrated increased incidence of adverse effects in HIV-infected children. Some clinicians, however, on theoretical grounds, advice to avoid live vaccines like polio. Although there are no efficacy data, some clinicians also recommend vaccination with pneumococcal vaccine. BCG vaccination poses particularly difficult problems through lack of

Recommendations for immunisation of HIV-infected infants and children (adapted from WHO 1987 and AAP 1991)

Type of vaccine	World Health Organisation (WHO)		American Academy of Paediatrics (AAP)	
	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic
Diphtheria-pertussis-tetanus (DPT)	yes	yes	yes	yes
Oral polio	yes	yes	no	no
Inactivated polio	—	—	yes	yes
Measles-mumps-rubella (MMR)	yes	yes	yes	yes
Influenza	yes	no	Should be considered	yes
Bacillus Calmette-Guerin (BCG)*	yes	no	no	
Pneumococcal	—	—	yes	yes
Haemophilus B conjugate	—	—	yes	yes
Hepatitis B vaccine	—	—	yes	yes

*WHO recommends use of BCG in areas of high tuberculosis prevalence

sufficient data in this population. The increasing incidence of tuberculosis in some populations and the uncertainty of the effectiveness of BCG in immunocompetent (let alone immunocompromised) persons make it very difficult to issue confident advice on BCG vaccination policy. The World Health Organisation advice is that in countries where the risk of TB is high. HIV-infected children should be given BCG at birth, while BCG should be withheld from children with symptomatic disease. In the light of the currently available data this seems appropriate.

BREAST-FEEDING: THE DEBATE

(Adapted from: Gabrielle Palmer, World AIDS, Nov. 1992)

Incontestable facts about breast-feeding and HIV transmission will not be available for many years.

Reasons for the shortage of satisfactory data are twofold: there is a huge diversity among groups studied, and it is hard to determine just when infection from mother to baby occurs. About a third of babies born to mothers with HIV become infected. Is HIV transmitted during pregnancy, delivery, or breast-feeding? It is almost impossible to know. Babies of HIV positive mothers are born with their mother's antibodies and only after about a year is it possible to determine whether the child has developed HIV.

There seems to be a disparity of risk between women who have become infected with HIV after the birth of the babies and women who already have HIV when they give birth. A recent research concludes that first group are at greater risk than the second is.

The first group includes women who received HIV-infected blood transfusion just after giving birth as well as those infected within a few months of giving birth, usually through sexual intercourse. These women seem to be at higher risk of transmitting the virus to their babies through breast-feeding, perhaps because HIV is very active in the body immediately after infection.

Researchers are often careless about defining breast-feeding; exclusive breast-feeding is ideal but rare. Mothers may say they are exclusively breast-feeding but sometime give extra water or herbal teas. Many mother and health workers mistakenly consider this practice to be harmless. Among its many anti-infective properties, breast-milk contains immunoglobulin A (IgA) which protectively "paints" the gut wall to stop viruses and other harmful microorganisms crossing through. Artificial milk, weaning foods, water, other fluids, and even dummies interfere with breast-feeding and may prevent nutrient absorption or inhibit the effect of IgA and other protective factors in breast-milk. Contaminated food or fluids may give the baby an infection, making the gut wall more vulnerable.

The problem with any study of breast-feeding and HIV is that variables such as exclusivity and feed supplements are rarely recorded or taken into consideration.

The picture is even more cloudy when looking at the second group of women who have an established HIV infection before the birth of their child. Researchers from the European Collaborative Study (ECS) found that 31% of babies breastfed by their HIV positive mothers developed their own HIV infection whereas only 14% of bottle-fed babies did so.

The ECS figures should be regarded with caution because the study included a very large number of bottle-feeders and comparatively few breast-feeders. The factor, which may be most crucial in determining whether breast-feeding, is safe or not—the level of HIV infectivity in the mothers—was never measured. Nor was exclusivity of breast-feeding recorded in the study; in many European hospitals early feeds of glucose water or artificial milk are still common.

If breast-feeding were as infectious as HIV-contaminated blood transfusions, there would be 100% infection in the infants of HIV positive mothers who breast-feed. But this is not happening. In contrast to semen or blood in needles—where a few drops may transmit HIV—breast-milk is a baby fluid delivered in substantial amounts and yet the majority of babies breastfed by mothers with HIV

remain infection-free. One significant and under-reported discovery which may provide an explanation for this phenomenon is that all breast-milk, irrespective of the mother's HIV status, contains a unique substance which prevents the virus from attaching itself to cells.

In their 'Consensus Statement on HIV and Breast-feeding' WHO/UNICEF acknowledge that the simplistic division between “developed” and “developing” countries is inappropriate and instead use the term “settings” to describe the range of conditions of poverty and wealth around the world. They suggest that if an alternative feeding method is possible then a mother known to be HIV positive may be advised to use it, but if this is going to risk illness and death from infectious diseases then breast-feeding is advised.

The reality is that in areas of high HIV prevalence most women do not know their HIV status. Because the choice of alternative method or product must not be influenced by commercial pressures, the Consensus Statement demands baby food companies abide by the WHO/UNICEF Code of Marketing of Breast-milk Substitutes.

Amidst the confusion about the risks of HIV transmission through breast-feeding one fact is clear: if breast-feeding stopped today, the results would be far more devastating than the current effects of HIV. There would be a vast increase in infant illness and deaths.

Alternative to breast-feeding

(WHO 1994 HIV and infant-feeding :essential issues for decision makers [draft policy guidelines])

Alternative infant feeding methods require access to a plentiful and clean supply of water to reduce risk of diseases such as diarrhoea. If a baby is not being breastfed, a clean cup or spoon should be used since bottles and teats are difficult to clean.

Infant formula is the most common alternative. However, it is expensive and hygienic preparation and feeding can be difficult in many households. To feed an infant for the first six months, 44 tins of 500 g are needed.

Animal milk such as cow or buffalo milk can also be given. It should be diluted and sweetened (one cup of water, three cups of milk, four level teaspoonfuls of sugar) and brought to a boil to reduce the amount of curd and kill harmful germs.

Breast-milk can be expressed by the mother **and made safe for the infant by heating** it to boiling point or by pasteurising it - heating to 62.5 C for 30 minutes. In some places, self-help groups for HIV-positive women, or support from health workers, have succeeded in enabling mothers to express and treat their milk. Continuing to express enough breast-milk over a long period may be difficult. Supplementing expressed breast-milk with formula milk and introducing solid foods earlier than usual should be considered.

In some places it may be acceptable for another woman to breast-feed the baby. This option is not advised where this woman might be, or become, HIV-positive herself.

We are worried that women may be wrongly advised, or decide themselves, not to breast-feed because of fear of HIV. Breast-feeding is one of the most important ways that a mother can help her infant stay healthy. Infants who are not breast-fed are upto 14 times more likely to die of common childhood illnesses than exclusively breast-fed infants, especially in low- income communities. Therefore it is suggested that in 'resource poor' settings breast-feeding should be continued. However, the risk of HIV transmission can not be simply overlooked. In one-to-one

counselling situations we are required to explain the available alternatives (see the chart).

Even the official recommendations regarding the alternatives put exclusive breast-feeding by manual expression of breast-milk and making it safe by heating –at the end of their lists.

The aggressive marketing of formula milk and substitutes does influence not only personal decisions but also policies at that level.

We also feel that problems with expression of breast-milk over a long

period are exaggerated. Basically if we agree that babies should be exclusively breast-fed for first 4 months – it should be feasible. We emphatically state that obstetricians, HIV physicians, counsellors and self help groups should strongly campaign for this option and against ‘infant formula’.

The argument that is put up against this option is that, heating breast-milk could destroy its protective properties. The other options also have none of those. Breast-milk has no problems of –

1. adjusting the dilutions,
2. Compensating for costs as it comes free.

It also would help strengthening the emotional bond between the mother and the infant.

We must explain the rationale of this option, and reduce the feeling of guilt that she may be infecting the infant.

We, the clinicians tend to take shortcuts and have a tendency to suggest formula feed. We must discourage ourselves from doing so.

Treatment

Treatment considerations for HIV infected children need to be individualised. The clinical status, degree of immune-deficiency and the available resources determine the choice of treatment. In our setting close medical follow up, nutritional support and aggressive diagnosis and treatment of opportunistic infection still remain the

mainstay of care. A greater focus on prophylaxis against specific infections and treatment with antiretroviral drugs and immunomodulators are likely to change the prognosis.

Prophylaxis

Pneumocystis carinii pneumonia (PCP) is the most common serious opportunistic infection. It could be the presenting illness. In perinatal HIV infection it is seen commonly between 3 and 7 months of age and is the most common AIDS defining illness in children who progress to AIDS during the first year of life. The mortality is high. Therefore it is important to identify all infants who are at risk for PCP early so that prophylaxis can be initiated.

It is recommended that all children ‘at risk’ or known to be infected with HIV and greater than 6 weeks of age be given TMP-SMX as PCP prophylaxis, till at least upto 18 months. If we know then that the baby is not infected then we discontinue TMP-SMX. We continue TMP-SMX for children infected with HIV.

Antiretroviral agents

There is general consensus that early antiretroviral treatment will be beneficial and prevent progression of HIV disease. The choice of drugs would depend upon the availability of the drugs and affordability to the patient’s family. Weight related doses of all the combinations of drugs used in the adults have been used with good results. The

complications need to be closely monitored.

Intravenous Gammaglobulin Therapy (IVIG):

The time of development of serious infections was prolonged in children receiving IVIG (baseline CD₄ cell count > 200/mm³). Survival rates, however, remained unchanged. The usual dose of IVIG is 400 mg/kg per dose given every 4 weeks.

Prognosis and outcome

Though improvement in management and therapy have improved survival of HIV-infected infants and children the overall prognosis remains poor. An early age at clinical diagnosis of HIV infection is related with poor prognosis.

PSYCHOSOCIAL SUPPORT:

The illness of child, especially when the parents also know that they are infected with HIV, could be disastrous on both the child and the family.

The guilt that the infection is caused by you, the anger in the mind of the mother if she feels that she and her child are “innocent victims” of her husband’s misbehaviour, the frustrations of living with a ‘deadly’ infection at a very young age, the stress of dealing with the fact that the child is going to die soon and also the parents are likely to develop the

disease sooner or later, the economic burden—all need to be tackled by an experienced physician and counsellor. Care of children with or without HIV infection but who have lost parents to HIV disease is another issue.

It is our experience that families who know that the parents are infected with HIV and are informed about the possibility of the child may be infected cope relatively better with the situation, as compared to the families where a sick young child happens to be the “index case” in the family. In a typical situation—a young infant—less than a year old—becomes seriously or sequentially ill, HIV disease is diagnosed, and the mother—a young lady—recently married—is also tested HIV positive and then her husband too. Within a span of couple of days the whole family is under severe stress.

We have also seen a couple of families where a first child has died of severe, serious recurrent infection – but was not investigated. A second child was lost in a similar way and the mother was detected to be infected with HIV during the antenatal check up during the third pregnancy.

High index of suspicion, careful handling and appropriate screening could help reduce a lot of psychological morbidity.

Further reading: Children and AIDS, a compilation by PRAYAS.

12.13

MALIGNANCIES ASSOCIATED WITH HIV

Dr. Anantbhushan Ranade

INTRODUCTION:

As the life expectancy in HIV affected patients is increasing day by day, the chances of malignancy also increase. Incidence data are not available for Indian patients. About 40% of patients some time during their life after infection with HIV develop malignancy.

These malignancies are common in all immunocompromised patients.

The most frequent being,

1. Kaposi's Sarcoma
2. Lymphoma
3. CNS Lymphoma
4. Cervical Neoplasia,
5. Anal Neoplasia
6. Other Neoplasia.

KAPOSI'S SARCOMA (KS)

Incidence

- Approx. 20-25% of homosexuals or bisexuals with HIV.
- 1% in haemophiliacs.
- 2% in injecting drug users or

transfusion recipients other than haemophiliacs.

VERY FEW INDIAN CASES REPORTED. EXTREMELY RARE IN WOMEN.

Special features:

- Genetic predisposition : HLA - DQ, in HIV + ve homosexuals
- Factors associated with development of Kaposi's Sarcoma
 - a) Immune suppression,
 - b) 'Oncostatin M': a protein produced by HIV infected CD4,
 - c) Cytokines produced by HIV-KS cells,
 - d) Unidentified sexually transmitted cofactor,
 - e) Steroids accentuating this protein.

Clinical features :

- Some grow very slow, some very rapid i.e. there is a vast spectrum natural history of KS with HIV.

- Sites of involvement
 - A) Skin - Hyperpigmented nodules and plaques, irregular, often remarkably symmetrical, generally not pruritic or painful unless they become large.
 - B) Lymphoedema.
 - C) Lymphadenopathy.
 - D) Oral cavity and gastrointestinal tract.
 - E) Lungs with worst prognosis and immediate need for chemotherapy

Diagnosis :

- Biopsy.
 Routine staging evaluation is not required.

Factors associated with prognosis :

1. Other opportunistic infections.
2. Presence of 'B' Symptoms.
3. CD4 < 200/ml

In the absence of these median survival of approximately 3 years.

Treatment

Not all patients with KS require therapeutic intervention, since treatment does not improve survival.

- A) Observe, Associated symptoms to be controlled.
- B) Local
 - i) Local radiotherapy.
 - ii) Intralesional chemotherapy (Vinblastine).

- iii) Cryotherapy
- iv) Surgery

C) Interferon alpha

D) Interferon alpha with concurrent Zidovudine.

E) Chemotherapy (Vincristine, Vinblastine, Doxorubicin, Bleomycin)

AIDS RELATED LYMPHOMA

Incidence

- Haemophiliacs 5.5%, 36 times more risk in HIV infected hemophiliacs
- 3% of all new cases.
- 'B' cell variety predominates. (Non Hodgkin's Lymphoma, NHL).
- 80% are immunoblastic
- In Indian settings other high grade lymphomas also are seen.

Features

- B symptoms usually present.
- Extranodal extension more commonly seen of the extranodal sites
 - 30% involve CNS
 - 25% GI tract.
 - 25% Marrow
 - 10% Liver

Diagnosis :

The staging biopsy of the disease and its diagnosis is same as that of non-HIV lymphoma.

The extra investigations required are.

- Lumbar puncture to rule out leptomeningeal involvement.
- CD4 counts.

Factors indicating poor prognosis

- H/o HIV prior to lymphoma.
- Marrow and /or other extranodal disease.
- Stage IV disease
- CD4 < 200

Performance (Karnofsky) status less than 60%.

Special Types.

A) Primary CNS lymphoma is seen in upto 25% of persons with NHL and HIV disease.

- Very poor prognosis.
- Median survival 70 days.
- Aggressive regimens have been tried.

B) Leptomeningeal involvement : if solid lesion is absent : good prognosis. Treatment is necessary.

Management

Indications of treatment

- No associated high risk factors
- CD4 > 200
- No other concurrent infections at the time.

Regimens

- Standard curative regimens.
- Low dose regimens.

Supportive care

- Granulocyte colony stimulating factor/Granulocyte-Macrophage

colony stimulating factor (GCSF/GMCSF)

- Prophylaxis against PCP and other opportunistic infections
- Antiviral agents

Conclusions of our Data

- No CNS relapse.
- Survival similar to non-HIV patients.
- CD4 should be the deciding factor.

PRIMARY CNS LYMPHOMA

80% Patients already have h/o HIV infection and only 20% are diagnosed to have HIV at the time of presentation.

- Usually CD4 < 75

Diagnosis :

- CT/MRI, Lumbar puncture, brain biopsy

Management

Whole - brain radiotherapy - controls the disease in 50-60%

Chemotherapy may be added.

HODGKIN'S LYMPHOMA

Not an AIDS defining condition. Incidence has gone up only in patients who are IDUs (Injecting Drug Users).

Clinical features

- Extranodal spread 90%.
- Prevalence of 'B' Symptoms.
- Unusual extranodal sites are anus, rectum and bone marrow.

- Mixed cellularity is the commonest.
- Management same as others.

CERVICAL NEOPLASIA

Now considered as an AIDS defining condition in the developed countries.

Biological factors

- Immunosuppression aggravates the condition.
- Associated with prior infection with Human Papilloma Virus (HPV) of serotypes 16, 18, 31, 35
- Clinical features and management same as in non-HIV patients.

(For details regarding evaluation of women with HIV infection for cervical neoplasia and treatment: see the chapter on gynaecological manifestation of HIV.)

ANAL NEOPLASIA

- These are currently under study for declaration as a defining condition as incidence is rising in epidemic proportions.
- Homosexual men are the most affected.
- Related with HPV infection.

Suggested screening for anal neoplasia (especially for homosexual men infected with HIV)

- Anal PAP smear.
- Annual anoscopy.
- Biopsy, if any abnormality is seen, and then regular anoscopic follow up.

COMMENTS

Many other cancers are also showing changes owing to the AIDS epidemic. In India one such group of malignancies is head and neck malignancy.

HIV infected patients are at a risk of developing oral malignancies more commonly.

Other such malignancies are

- Lung cancer.
- Squamous and basal cell carcinomas.
- Testicular cancers.

The treatment in general depends on

- Performance status.
- Prognosis.
- CD4 counts.
- Cost of the treatment.

12.14

CARDIAC PROBLEMS IN HIV DISEASE

Clinical cardiac involvement in HIV disease is unusual. The most commonly seen clinical problem is pericarditis and/or pericardial effusion. Patients occasionally develop dilation of the right ventricle due to pulmonary hypertension. Focal myocarditis at autopsy is common, as are wall action abnormalities as seen by echocardiography. Clinical cardiomyopathy is unusual.

The most obvious of these abnormalities has been pericarditis, at times with

large effusions and often with cardiac tamponade. Frequently the reports did not identify the aetiology of pericarditis, although in some cases known pathogens such as *Mycobacterium tuberculosis*, staphylococcus, cryptococcus, and herpes simplex were found, presumably functioning as opportunistic infections.

Reports describe Kaposi's sarcoma (KS) and non-Hodgkin's lymphomas involving the heart and pericardium.

12.15

ENDOCRINE ABNORMALITIES

A number of endocrine abnormalities develop in patients with HIV infection, although many are likely to be non-specific responses to infection, stress, and malnutrition. Others are due to infiltration of endocrine glands by tumor or infection.

ADRENAL DYSFUNCTION

Of all endocrine deficiencies in patients with HIV disease, adrenal insufficiency has received the most attention.

Cytomegalovirus (CMV), Kaposi's sarcoma (KS), and cryptococcosis, toxoplasmosis, and tuberculosis were the most common causes.

Certain drugs used in patients with advanced HIV disease can affect adrenal function. Ketoconazole, which is used to treat certain fungal infections, inhibits adrenal corticosteroid synthesis and blunts the cortisol response to ACTH. This may be an underrecognized cause of impaired adrenal reserve and even frank adrenal insufficiency with Addisonian crisis. Rifampin also alters

the metabolism of glucocorticoids, thereby increasing hormone excretion values or necessitating higher exogenous steroid doses to maintain therapeutic effect.

Diagnosing adrenal insufficiency in patients with advanced HIV disease can be difficult when classic biochemical criteria are not met (e.g., basal cortisol levels less than 5 μ g/dl and ACTH-stimulated increase of less than 7 μ g/dl).

Treatment of proven adrenal insufficiency in HIV disease is essentially the same as in other clinical settings. Stress doses (180-200 mg of hydrocortisone in divided doses) are indicated during acute illnesses. Chronic replacement with supraphysiologic doses of glucocorticoids (e.g., greater than 30 mg hydrocortisone/day) should be avoided as it may worsen an already immunosuppressed condition. However, HIV disease is not a contraindication to pharmacologic glucocorticoid therapy (e.g., in central nervous system toxoplasmosis). Ketoconazole should be used with caution and adrenal function

monitored. Clinicians should also be aware of the effects of rifampin on steroid metabolism.

TESTICULAR DYSFUNCTION

The most common endocrine abnormality in one study of patients with HIV disease was a low serum testosterone level. Thus, Central hypogonadism or primary testicular failure may both be common in advanced HIV infection and correlate with degree of illness. Since there have been no studies on the effects of testosterone replacement in patients with chronic illnesses, the net benefits and risks remain unknown. Subjective or performance benefits of sex steroid replacement remain untested.

PANCREATIC FUNCTION

Pentamidine-induced hypoglycemia is extremely common in patients with advanced HIV disease treated for PCP and is most important pancreatic disturbance.

A small proportion of patients treated for HIV disease who receive the antiviral drug didanosine (ddI) develop diabetes, which may be preceded by low level or subclinical pancreatitis.

THYROID FUNCTION

Any chronic illness associated with malnutrition or inflammation can cause abnormalities in thyroid function tests. This is called “euthyroid sick” syndrome, to indicate that the thyroid gland is normal but that systemic illness has altered thyroid hormone physiology. It would therefore not be surprising if thyroid function abnormalities were common in patients with advanced HIV disease.

12.16

HEMATOLOGIC ASPECTS OF HIV INFECTION

Clinically significant hematologic abnormalities are very common in persons with HIV infection. Impaired hematopoiesis, immune-mediated cytopenias, and altered coagulation mechanisms have all been described in HIV-infected individuals. These abnormalities may occur as a result of HIV infection itself, as sequelae of HIV-related opportunistic infections or malignancies, or as a consequence of therapies used for HIV infection and associated conditions.

ANEMIA

Anemia is a very common finding in patients with HIV infection, particularly in those with more advanced HIV disease.

There are a number of possible aetiologies of anemia in patients with HIV infection. HIV infection alone, without other complicating illness, may produce anemia in some patients. A study of serum immunoreactive erythropoietin in HIV-infected patients

in various stages of illness showed that levels of the hormone failed to rise commensurately with increasing anemia, suggesting that insufficient amounts of erythropoietin may be one cause of anemia in this setting. Other studies have suggested that soluble factors in the serum of HIV-infected patients may inhibit hematopoiesis, or that direct HIV infection of marrow progenitor cells may play a role in producing anemia and other hematologic abnormalities associated with HIV infection.

Drug-induced anemia

Zidovudine (AZT) therapy is probably the most common cause of anemia in HIV-infected patients. It is generally observed that people with advanced disease are more prone to development of drug induced anemia.

This fall in hemoglobin was accompanied by a progressive rise in erythrocyte mean corpuscular volume that has now become familiar to physicians treating patients with AZT.

Effective therapy for AZT-induced anemia is available in the form of recombinant human erythropoietin.

Antimicrobial and antineoplastic agents used for treatment or prophylaxis against HIV-related conditions also cause anemia. For example, dapsone for treatment or prevention of *Pneumocystis carinii* pneumonia (PCP) may cause hemolytic anemia or generalized myelosuppression, and anemia routinely occurs when myelosuppressive chemotherapy is used to treat HIV-related non-Hodgkin's lymphoma.

Anemia caused by bone marrow infections

Infection with *Mycobacterium avium* complex (MAC) is another common cause of anemia in advanced HIV disease.

Other conditions associated with HIV infection can cause anemia as a result of direct involvement of the bone marrow. Tuberculosis, histoplasmosis, cryptococcosis, pneumocystosis, and non-Hodgkin's lymphoma can all infiltrate the bone marrow, generally causing pancytopenia.

Other causes of anemia

Gastrointestinal bleeding should also be considered in the evaluation of HIV-infected patients with anemia.

THROMBOCYTOPENIA

There are a number of possible aetiologies of thrombocytopenia in patients with HIV infection, including immune-mediated destruction, thrombocytopenic purpura, impaired hematopoiesis and toxic effects of medications. In many instances, however, thrombocytopenia is a relatively isolated hematologic abnormality associated with a normal or increase number of megakaryocytes in the bone marrow and elevated levels of platelet-associated immunoglobulin. These patients have the clinical syndrome commonly referred to as immune thrombocytopenic purpura (ITP).

Treatment of HIV-ITP should be reserved for patient with clinically significant symptoms such as recurrent epistaxis, gingival or subconjunctival bleeding, or gastrointestinal hemorrhage. Therapy is also recommended for hemophiliacs with HIV-ITP because of the substantial morbidity and mortality associated with bleeding in this group.

For treatment of ITP in patients without HIV infection, therapy with corticosteroids, cytotoxic agents, danazol, intravenous immunoglobulin infusions, plasmapheresis, interferon-alpha, and splenectomy have all been used with varying degrees of success. Many of these have also been used for treatment of HIV-ITP, but relatively unsatisfactorily.

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is a clinical syndrome characterized by the classic pentad of fever, neurologic dysfunction, renal dysfunction, microangiopathic hemolytic anemia, and thrombocytopenia.

Plasmapheresis is generally accepted as standard therapy for TTP, although plasma infusions, exchange transfusions, antiplatelet drug therapy, corticosteroids, and splenectomy have all been used with varying degrees of success.

Other causes of thrombocytopenia in HIV disease

Any of the infectious or neoplastic conditions that involve the bone marrow and any of the medications that cause generalized myelosuppression in patients with HIV infection can produce thrombocytopenia.

GRANULOCYTOPENIA AND ABNORMAL GRANULOCYTE FUNCTION

Although low granulocyte counts usually reflect the toxicity of therapies for HIV infection or associated conditions,

studies of untreated patients have also shown a high incidence of granulocytopenia, particularly in patients with more profound immunodeficiency.

Drug-induced Granulocytopenia

AZT therapy is probably the most common cause of low granulocyte counts in patients with HIV infection.

Ganciclovir therapy for symptomatic cytomegalovirus infection is another common cause of granulocytopenia in patients with advanced HIV disease.

A number of other medications commonly used in the setting of HIV infection can cause granulocytopenia. Trimethoprim-sulfamethoxazole and pentamidine are standard therapy for PCP. Granulocytopenia has been reported in a high percentage of patients receiving these antibiotics in clinical trials, but bacterial infections have not occurred as a consequence. Interferon-alpha therapy, both alone and in combination with AZT, can also cause granulocytopenia.

Antineoplastic chemotherapy is probably the most common cause of low granulocyte counts in patients without HIV infection.

12.17

RENAL ASPECTS OF HIV DISEASE

Since the onset of the world-wide HIV epidemic, reports have clearly documented that both functional disorders and structural damage of the kidney are common clinical complications of HIV infection. a pathologically unique renal disease called HIV nephropathy (HIVN) occurs in 5 to 10 percent of patients with HIV infection and usually progresses to end-stage renal disease (ESRD), necessitating dialysis therapy.

The major categories of clinical abnormalities associated with HIV infection occurring in nephrology practice today, and include (1) fluid and electrolyte abnormalities; (2) acute renal failure (ARF); (3) parenchymal renal disease, which may or may not result in significant renal dysfunction; (4) chronic, progressive renal insufficiency, primarily HIVN; and (5) ESRD and dialysis.

Nephrologic complications of HIV infection

Fluid and electrolyte abnormalities

- | | |
|--|--|
| Acute renal failure | Acute tubular necrosis |
| | Acute interstitial nephritis |
| | Postinfectious glomerulonephritis |
| | Hemolytic-uremic thrombotic thrombocytopenia |
| | Tumor lysis syndrome |
| Parenchymal renal disease | Opportunistic infection |
| | Malignancy |
| | Immune-mediated glomerulonephritis |
| | Tubulointerstitial disease |
| Progressive renal insufficiency
(HIV nephropathy) | |

(cont.)

End-stage renal disease (ESRD) Primary HIV
HIV secondary to risk factors in patients with
ESRD due to other causes

Hyponatremia from Syndrome of Inappropriate Secretion of Antidiuretic Hormone

Hyponatremia from Adrenal Insufficiency

Hyponatremia from Volume Loss and Replacement with Dilute Fluids

Common fluid and electrolyte abnormalities in patients with HIV infection

Hyponatremia	Volume depletion Inappropriate secretion of antidiuretic hormone Adrenal steroid synthesis abnormalities
Hypokalemia	Renal losses due to metabolic alkalosis Extrarenal losses due to diarrhea Amphotericin toxicity
Hyperkalemia	Type IV renal tubular acidosis Renal insufficiency Isolated mineralocorticoid deficiency Adrenal insufficiency
Acid-base abnormalities	Respiratory alkalosis Respiratory acidosis Metabolic acidosis Non-gap tubulointerstitial disease Non-gap diarrhea Gap chronic renal failure

Drug therapy in HIV infection

Drug causing acute renal failure	Amphotericin B Acyclovir Aminoglycosides Dapsone Foscarnet Rifampin Sulfadiazine Trimethoprim-sulfamethoxazole (cont.)
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Drugs requiring dose adjustment in renal insufficiency

- Acyclovir
- Ethambutol
- Fluconazole
- Ganciclovir
- Pyrazinamide
- Zidovudine (AZT)
- Didanosine (ddI)
- 2', 3' dideoxycytidine (ddC)

HIV –associated nephropathy

Clinical presentation of HIV nephropathy

- Heavy proteinuria-nephrotic syndrome
- Azotemia
- Normal blood pressure
- Enlarged kidneys on ultrasound

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ANTIRETROVIRAL THERAPY

Dr. Sanjay Pujary

Apart from treatment and prevention of opportunistic infections, antiretroviral therapy (ARV) is an important component of clinical management of HIV disease. Antiretroviral therapy has had a significant impact on the mortality and morbidity profile of the HIV epidemic in the developed world. Much of this success can be attributed to four independent factors: 1) advances in understanding of immune-pathogenesis of HIV infection; 2) Development of viral load (VL) assays; 3) development of potent drugs like protease inhibitors (PI's) and non nucleoside reverse transcriptase inhibitors (NNRTIs); and 4) results of three large clinical end point studies demonstrating that combination therapy significantly delayed progression of HIV disease and improved survival.

New antiretroviral drugs and treatment strategies, if used correctly, can substantially benefit HIV-infected persons. However, as the understanding of HIV disease has improved and the number of available beneficial therapies has in-

creased, clinical care of HIV-infected patients has become much more complex. Therapeutic success increasingly depends on a thorough understanding of the pathogenesis of HIV disease and on familiarity with when and how to use the more numerous and more effective drugs available to treat HIV infection. Even these new potent antiretroviral therapies will be of little clinical utility for treated patients unless they are used correctly and that, used incorrectly, they may even compromise the potential to obtain long-term benefit from other antiretroviral therapies in the future.

Hence, a working knowledge of ARV therapy is needed for every physician interested in managing HIV infection. It should be noted that knowledge in ARV therapy is constantly evolving and this article includes current information, which is the standard of care in the developed world.

Rationale for ARV therapy has developed from remarkable advances in the understanding of pathogenesis of HIV

infection. It is important to understand the principles of therapy of HIV infection, prior to offering therapy to patients.

Principles of therapy:

Following are the principles on which the rational use of ARV therapy is based:

1. HIV replication is relentless and leads to immune system damage and progression to AIDS: HIV is a rapidly multiplying virus and is constantly damaging CD4 cells. However, the CD4 cells also rapidly turnover, producing new cells as they are destroyed. In this intense war which goes on for years, the immune system finally gets fatigued and can no longer contain HIV leading to development of clinical disease. In the absence of ARV therapy, all infected persons will suffer progressive deterioration of immune function and finally develop AIDS and die. The average time of progression to AIDS after infection in the developed world is 10-11 years. However, similar studies from India are lacking.
2. Measuring Plasma Viral Load (PVL) and CD4 counts are crucial for initiating and modifying ARV therapy: While PVL indicates the magnitude of viral replication, CD4 counts indicate the extent of immune system damage. In addition, changes in PVL occur much earlier than those in CD4 counts and hence PVL should be monitored in all patients on ARV therapy. An analogy would be using blood sugar levels and glycosylated hemoglobin while monitoring control of diabetes. Imagine monitoring diabetes without blood sugar levels. Both PVL and CD4 counts should be measured prior to initiation of ARV therapy and then every 3-6 months on treatment.
3. Treatment decisions should be individualized by level of risk indicated by PVL levels and CD4 counts: There is substantial data in the West about the spectrum of PVL and CD4 values and hazards of progression based on the same. Hence, beyond certain cut off CD4 and PVL values treatment is indicated to prevent clinical progression. However, there is dearth of similar data in India. It is reasonable to offer ARV therapy to patients who have current or history of HIV related complications and/or have high PVL's (>10-20,000 copies/ml RT PCR) and/or low CD4 counts (<350/mm³) in our set-ups.
4. Maximum achievable suppression is the goal of therapy. This would mean bringing down the PVL to undetectable levels as measured by *ultra sensitive assays*. One of the predictors of durable suppression of HIV is to bring the PVL down to undetectable levels.
5. The most effective means to achieve durable and maximal suppression of HIV is simultaneous initiation of combinations of effective anti-HIV drugs. Current recommended

combinations is mentioned in table. It is also important to remember that current data on sequential therapy and induction-maintenance regimes is not encouraging and hence are not recommended.

6. Each anti-retroviral drug needs to be used according to optimum schedules and dosages. Reducing dosages of drugs on a trial and error basis is not advisable.
7. Number of drugs available for therapy are limited and moreover cross-resistance between specific drugs has been documented. Any change in ARV regimes increases future therapeutic constraints.
8. Women should receive optimal ARV therapy irrespective of pregnancy status.
9. Persons with primary HIV infection should be treated.
10. Patients on ARV therapy should be counselled to practice safer behaviors.

Perinatal transmission and ARV therapy:

One of the remarkable advances made over the last five years is development of interventions to reduce perinatal transmission of HIV. Using these interventions rationally is the most effective way to reduce the number of children born with HIV infection. Table 1 depicts the three most important trials to date addressing this issue.

Another important intervention is an Elective C-Section (prior to rupture of membranes and onset of labor). A meta-analysis of 15 prospective studies demonstrated that transmission of HIV was reduced by 50% when an elective C-section was performed. When combined with the PACTG 076 protocol, this procedure reduced the likelihood of transmission of HIV by 87%.

ARV therapy in adults: When to offer?

There is still a controversy on when to offer ARV therapy in adults. Reasonable guidelines are described in table 2. However, it is emphasized that an intense discussion with the patient should be done before starting ARV therapy. Remember, starting ARV therapy is eventually the patient's decision. The treating physician needs to make the patient understand the pros and cons of ARV therapy. Following points should be highlighted:

- Treatment is extremely costly.
- Treatment is life-long and stopping in between may be more harmful.
- Treatment would mean taking 15-20 tablets/capsules every day.
- Adherence to the regime is critical and drug holidays are not allowed.
- Long term side effects like lipodystrophy, diabetes with protease inhibitors need to be told to the patient.
- Treatment is not curative and the goal of therapy is to prevent progression and provide disease free survival.

ARV therapy: What to offer?

Table 3 enlists the currently approved ARV drugs in the US. All these drugs are virustatic. Many more drugs are in the pipeline and the list will increase in the coming years. It is important to use these drugs in rational combinations.

The recommendations of the HHS panel on what combinations to use are displayed in Table 4. Note that durable suppression of HIV can be achieved only with three drug combinations (2 NRTI's and 1 PI/NNRTI). The advantage of using an NNRTI (particularly direct comparison data with PI is available only with Efavirenz) is that PI's are spared for future use.

ARV therapy: How to follow up?

Once a patient decides to take ARV therapy the following baseline investigations need to be performed:

- Hemogram
- Serum chemistry
- Liver function tests
- Lipid profile
- CD4 counts and PVL

Clinical follow up of patients on ARV therapy needs to be done monthly. During initial visits, check for any acute adverse events e.g. nausea, diarrhea, abdominal cramps, rashes etc. Many of these acute adverse reactions are self-limiting. However, if severe then treatment may be stopped and re-introduced. Make sure that you stop all the

drugs simultaneously and restart them together after a short gap. Very rarely, drug regime needs to be changed because of severe toxicity.

Laboratory follow up is extremely crucial. Plasma Viral load needs to be repeated after 1 month, 3 month, 6 month and every 6 months subsequently. In most patients adherence to a regimen of potent antiretroviral agents should result in a large decrease (~ 0.5 to $0.75 \log_{10}$) in viral load by 1 month. The PVL should continue declining subsequently and in majority becomes undetectable by 12-16 weeks. With optimal therapy PVL should be undetectable at 6 months. If HIV RNA remains detectable in plasma after 6 months of therapy, the plasma HIV RNA test should be repeated to confirm the result and a change in therapy should be considered. The frequency of CD4 estimations during follow up is every 3-6 months.

While the patient is on ARV therapy, be careful about using concomitant medications. A wide range of interactions occur between ARV drugs (particularly PIs and NNRTIs) and commonly used drugs. Detailed descriptions of these are beyond the scope of this article. However, the most important and relevant interaction is between rifampicin and PIs and NNRTIs. Rifampicin reduces the levels of both of these drugs and hence use of them together is contraindicated.

Long term side effects of PIs include

glucose intolerance, diabetes and lipodystrophy and serum lipid abnormalities. Recently, two patients with Coronary heart disease due to accelerated atherosclerosis subsequent to PI use has been documented. It would be prudent to repeat chemistry profile quarterly and lipid profile yearly.

ARV therapy: When to change?

The decision to change a failing regime is extremely crucial and needs to be thought of very carefully. For optimal advantage diagnosis of drug failure needs to be done as early as possible. Response to the second regime depends on early detection of drug failure and subsequently early switching to the proposed regime.

Following are the criteria for changing therapy:

- Less than a 0.5-0.75 log reduction in plasma HIV RNA by 4 weeks following initiation of therapy, or less than a 1 log reduction by 8 weeks
- Failure to suppress plasma HIV RNA to undetectable levels within 4-6 months of initiating therapy. In this regard, the degree of initial decrease in plasma HIV RNA and the overall trend in decreasing viremia should be considered.
- Repeated detection of virus in plasma after initial suppression to undetectable levels, suggesting the development of resistance. However, the degree of plasma

HIV RNA increase should be considered.

- Any reproducible significant increase, defined as 3-fold or greater, from the nadir of plasma HIV RNA not attributable to intercurrent infection, vaccination, or test methodology.
- Undetectable viremia in the patient on double nucleoside therapy. Patients currently receiving 2 NRTIs who have achieved the goal of no detectable virus have the option of continuing this regimen or may have modification to conform to regimens in the preferred category (Table 4). Prior experience indicates that most of these patients on double nucleoside therapy will eventually have virologic failure with a frequency that is substantially greater compared to patients treated with the preferred regimens.
- Persistently declining CD4+ T cell numbers, as measured on at least two separate occasions. This will essentially mean a decline in the absolute CD4 counts of more than 30% of baseline or decline of more than 3% in percentage CD4 counts.
- Clinical deterioration.

Before attributing drug failure to development of viral resistance the physician should rule out poor adherence, absorption abnormalities and drug interactions. Only after ruling out these issues should viral resistance as a cause of drug failure be considered.

For changing a drug regime the physician needs to have a thorough understanding of the resistance and cross-resistance profile of ARV drugs. The detailed list of what drugs to change to is exhaustive and beyond the scope of this article. In general, do not change a single drug or add a single drug to a failing regimen; it is important to use at least two new drugs and preferably to use an entirely new regimen with at least three new drugs. Resistance testing kits are now available. They are of two types—genotypic and phenotypic. The exact clinical utility of these tests is yet to be fully defined.

Conclusion:

In the last few years, the availability of new drugs and new drug combinations

to combat HIV infection has translated into progressive clinical benefit for patients. We have entered an era of improved therapeutic success, with reduced rates of opportunistic infections, hospitalizations, and mortality. At least in countries that can afford the cost of the new antiretroviral therapies, the perspective has changed from viewing HIV disease as inevitably fatal to viewing it as a disease that is potentially manageable for several decades. Following the discovery that the high replication rate of HIV is the leading pathogenic force that drives the progression of HIV disease, and the characterization of mechanisms of HIV resistance to antiretroviral drugs, new principles of antiretroviral therapy have been defined.

Table 1: Important ARV-Perinatal transmission trials

	PACTG 076	Bangkok-CDC	PETRA (Interim)
Intervention	AZT 200 mg po tid (14 th -36 th week) IV AZT (2 mg/kg Loading, 1 mg/kg/hr) AZT to baby (2 mg/kg q6h for 6 weeks) No breast feeding	AZT 300 mg bd (36 th wk. onwards) AZT 300 mg 3 hrly (from onset of labor) No AZT to baby No breast feeding	AZT/3TC• (36 th wk.onwards) AZT/3TC (labor) AZT/3TC (neonate 1 wk) Breast feeding optional
Efficiency of reduction	67%	51%	50%

• Doses: 300 mg bid AZT and 150 mg bid 3TC during gestation; 300 mg AZT 3 hrly and 150 mg 3TC 12 hrly intrapartum; and 4 mg/kg of AZT 12 hrly and 2 mg/kg 3TC 12 hrly to the new-born.

Table 2: ARV therapy-When to start?

Clinical Category	CD4/PVL value	Recommendation
Symptomatic	Any value	Start
Asymptomatic	CD4<500 And/or PVL>10,000 copies/ml	Start
Asymptomatic	CD4>500 And/or PVL<10,000 copies/ml	?Start ?Observe

Table 3: Current approved ARV drugs

NRTIs	NNRTIs	PIs
Azidothymidine (AZT)	Nevirapine	Saquinavir-SGC
Stavudine (d4T)	Delavirdine	Ritonavir
Lamivudine (3TC)	Efavirenz	Indinavir
Dideoxycytidine (ddC)		Nelfinavir
Dideoxyinosine (ddI)		
Abacavir		

NRTIs – Nucleoside analog reverse transcriptase inhibitors

NNRTIs- Non Nucleoside reverse transcriptase inhibitors

PIs – Protease inhibitors

Schematic representation of the HIV life cycle

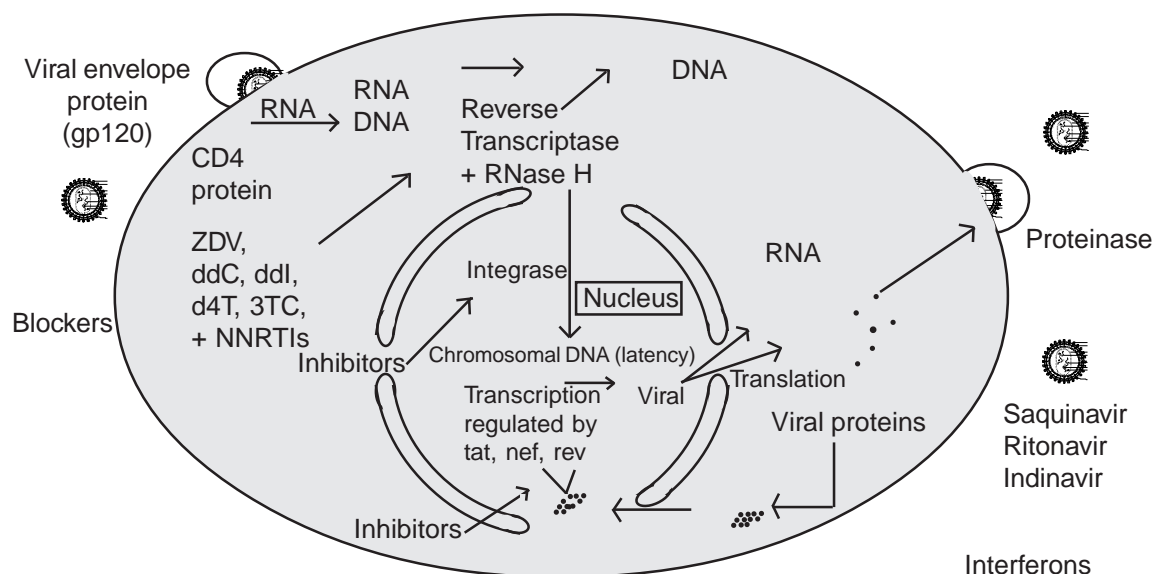


Table 4: HHS panel recommendations on use of ARV drugs(Dec.1998)

Preferred	Strong evidence of clinical benefit and/or sustained of PVL. One choice each from Column A and Column B
	Column A
	Indinavir
	Nelfinavir
	Ritonavir
	Saquinavir-SGC
	Ritonavir/Saquinavir SGC or HGC
	Efavirenz
	Column B
	AZT/ddI
	d4T/ddI
	AZT/ddC
	AZT/3TC
	d4T/3TC
Alternative	Less likely to provide sustained suppression, or data inadequate Nevirapine or delavirdine + 2 NRTIs
Not generally recommended	Strong evidence of clinical benefit but initial virus suppression is not sustained in most patients 2NRTIs Saquinavir-HGC + 2 NRTIs
Not recommended	Evidence against use, virologically undesirable, or overlapping toxicities All monotherapies D4T/AZT DDC/DDI DDC/D4T DDC/3TC

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CHARACTERISTICS OF AVAILABLE ANTIRETROVIRAL DRUGS

NUCLEOSIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

Didanosine (dideoxyinosine) (ddl), (VIDEX)

Dosage

Neonatal dose (infants aged <90 days): 50 mg per m² of body surface area every 12 hours.

Pediatric dosage range: 90 to 150 mg per m² of body surface area every 12 hours. (Note: may need higher dose in patients with central nervous system disease.)

Adolescent/Adult dose: Body weight ≥ 60 kg: 200 mg twice daily. Body weight <60 kg: 125 mg twice daily.

Major toxicities

Most frequent: Diarrhea, abdominal pain, nausea, and vomiting.

Unusual (more severe): Peripheral neuropathy (dose related), electrolyte

abnormalities, and hyperuricemia.

Uncommon: Pancreatitis (dose related, less common in children than adults), increased liver enzymes, and retinal depigmentation.

Drug interactions

- Possible decrease in absorption of ketoconazole, itraconazole, and dapsone; administer at least 2 hours before or 2 hours after ddl.
- Tetracycline and fluoroquinolone antibiotic absorption significantly decreased (chelation of drug by antacid in pediatric powder and tablets);
- Concomitant administration of ddl and delavirdine may decrease the absorption of these drugs; separate dosing by at least 2 hours.
- Administration with protease inhibitors: indinavir should be administered at least 1 hour before or after ddl on an empty stomach, ritonavir should be administered at least 2 hours before or after ddl.

Lamivudine (3TC), (EPIVIR/LAMIVIR)

Dosage

Neonatal dose (infants aged <30 days): 2 mg per kg of body weight twice daily.

Pediatric dose: 4 mg per kg of body weight twice daily.

Adolescent/Adult dose: Body weight ≥ 50 kg: 150 mg twice daily. Body weight <50 kg: 2 mg per kg body weight twice daily.

Major toxicities

Most frequent: Headache, fatigue, nausea, diarrhea, skin rash, and abdominal pain.

Unusual (more severe): Pancreatitis, peripheral neuropathy, decreased neutrophil count, and increased liver enzymes.

Drug interactions

- Trimethoprim/sulfamethoxazole (TMP/SMX) increases 3TC blood levels
- When used with zidovudine (ZDV) may prevent emergence of ZDV resistance and for ZDV – resistant virus, reversion to phenotypic ZDV sensitivity may be observed.

Stavudine (d4T), (ZERIT/STAVIR)

Dosage

Neonatal dose: Under evaluation in Pediatric AIDS Clinical Trial Group protocol 332.

Pediatric dose: 1 mg per kg of body weight every 12 hours (up to weight of 30 kg).

Adolescent/Adult dose: Body weight ≥ 60 kg: 40 mg twice daily. Body weight <60 kg: 30 mg twice daily.

Major toxicities

Most frequent: Headache, gastrointestinal disturbances, and skin rashes.

Uncommon (more severe): Peripheral neuropathy and pancreatitis.

Other: Increased liver enzymes.

Drug interactions

- Drugs that decrease renal function could decrease clearance.
- Should not be administered in combination with zidovudine (poor antiretroviral effect).

Zalcitabine (ddC), (HIVID)

Dosage

Neonatal dose: Unknown.

Pediatric usual dose: 0.01 mg per kg of body weight every 8 hours.

Adolescent/Adult dose: 0.75 mg three times a day.

Major toxicities

Most frequent: Headache, gastrointestinal disturbances, and malaise.

Unusual (more severe): Peripheral neuropathy, pancreatitis, hepatic toxicity, oral ulcers, esophageal ulcers, hematologic toxicity, and skin rashes.

Drug interactions

- Cimetidine, amphotericin, foscarnet, and aminoglycosides may decrease renal clearance of ddC.
- Antacids decrease absorption of ddC.
- Concomitant use with ddl is not recommended because of the increased risk of peripheral neuropathy.
- Intravenous pentamidine increases the risk for pancreatitis; do not use concurrently.

Zidovudine (ZDV, AZT), (RETROVIR/ZIDOVIR)

Dosage

Neonatal dose: Oral: 2 mg per kg of body weight every 6 hours.

Pediatric usual dose: Oral: 160 mg per m² of body surface area every 8 hours.

(Pediatric dosage range: 90 mg per m² of body surface area of 180 mg per m² of body surface area every 6-8 hours.)

Adolescent/Adult dose: 200 mg three times a day or 300 mg twice daily.

Major toxicities

Most frequent: Hematologic toxicity, including granulocytopenia and anemia, and headache.

Unusual: Myopathy, myositis and liver toxicity.

Drug interactions

- Increased toxicity may be observed with concomitant administration of: ganciclovir, interferon-alpha, TMP/SMX, acyclovir and other drugs that can be associated with bone marrow suppression.
- Atovaquone, methadone, valproic acid and fluconazole may increase ZDV concentration (and therefore potential toxicity).

- Decreased renal clearance may be observed with co-administration of cimetidine.
- ZDV metabolism may be increased with co-administration of rifampin and rifabutin; clarithromycin may decrease concentrations of ZDV.
- Ribavirin decreases the intracellular phosphorylation of ZDV (conversion to active metabolite).
- Phenytoin concentrations may increase or decrease.
- Should not be administered in combination with d4T (poor antiretroviral effect).

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Delavirdine (DLV), RESCRIPTOR

Dosage

400mg three times a day.

Major toxicities

Most frequent: headache, fatigue, gastrointestinal complaints and rash (may be severe).

Drug interactions

- Metabolized in part by hepatic cytochrome P450 3A (CYP3A). There could potentially be multiple drug interactions.
- DLV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity.

- DLV is not recommended for concurrent use with antihistamines (e.g., astemizole or terfenadine); sedative-hypnotics (e.g., alprazolam, midazolam, or triazolam); calcium channel blockers (e.g., nifedipine); ergot alkaloid derivatives; amphetamines; cisapride; or warfarin.
- DLV clearance is increased, resulting in substantially reduced concentrations of DLV, with concurrent use of rifabutin, rifampin, or anticonvulsants (e.g., phenytoin, carbamazepine, or phenobarbital). Concurrent use is not recommended.
 - Absorption of DLV is decreased if given with antacids or histamine₂ receptor antagonists.
 - Increased trough concentrations of DLV if given with ketoconazole or fluoxetine; increased levels of both drugs if DLV is given with clarithromycin.
 - DLV increases levels of dapsone and quinidine.
 - Administration with protease inhibitors: decreases metabolism of saquinavir and indinavir, resulting in a significant increase in saquinavir and indinavir concentrations and a slight decrease in DLV concentrations.

Nevirapine (NVP), (VIRAMUNE)

Dosage

Pediatric dose: 120 to 200 mg per m² of body surface area every 12 hours.

Adolescent/Adult dose: 200 mg every 12 hours. Note: Initiate therapy at half dose for the first 14 days. Increase to full dose if there is no rash or other untoward effects.

Major toxicities

Most frequent: Skin rash (some severe and life-threatening, including Stevens-Johnson syndrome), sedative effect, headache, diarrhea and nausea.

Unusual: Elevated liver enzymes and rarely, hepatitis.

Drug interactions

- Induces hepatic cytochrome P450 3A (CYP3A); autoinduction of metabolism occurs in 2-4 weeks with a 1.5-fold to twofold increase in clearance. There could potentially be multiple drug interactions.
- Drugs having suspected interactions and should be used only with careful monitoring: rifampin and rifabutin; oral contraceptives sedative-hypnotics (e.g., triazolam or midazolam); oral anticoagulants; digoxin; phenytoin; or theophylline.
- Administration with protease inhibitors: indinavir and saquinavir concentrations are decreased significantly and ritonavir concentration may be decreased. Whether increased doses of protease inhibitors are needed is unknown.

PROTEASE INHIBITORS

Indinavir, (CRIXIVAN)

Dosage

Should not be given to neonates.

Pediatric Dose: Under study in clinical trials: 500 mg per m² of body surface area every 8 hours.

Adolescent/Adult dose: 800 mg every 8 hours.

Major toxicities

Most frequent: Nausea, abdominal pain, headache, metallic taste, dizziness and asymptomatic hyperbilirubinemia (10%). Unusual (more severe): Nephrolithiasis (4%) and exacerbation of chronic liver disease.

Rare: Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, ketoacidosis, diabetes and hemolytic anemia.

Drug interactions

- Cytochrome P450 3A4 (CYP3A4) responsible for metabolism. There could potentially be multiple drug interactions.
- Indinavir is not recommended for concurrent use with antihistamines (e.g., astemizole or terfenadine); cisapride; ergot alkaloid derivatives; or sedative-hypnotics (e.g., triazolam or midazolam).

- Indinavir levels are significantly reduced with concurrent use of rifampin. Concurrent use is not recommended.
- Rifabutin concentrations are increased, therefore a dose reduction of rifabutin to half the usual daily dose is recommended.
- Ketoconazole and itraconazole cause an increase in indinavir concentrations.
- Co-administration of clarithromycin increases serum concentration of both drugs (dosing modification not needed).
- Co-administration of nevirapine may decrease indinavir serum concentration.

Nelfinavir, (VIRACEPT)

Dosage

Pediatric dose: 20 to 30 mg per kg of body weight three times a day.

Adolescent/Adult dose: 750 mg three times a day.

Major toxicities

Most frequent: Diarrhea.

Less common: Asthenia, abdominal pain, rash and exacerbation of chronic liver disease.

Rare: Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, ketoacidosis and diabetes.

Drug interactions

- Nelfinavir is in part metabolized by cytochrome P450 3A4 (CYP3A4). There could potentially be multiple drug interactions.
- Nelfinavir is not recommended for concurrent use with antihistamines (e.g., astemizole or terfenadine); cisapride; ergot alkaloid derivatives; certain cardiac drugs (e.g., quinidine or amiodarone); or sedative hypnotics (e.g., triazolam or midazolam).
- Nelfinavir levels are greatly reduced with concurrent use of rifampin. Concurrent use is not recommended.
- Rifabutin causes less decline in nelfinavir concentrations; if co-administered with nelfinavir, rifabutin should be reduced to one half the usual dose.
- Co-administration with delavirdine (DLV) increases nelfinavir concentrations twofold and decreases DLV concentrations by 50%.

Ritonavir, (NORVIR)

Dosage

Pediatric dosage range: 350 to 400 mg per m² of body surface area every 12 hours.

Adolescent/Adult dose: 600 mg twice daily. To minimize nausea/vomiting, initiate therapy starting at 300 mg twice daily and increase stepwise to full dose over 5 days as tolerated.

Major toxicities

Most frequent: Nausea, vomiting, diarrhea, headache, abdominal pain and anorexia.

Less common: Circumoral paresthesias and increase in liver enzymes.

Rare: Spontaneous bleeding episodes in hemophiliacs, pancreatitis, increased levels of triglycerides and cholesterol, hyperglycemia, ketoacidosis, diabetes and hepatitis.

Drug interactions

- Ritonavir is extensively metabolized by hepatic cytochrome P450 3A (CYP3A). there could potentially be multiple drug interactions.
- Not recommended for concurrent use with analgesics (e.g., meperidine, piroxicam, or propoxyphene); antihistamines (e.g., astemizole or terfenadine); certain cardiac drugs (e.g., amiodarone, or quinidine); ergot alkaloid derivatives; cisapride; sedative-hypnotics (e.g., alprazolam, clorazepate, diazepam; certain psychotropic drugs (e.g., bupropion hydrochloride, clozapine, or pimozide); rifampin; or rifabutin.
- Ritonavir increases metabolism of theophylline (levels should be monitored, and dose may need to be increased).
- Ritonavir increases levels of clarithromycin (dose adjustment may be necessary in patients with impaired

renal function); desipramine (dose adjustment may be necessary); and warfarin (monitoring of anticoagulant effect is necessary).

- Ritonavir may increase or decrease digoxin levels (monitoring of levels is recommended).
- Drugs that increase CYP3A activity can lead to increased clearance and therefore lower levels of ritonavir include carbamazepine, dexamethasone, phenobarbital, and phenytoin (anticonvulsant levels should be monitored because ritonavir can affect the metabolism of these drugs as well).

Saquinavir, (INVIRASE) [(hard gel capsule) and FORTOVASE (soft gel capsule)]

Dosage

Adolescent/Adult dose: Hard gel capsules: 600 mg three times a day; Soft gel capsules: 1200 mg three times a day.

Major toxicities

Most frequent: Diarrhea, abdominal discomfort, headache, nausea, paresthesias, and skin rash.

Less common: Exacerbation of chronic liver disease.

Rare: Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, ketoacidosis, and diabetes.

Drug interactions

- Saquinavir is metabolized by the cytochrome P450 3A4 (CYP 3A4) system in the liver, and there are numerous potential drug interactions.
- Saquinavir decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. Saquinavir is not recommended for concurrent use with antihistamines (e.g., astemizol or terfenadine); cisapride, ergot alkaloid derivatives, or sedative-hypnotics (e.g., midazolam or triazolam).
- Saquinavir levels are significantly reduced with concurrent use of rifampin (decreases saquinavir levels by 80%), rifabutin (decreases saquinavir levels by 40%), and nevirapine (decreases saquinavir levels by 25%).
- Saquinavir levels are decreased by carbamazepine, dexamethasone, phenobarbital and phenytoin.
- Saquinavir levels are increased by delvirdine and ketoconazole.
- Saquinavir may increase levels of calcium channel blockers, clindamycin, dapsone, and quinidine. If used concurrently, patients should be closely monitored for toxicity.

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UNIVERSAL PRECAUTIONS IN HOSPITAL SETTINGS

Dr. R. R. Gangakhedkar

INTRODUCTION

The rapidly increasing HIV prevalence rates in Indian population along with the high morbidity associated with late stage HIV disease increases the likelihood of a physician or any health care worker - knowingly or unknowingly extending care to symptomatic or asymptomatic HIV infected individuals attending the health care settings. HIV is present in different concentrations in almost all the bodily fluids. Health care workers are likely to develop a serious concern due to the likelihood of occupational exposure to HIV. However, *the risk of HIV transmission due to occupational exposure is very low (0.42%)* and very few health care workers have acquired it through this route, world over. It is important to remember that this very low risk can be minimized further by following universal precautions for all the patients, irrespective of HIV sero-status.

HIV transmission

HIV is isolated from almost all bodily fluids including amniotic, synovial,

pleural, peritoneal, pericardial, cerebrospinal fluids, sweat, faeces, nasal secretions, sputum, tears, urine, breast milk etc. Amongst all the bodily fluids, HIV concentration is the highest in CSF. However, it is present in infective dosages in semen, vaginal and cervical fluid, and blood. Naturally, the acts, where such bodily fluids are exchanged, are important from the point of view of transmission i.e. sexual intercourse, transfusion of HIV infected person's blood, needle sharing, and vertical route from HIV infected mother to the baby. Despite high concentration of HIV in CSF, the low likelihood of its exchange reduces the risk of HIV transmission through CSF. The risk of transmission through exchange of fluids, other than sexual fluids and blood tends to be either extremely low or insignificant. The risk through such bodily fluids can increase only when it additionally shows visible contamination of blood.

Mandatory testing

AIDS was discovered 1980's. Naturally, most of the presently practising doctors

have not been taught about it in their medical curriculum. Even their initial response is likely to be similar to that of lay persons. The unrealistic, unjustified demand of mandatory testing of all the patients under care follows immediately. Mandatory testing is in an extremely costly proposition. Secondly, it is likely to drive individuals indulging in *at risk* behaviours underground. There is a high viraemia, during the window period when the ELISA for HIV infection is non-reactive. Mandatory screening will not identify such individuals and will not serve the desired purpose. A non-reactive HIV test might lead to complacency and failure to adhere to universal precautions by the health care worker, thereby, increasing the risk. Additionally, the possibility of refusal to extend health care delivery to the hapless HIV disease patient based on non-scientific, unreasonable, fear-based conclusions is likely to increase after knowing his/her HIV sero-status. Therefore, adopting standard 'Universal Precautions' for every patient rather than extending this privilege only to the HIV infected individuals or mandatory testing is desirable.

One must also remember that HIV is very sensitive to chemical decontamination. The microbial resistance to chemical decontamination in decreasing degrees is as follows:

Highest for Bacterial spores
Mycobacteria
Non-lipid viruses

(polio, rhino etc)
Fungi (candida, cryptococci etc)
Bacteria (pseudomonas, staphylococcus etc)

Lowest for Lipid viruses (HSV, CMV, Hepatitis B, HIV).

The virus is easily inactivated by boiling for 20 minutes, use of soap for 2 minutes and autoclaving in addition to the other chemical disinfectants like 2% gluteraldehyde, 70% alcohol, hypochlorite solution and undiluted savlon.

HIV infected health care workers

The sensational report of a Florida based dentist allegedly transmitting created a major controversy amongst the patient population. At that moment, some of the state medical associations were demanding mandatory screening of all the patients attending medical establishments for their safety (?). A similar demand followed in response to it that all the health care workers must also be screened for anti-HIV antibodies. The CDC recommended that the HCWs knowing their HIV status should voluntarily refrain from performing exposure-prone, invasive procedures. However, later investigations in the dentist's case cast doubts about the mechanism of transmission and the controversy settled down.

Basic steps to avoid exposure to HIV in the hospital setting

- Apply good basic hygienic practices with regular hand washing.
- Cover existing wounds or weeping skin lesions with waterproof dressing. Such workers should not perform direct patient care or invasive procedures without dressing.
- Take simple protective measures to avoid direct physical contact with blood such as; use of gloves, and clothing such as; use of gown and plastic apron.
- Protect mucous membranes of eyes, mouth & nose from blood splashes using spectacles and mask.
- Prevent puncture wounds, cuts & abrasions in the presence of blood.
- Avoid usage of sharp instruments wherever possible especially for suturing muscles.
- Follow a safe procedure for handling and disposal of sharps (use puncture-proof containers).
- Clear up spillage of blood promptly and disinfect such surfaces.
- Establish a procedure for safe disposal of contaminated waste.
- Provide information & yearly training to avoid the risk of exposure to health care workers & establish a needle stick audit to prevent future recurrence of such situations.

Barrier precautions for high risk procedures

- Double gloves (Outer pair half-size larger)
- Plastic apron.
- Water resistant shoe-cover or shoes.
- Face shield or goggles.

Use of gloves

Indiscriminate, unnecessary use of gloves is wasteful. Latex rubber is a natural product and its availability is limited. Hence, prudence must be exercised in its usage. It should be used where uncontrolled bleeding can occur or splashing is expected e.g. major surgical procedures.

- Intra-arterial punctures
- Removal of intravenous/ intra-arterial lines
- Inexperienced venepuncturist/ restless patient
- All internal bodily examinations i.e. per vaginal, per rectal examination and for STDs etc
- Cleaning blood spills
- Cleaning and disinfecting equipment
- Handling chemical disinfectants
- While performing invasive operative procedures

Care of gloves

Surgical and examination gloves are manufactured for single use only. Nevertheless, in some situations, reuse

of these gloves will be required. Gloves can be reused four to five times after testing for quality by conducting insufflation test. Gloves may be reprocessed by the following method:

- Rinse your gloved hands thoroughly in hypochlorite solution.
- Then rinse your gloved hands in clean tap water to remove the disinfectant, since detergents may cause deterioration of the gloves.
- Then wash your gloved hands with soap and water and rinse thoroughly, since detergents may cause 'weakening', leading to enhanced penetration of liquids through undetected holes.
- Remove the gloves and hang them up by the cuffs to dry.
- Wash your hands thoroughly again for 2 minutes in soap and water.
- Test for holes in the gloves before re use by filling each glove with 325 ml +/- 25 ml of water/air at room temperature, twist them 360 degrees and place them in a rack for two minutes to detect leakage by visual and tactile means. If possible, dust them with French chalk or talcum powder before testing.

Needle stick injuries

The risk of acquiring HIV infection through this route is less than 0.4% (1 in 250 HIV contaminated needle stick injuries). It depends on the following factors (Adapted from Burke RA, Garvin GM, Sulis CA. *Infection Control*

and risk reduction for health care workers in HIV infection: A clinical Manual, 2nd Edition, 1993, Eds: Libman H, Witzburg RA, Little, Brown and Company, Boston.):

- Number of exposures - single or multiple
- Type of exposure-Percutaneous, Mucosal, Cutaneous
- Type of bodily fluid - Blood, blood stained bodily fluids, other bodily fluids, HIV culture material, age of fluid -fresh or old
- Severity of injury-
Depth of injury (superficial/deep)
Size of wound
Duration of contact
Type of needle (solid / hollow)
Bore size of the needle
Site of injury (its vascularity)
Estimate amount of alleged fluid injected
- Patient Characteristics-HIV disease stage
HIV viremia
Use of antiretroviral medications
- HCW characteristics - First aid procedures following exposure
Skin integrity
Use of barriers at the time of exposure
Immunologic status
Use of post-exposure antiretroviral prophylaxis

Most of the needle stick injuries are preventable. The overall transmission rate was found to be 9/3791 for

percutaneous (0.23%) and 1/1206 for mucocutaneous exposures (0.08%), in a study. Another study reported the transmission efficiency for percutaneous exposure as 0.18% (95% C.I. 0.04-0.53) comprising of hollow-bore needle stick injury 0.19% (95% C.I. 0.02-0.67), scalpel injuries 0.28% (95% C.I. 0.01-1.58) and almost none after non-intact skin contamination (upper confidence limit 0.79%). Less than 100 health care workers world over have acquired HIV through occupational exposure despite the fact that millions of HCWs are attending & managing knowingly or unknowingly HIV infected individuals. Of the 52 confirmed cases of acquisition of HIV infection through occupational route, majority is paramedical workers and the accidents involved were with blood or bloody body fluids. No seroconversions have been reported through needle sticks amongst the surgeons as yet.

Recommendations

- Wear two gloves during operations or when there is likely to be a prolonged contact with blood/body fluids. This prevents perforations on gloves at the same site & the risk of direct contact with such fluids.
 - Generally the needle stick injuries occur on the index finger & thumb of non-dominant hand while suturing the layers in small cavities. Exercising caution, especially avoiding a rash approach due to fatigue at the end of operation, reduces their number dramatically.
- Never hand over instruments during surgery by hand. Put them in a tray and the surgeon should take the instrument by the blunt end.
 - Handle needles minimally. **Do not recap them.** Recapping is likely to be associated with needle stick injury.
 - Surgical procedures requiring blind manipulations and hand-held sharp instruments should be modified wherever possible.
 - When disposable needles are not available & recapping is necessary, place the cap in a flat or suitable surfaces so that the needle can be inserted without any injury.
 - Dispose off needles & scalp blades etc. in a puncture resistant container-metallic or plastic-filled with freshly prepared 1% hypochlorite solution. Decontaminate the needles using 10% hypochlorite solution for at least half an hour or incinerate them. Needle incinerator costs about Rs.12-15000. While disposing syringes, one may just heat-seal the nozzle of the syringe or incinerate them. It is advisable to operate a common incinerator facility on shared cost basis between a few hospitals in the city.
 - Workers disposing off sharp instruments should use reusable postmortem (thick) gloves when handling the hospital waste.

In case of needle stick injury

1. Let the wound bleed freely without pressing it.

2. Wash the wound thoroughly under running water with soap for about two minutes.
3. Dip the hand in undiluted savlon for 15 seconds.
4. *Do not panic.*
5. *Test the blood of patient for HIV infection.*
6. Report your injury to the appropriate hospital authorities.
7. *If the patient is found to be HIV infected repeat the ELISA test on the health care worker at 3 weeks, 12 weeks, 24 weeks. In case, the patient is not HIV infected, take his/her sexual history. He/she should be explained the situation and be requested to come for follow up and HIV testing at 3 weeks, 12 weeks, and 24 weeks. This will take care of the window period. A small aliquot of the serum must be sealed in screw cap vial and store it at - 20^o even if the patient is not HIV infected. This may be useful in future if need to test arises later.*
8. Additional tests for HBV and HCV, which are mainly transmitted parenterally, should be conducted in the patient; and if necessary amongst the health care workers in the event the patient is positive to them.
9. Use condoms regularly with the sexual partner/s for 6 months. Such a person must refrain from donating blood or organs.
10. Utility of prophylactic post-exposure antiretroviral drugs for post exposure prophylaxis is debatable. The

protection that can be conferred through its use may not be as high as one may expect. However, the health care worker should be counseled and the risk and benefits of post-exposure prophylaxis (PEP) should be explained to him/her enabling the person to make the choice.

Post-exposure prophylaxis with antiretroviral drugs

Although prevention of occupational exposure to HIV infection is the first and most effective step, the reported ability of AZT to reduce the risk of acquisition of HIV warrants its consideration for formulating strategies for workplace safety. A case control study demonstrated a 79% decrease in the risk after PEP with AZT. PEP reportedly prevented or ameliorated retroviral infection in some studies in animals. Now it is well known that use of AZT during pregnancy reduces the risk of transmitting HIV to the fetus and/ or infants by two thirds. This reduction is partially attributable to the reduction in HIV titre in mother's blood. Despite the theoretical possibility, its efficacy in preventing acquisition of infection amongst humans is still not clearly established. At least 10 treatment failure cases are documented in the literature. Moreover, the risk of acquisition of HIV after occupational exposure is as low as 0.3% for percutaneous exposure, about 0.1% for mucous membrane exposure and 0.1% for skin exposure. However, use of PEP depends essentially on the choice of the health care worker and on

the exposure level. Newer drugs belonging to the class of protease inhibitors are reported to be more potent for reducing viral load in the blood. Use of two drugs for PEP is now being considered as more potent as compared to AZT. Indinavir is considered to be more potent than saquinavir at the currently recommended doses and also appears to have fewer drug interactions and short-term adverse effects than ritonavir. Use of AZT alone is associated with minor adverse effects such as nausea, headache etc in PEP. However, there is hardly any data on long-term toxicity of such drugs in persons who are not infected with HIV.

In populations where AZT has been used as an antiretroviral agent, the AZT resistant 'community' strains prevalence of about 10-20% in US are common. In such situations use of two drugs could be very useful. This essentially means that in India where the population is AZT- naive, the proportion of AZT resistant strains would be low. Hence use of AZT monotherapy should suffice for PEP.

If the exposure is:

Definite parenteral as in intramuscular/venous injection - Endorsable.

Possible parenteral as in subcutaneous or mucosal - Available.

Doubtful parenteral as in non-bloody fluid exposure - Discouraged

Non-parenteral as in cutaneous(intact skin) - Not necessary.

Recently, CDC has published its recommendations for PEP where evaluation of exposure is slightly different. Exposure codes are determined as follows:

EC 1: Exposure to small volume (a few drops & short duration) of blood or bloody fluid in an individual having compromised mucous membrane or skin integrity.

EC 2: Exposure to large volume (several drops, major blood splash and/or long duration) of blood or bloody fluid in an individual having compromised mucous membrane or skin integrity.

OR

Percutaneous exposure of low severity such as with a solid needle, superficial scratch

EC 3: Percutaneous exposure of a severe nature such as large-bore hollow needle, deep puncture, visible blood on device or with a needle used in source patient's artery or vein).

However, those who wish to take antiretrovirals must do so as early as possible ideally within 15 minutes of exposure (preferably within 1-2 hours). AZT alone may be taken in the dosages of 500 mg orally 6 hourly for 8 days or 200 mg 8 hourly for 4 weeks. The optimal duration of treatment for PEP in humans is

MMWR Recommendations for PEP (1998) are:

Exposure Category (EC)	HIV RNA (Source)	PEP Recommendation
1	1 (Low)	PEP may not be warranted Exposure risk of drug toxicity may outweigh the risk of HIV transmission
1	2 (High)	Consider AZT + 3TC Exposure poses negligible risk.
2	1 (Low)	Recommend AZT + 3TC. Most exposures are in this category but risk of HIV acquisition is not high.
2	2	Recommend AZT + 3TC+ Indinavir or Nelfinavir.
3	1 or 2	Increased risk of HIV transmission observed.

unknown. However, a four- week course with the identified antiretroviral/s should be taken according to the 1998 CDC guidelines. Use of PEP after 24-36 hours is shown to be not effective in animals same animal studies. Remember to monitor hematologic parameters. Prophylaxis is not advocated for women who are pregnant and are in first trimester or breast feeding. Those who receive AZT should be advised to defer pregnancy for 6 months.

PEP combination regimes

1. AZT, 200 mg 8 hourly (or 300 mg bd) along with lamivudine (3 TC), 150 mg 12 hourly for four weeks. Lamivudine cause minor gastrointestinal symptoms and some times may cause pancreatitis.

2. AZT and lamivudine in the standard doses along with indinavir in the dose of 800 mg 8 hourly, before meals or two hours after meals, for four weeks. If indinavir is not available, one may use nelfinavir in the dosage of 750mg 8 hourly with meal or a snack. About 0.8% patients receiving indinavir are likely to develop kidney stones which can be reduced to some extent by asking patients to drink at least 1.5 liters of water every day. The patients must be advised about drug-drug interaction while receiving indinavir.

Precautions during labor

For all the health care workers attending the patient, *whether it be a Dai, ANM or a clinician*, these precaution are necessary.

- Always wear separate gloves during each internal examination or when touching any area of body or a place soiled with contaminated body fluids. e.g. PV examination, amniotomy, episiotomy, disposal of placenta.
- Always wear a gown or plastic apron where splash of blood or bodily fluids is expected. e.g. amniotomy, delivery, episiotomy, caesarian section & cutting an umbilical cord.
- Always wear gloves & a gown/ plastic apron while handling a new-born till blood and amniotic fluid is washed off the infant's skin.
- Wear glasses & mask to protect mouth, nose & eyes from a splash.
- Dispose of placenta by incineration, burying or throwing down a pit latrine.
- If the worker has cuts, open wounds or weeping skin lesions, cover it with water-proof dressing. Otherwise they should refrain from taking direct patient care.

If there is a splash on the skin/ gloves are torn

Wash the hands thoroughly with soap and water for 2 minutes after the removal of gloves under running water. Dip your hands for 15 seconds in undiluted Savlon as an added precaution. Wear fresh pair of gloves before restarting the work.

Sterilization and disinfection of equipment

All reusable equipment must be

appropriately sterilized. Whether it is needles, syringes, scissors, specula, extractor cups or forceps. HIV is a heat sensitive virus. Standard methods of sterilization & disinfection are sufficient. Autoclaving for about 20 minutes at 121⁰ C -one atmospheric pressure above i.e. 101 kPa, 15 lb/in² inactivates the virus. One could use a modified pressure cooker of WHO/ UNICEF type if autoclave is not available. All used disposable needles and syringes must be initially treated first by soaking in a chemical disinfectant.

Equipment such as blood pressure cuff, stethoscopes, ECG electrodes need not be sterilized.

- All other reusable equipment must be appropriately sterilized such as needles, scissors, specula, extractor cups or forceps, etc.
- All used equipment must be initially cleaned by soaking in a chemical disinfectant or detergent before further processing.
- Autoclaving : Reusable equipment must be initially cleaned by soaking in a chemical disinfectant or detergent before further processing.
- Boiling-needle and syringes completely immersed in water and boiled for 20 minutes in batches.
- Chemical disinfectants should not be used for cleaning or disinfecting needles or syringes.
- For endoscopes - 2 % gluteraldehyde, complete immersion for 30 minutes.

Sterilizing endoscopes

1. Mechanical cleansing should be carried out before the secretions dry with water. Alcohol and aldehyde compounds should not be used for mechanical cleansing as they coagulate proteins.
2. After removing endoscope from the patient, flush air/ water channel for 10-15 seconds. Aspirate detergent through biopsy/suction channel for 10-15 seconds.
3. Immerse the endoscope, completely, in warm water & detergent.
4. Brush through suction biopsy channel.
5. Rinse it with water/ detergent.

Disinfection and storage

Complete immersion in 2% gluteraldehyde for not less than 5 minutes (preferably 30 minutes). Rinse it with water , then dry. After disinfection, rinse each channel with 70% alcohol, dry with compressed air. Store in hanging position & not in the box.

Mouth to mouth resuscitation

The risk of HIV transmission while imparting mouth to mouth resuscitation is low. However, the practice of giving mouth to mouth resuscitation without a barrier needs to replace by advocating placement of atleast a gauze piece on the mouth while performing it.

Specimen transport

Every fluids and tissue specimen should be considered as potentially infectious. They should be kept in a tightly closed container, which should in turn be kept in leak-proof transparent bags with clear biohazard label. In developing countries, using such approach is essential atleast for CSF and blood, for all the specimen and not for those of HIV infected patients only.

Precautions for handling spilled, potentially contaminated fluids

1. Spills of infected or potentially infected material should first be covered with paper toweling or other absorbent material (thick quality blotting paper and if nothing is available atleast use old newspaper). Freshly prepared hypochlorite solution at a concentration of 1.0 % available chlorine (10g/liter;10000 ppm) should be poured around the spill area and covered with some absorbent material and placed in the contaminated waste container. The surface should then be wiped again with the disinfectant. Heavy-duty gloves should be worn throughout the procedure and still, direct contact with the gloved hands with the disinfected spill should be avoided. Broken glass or fractured plastic should be swept up using a dustpan and brush.
2. Needle stick or other puncture wounds, cuts and skin contaminated by spilled or splashed specimen

material should be thoroughly washed with soap and water; bleeding from any wound should be encouraged with gravitational pressure.

3. All spills, accidents, and overt or potential exposure to infectious material should be reported immediately to the laboratory supervisor. A written record should be prepared and maintained. Needle stick audit should be initiated in every hospital. After critical analysis, work related suggestions to reduce the risk could be issued to the worker.

Laundry and linen

The risk is negligible. There should be minimal handling of soiled linen. Washing linen with detergent is adequate. Severely soiled ones may be burnt.

- Soiled linen must be handled as little as possible.
- All soiled linen must be handled with gloved hands.
- All soiled linen must be put in plastic bags immediately and bags must be tied and sent to the laundry.
- Persons sorting linen in the laundry must put on gloves.
- Use of detergent and hot water washing (at 160^o F) of dishes and laundry provides adequate decontamination for HIV.
- In laundry, detergent in hot water (71^oC or 160^oF) must be used at least for 25 minutes for complete

decontamination. Use of bleach in the laundry is highly recommended.

- Laundry or linen, which is grossly soiled with blood, should be discarded as hazardous infectious waste. It should be burnt.

Toilet care and sluice

- Toilets, bathrooms, urinals and bed pans do not spread HIV infection.
- Sluice disposal can be carried out exactly as for any other infected patient.
- Sluice, blood, suctioned fluid, excretions and secretions can be poured down the sanitary drain connected to sewer. The use of municipal sewerage does not create any significant health problems as viruses require living cell as for survival and are unlikely to survive longer this way.
- Urine pot, bed-pan, suction jars etc., can be cleaned with soap and rinsing water followed by 30 minutes in 1% household bleach or by autoclaving.

Liquid or solid waste

Blood, suction fluid, excretory or secretory fluids. Disinfect with 10% hypochlorite solution for half an hour.

Dispose it off in a drain connected to sewer system or in a pit latrine. Solid waste should be buried/ incinerated, or dumped in pit latrine. Soiled dressings, diapers, menstrual pads should be burnt/ buried/dumped in pit latrine.

Note: UNIVERSAL PRECAUTIONS DO NOT APPLY for Colostrum, breast milk, meconium, faeces, nasal secretions, sweat, tears, sputum, urine and vomit unless they contain visible blood.

Conclusion

The risk of transmission of HIV through occupational exposure is negligible. Mandatory screening of HIV infected patients is unethical, a costly proposition and can lead to complacency amongst health care providers thereby increasing risk. Adoption of universal precautions is a feasible, better alternative. Risk management through training of health care workers, provision of adequate, regular protective supplies of standard quality is essential to avoid discrimination against HIV infected patients.

For further reading:

1. Burke RA, Garvin GM, Sulis CA. *Infection Control and risk reduction for health care workers in HIV infection: A clinical Manual*, 2nd Edition, 1993, Eds: Libman H, Witzburg RA, Little, Brown and Company, Boston.
2. Centers for Disease Control. Recommendations and Reports: *Public Health Service Guidelines for the Management of Health-Care Worker Exposures to HIV and Recommendations for Postexposure Prophylaxis*. MMWR, 1998;47 RR-7):1-33.
3. Centers for Disease Control. *US Public Health Service statement on management of occupational exposure to human immunodeficiency virus(HIV), including considerations regarding zidovudine post-exposure use*. MMWR, 1990, 39(RR-1): 1-14.
4. Pavri K.M. “ *Standard Biosafety Guidelines*”, Center for AIDS Research and Control, Bombay. 2nd Edition, 1991.

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WOMEN AND AIDS

Dr. Sanjeevane Kulkarni

In the beginning of the HIV epidemic, even in the later part of 1980s, women were on the periphery. Today they are at the center of the concern. WHO estimates almost 50% of the newly infected adults are women. Especially in developing countries like ours this percentage is likely to outnumber its counterpart. Among both men and women, the hardest hit group is the youth. In nearly all parts of the world, the peak age of infection is lower in girls than boys. In many countries 60% of all new HIV infections are among 15-24 year olds, with female to male ratio of two to one.

When we start realizing this world-wide reality and see it in a concave mirror of the setting of our clinic, we cannot afford to look at women merely as persons, as patients, but we need to see, to understand, to think about their socio-political, cultural, economic aspects and the resultant sexual subordination. Therefore in this article, along with the physio-pathological aspects, we would discuss these.

This is not just an academic exercise. If we intend to provide comprehensive care to a woman infected with HIV, then the understanding of her status in her family and in the society becomes crucial.

Let's try and analyze this by addressing some important questions:

1. Why are women more vulnerable to the infection?
2. What could be the impact of HIV infection on the women?
3. What should be our strategy?

Why are women more vulnerable?

1. The major route of transmission of HIV in our country is through heterosexual intercourse. As is the case with all sexually transmitted diseases (STDs) women are more vulnerable than men. There are several reasons.
 - a) Semen, which has high concentration of the virus remains in the vaginal canal for a relatively longer time.

- b) An extensive area of mucous surface of vagina and cervix is exposed to the semen.
 - c) It is physically and culturally more difficult for women to clean the vagina after intercourse.
 - d) Transmission of HIV is facilitated by the presence of other STDs. Women may have these infections without realizing it. More than 50% STDs in women are asymptomatic and go unnoticed, as they are internal.
 - e) Women are less likely to seek timely treatment for STDs. Stigma attached to STDs, inaccessibility of the clinics, lack of money, less priority given to women's health problems in the families further prevent them from getting care for STDs.
- 2) Young women are at a greater risk than mature women. A teenager's vagina is not as well lined with protective cells, her cervix may be more easily eroded. Potential bleeding at the time of first intercourse could be a risk factor. Even in our country many times very young girls are married to men much older their age.
 - 3) Young women are the most vulnerable at such a time when their negotiating and economic power is the least. This makes them easier targets for sexual coercion and exploitation. The situation is worsened when men start feeling that "younger girls are safer for sex."
- 4) In India, women have little control over the sexual behaviour of their sexual partners. A society, which holds monogamy and mutual fidelity in high esteem, however condones multi-partner sex by males but stigmatizes the same by women. So women are more likely to be monogamous or have fewer lifetime partners. Yet they can get infected from their steady partners.
 - 5) Males resist condom use and women are unable to negotiate safe sex putting themselves (as well as men) at a greater risk of HIV infection.
 - 6) Lack of education that leads to lack of awareness as well as lack of economic self – sufficiency make women more dependent on males for support. In the setting of poverty this helps sex trade to flourish. Apart from induction into organized sex work there are several women who may be driven to casual commercial sex or sex for petty benefits in cash or kind. Women in these situations can hardly negotiate safer sex.

Impact of HIV/AIDS on women

- 1) The most visible impact of increasing number of women in childbearing age getting infected with HIV will be increasing number of children being born with HIV infection. A corollary of the same is increase in the number of children orphaned due to death of parents because of HIV disease.

- 2) As this would be realized, women infected with HIV would be pressurized not to become pregnant or would be forced to get sterilized. If they were already pregnant they would be forced to terminate their pregnancies. Lack of access to contraception or safe abortion may force them to bear unwanted children or face unsafe, illegal abortions.
- 3) Women being sexually, economically and biologically vulnerable to HIV/AIDS, they are often stigmatized and blamed for spreading HIV/AIDS and other STDs. They are often identified as reservoirs of infection or as vectors of transmission to their male partners and their offspring. This view fails (a) to focus on men's equal responsibility, (b) to develop services meeting needs of women and (c) to develop specific interventions to enable women to protect themselves.
- 4) Women are supposed to be the voluntary caregivers of their families. Yet if they become sick they may not be provided with enough support. On the other hand if the man is sick not only would she be expected to provide all the care but also it is seen that all the resources may be exhausted in caring for the sick man. There is no proper and equitable planning and allocation of resources. After the death of the man, a woman will be expected or forced to take up economic responsibilities too. More often than not they are not

capable of shouldering this responsibility due to lack of education, training, exposure and their own sickness.

- 5) It is seen that the major brunt of all social inequalities has to be borne by the most disadvantaged persons in any community. Women with HIV infection being such persons—increasing HIV epidemic would affect them in all aspects of life.

What should be our strategy?

We have to tackle three areas.

- 1) Reducing the vulnerability of women to HIV/AIDS,
- 2) Preventing HIV infection among women and
- 3) Caring for women with HIV/AIDS.

Reducing vulnerability:

Men and women must work together to counter gender discrimination and the subordination of women by improving women's social and economic status.

The issue has to be tackled at cultural, social, political, economic and policy levels.

Prevention of HIV infection among women:

By increasing awareness and empowerment we should help women to negotiate safer sex or to avoid unwanted sex so that they can protect themselves.

We should develop and provide such a method for protection against HIV infection that they have more control over.

We should develop women friendly STD diagnosis and treatment facilities.

Caring for women with HIV/AIDS:

We should provide care and support for these women. This should include

clinical care as well as support for their families. Counselling regarding various decisions about contraception, pregnancy and abortions must be made available. We should also provide help regarding planning and allocation of their available resources. Planning foster care for children with HIV or for children orphaned by AIDS also should be a part of such a support programme.

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AIDS AND MEN WHO HAVE SEX WITH MEN

UNAIDS Point of View

Sex between men occurs in most societies. Its existence, and its importance for AIDS prevention, though, is frequently denied.

Sex between men is the main route of transmission of HIV in some parts of the world. In some other places it is a secondary route of transmission. Nearly everywhere, it is a significant and interconnected part of the epidemic and needs to be taken seriously into consideration.

Some 5-10% of all HIV infections worldwide are due to sexual contact between men, but the figures vary considerably from one place to another. In North America, parts of Latin America, most of Europe, Australia and New Zealand, the rates are often as high as 70%.

The key steps that need to be taken to deal effectively with HIV transmission in male-to-male sex are:

- for political leaders and all other key players to accept that sex between men exists, and is relevant to AIDS prevention, care and support work
- for national AIDS programs to include the issue of male-to-male sexual transmission of HIV in their planning and implementation
- for donor agencies to commit themselves to giving serious consideration to funding AIDS prevention, care and support among MSM
- for both governments and nongovernmental organizations (NGOs) to promote safer sex and the provision of condoms, conducting programs involving: outreach work; peer education projects; and mass media and 'small media' campaigns, as appropriate
- for national AIDS programs and other partners to encourage the creation of gay organizations and strengthen existing networks of men who have sex with men
- for national AIDS programs and other partners to reproduce or expand HIV prevention approaches that have proved successful among MSM, locally and abroad

- for political leaders and influential people in society to support HIV programs directed at MSM
- for national AIDS programs and donor agencies to ensure that effective HIV interventions among MSM are maintained. In the past, good projects have sometimes been stopped, or had funding decreased, when it was thought that they had been successful, or that the risk to MSM had declined.

Sex between men

Sex between men occurs virtually in most societies. It is often stigmatized by society, and its public visibility, therefore, varies considerably from one country to another. Good HIV programs addressing men who have sex with men (MSM) are thus vitally important-though up to now they have often been seriously neglected.

Though common-often denied, suppressed and stigmatized, extent of sex between men certainly varies from place to place, for cultural or other reasons. Its existence, however, is frequently denied by the authorities in many places-because of religious teachings or cultural taboos, or because as individuals they feel uncomfortable with the subject. Details on the prevalence of same-sex behavior are lacking in most areas, for lack of proper research on the subject-often itself the result of denial.

Sexual acts between men have often

been condemned, by civic and religious leaders, and criminalized by law. In some countries, penalties for those accused of sexual acts between men are among the severest available. Elsewhere, even where same-sex behavior is not illegal, there is frequently unofficial persecution by the authorities (the police or military, for instance), or discrimination against or stigmatization of those men known or thought to be having sexual relations with other men. For these reasons, in many parts of the world, much sex between men is hidden or secretive. This makes an assessment of its extent, and of the various types of sexual acts that occur, even more difficult. Hidden — and therefore overlooked Many men who have sex with other men -whether occasionally or frequently- do not regard themselves as ‘homosexual’ or ‘bisexual’ in any way.

They are very often married. Even if they are not, they may have sex with women as well. This observation applies particularly to those societies where marriage is strongly urged by society and the family. This contributes to the hiddenness of much sex between men.

In most countries, a certain proportion of sex between men is in some way done in return for payment. While some of this sex work is full-time and professional, a large proportion, on the other hand, is highly informal-unlike the situation with female sex work-and is conducted, perhaps, with the expectation of a small present in return for services given.

Many male sex workers have a wife or regular female partner, and would not self-identify as homosexual. Frequently, their clients are married men or men who also have sex with women.

In most parts of the industrialized world, and in a growing number of other centers, a significant number of MSM have developed an awareness about their sexuality, and identify to a greater or lesser extent as 'gay' or 'homosexual'. In many places in these countries a specific gay social scene has developed, including gay bars, discos, gyms, restaurants and radio stations. Also, groups of gay men concerned with issues of human rights or of AIDS prevention have proliferated in recent years. Even in these places where there is a visibility and certain openness of MSM, there are many other men-possibly a majority of the total-who do not self-identify as gay or bisexual, because of stigmatization or fear of discrimination or because of a lack of role models, among other reasons. However, self-identification is not essential for a recognition that same-sex behavior exists.

Why is the issue of sex between men important for AIDS prevention?

Sexual practices penetrative anal sex often occurs in sex between men. Other common sexual acts that occur are oral sex (mouth-to-penis), ejaculation between the partner's thighs or elsewhere on the surface of his body, and mutual masturbation. The proportion of sex acts between men involving

penetrative sex is thought to vary considerably from one location to another, depending on local culture and other factors. As with other matters relating to sex between men, precise figures are absent almost everywhere, because of lack of research and the essentially private nature of the subject matter. The amount of unprotected penetrative anal sex that occurs, though, is highly important as regards AIDS prevention, since-among all the possible sexual acts between two men-HIV can only be easily transmitted by anal sex.

Risk of HIV transmission relatively high

The risk of HIV transmission through anal intercourse (and anal sex can also be practised between a man and a woman) is especially high, when condoms are not used. The risk to the receptive partner in unprotected anal sex is, on average, several times higher than the next most risky category in sexual transmission, that of a woman having unprotected vaginal intercourse with an HIV-infected man. The reason for the increased risk in anal sex is that the lining of the rectum is thin and can easily tear, and even only small lesions in the lining are enough to allow the virus easy access. Even without such lesions, it is thought that there may be a lower immunity in the cells of the rectal lining to resist HIV than there is, for instance, in the lining of the vagina. Unprotected anal sex also poses a risk to the insertive partner (when HIV is present in the other person). The presence of other,

untreated sexually transmitted diseases (STDs), such as syphilis, gonorrhoea and chlamydial infections, can greatly magnify the risk of HIV transmission, where HIV is present.

When condoms are used in anal sex-and used properly, with water-based lubricant, in each and every such sexual encounter-then the risk of HIV transmission becomes very low. Risk of HIV transmission is also very low (and may be non-existent) where non-penetrative acts take place-the practice of so-called 'safer sex'. In theory, HIV can be also transmitted through oral sex if a condom is not used for protection, but the risk here is generally considered very low.

The attitude that has prevailed in some places-that "these things don't exist (or hardly exist) in our society, so we don't need to take any action"-is both wrong and dangerous, since it is likely to ignore a significant (even if relatively small) part of the overall epidemic.

What needs to be done?

It is highly important to do HIV prevention work among MSM along the lines laid out below. Experience from many countries shows that such efforts are likely to be more credible and effective when carried out alongside health care for men who are already infected. This includes counselling for those with concerns relating to their sexuality or to actual or possible infection with HIV.

All health-care staff, including those in STD clinics, should be made aware of the needs of MSM and should treat their clients in a welcoming and sympathetic manner.

Accept that male-to-male sex exists and is relevant to AIDS prevention In those places where there is a refusal to accept that sexual behavior between men exists and is furthermore an issue that is highly relevant to AIDS prevention, it is important that advocacy work be carried out to remedy this shortcoming. Such advocacy will be based partly on research and should be done by the national AIDS program or by NGOs. Its aim must be to get all the key players-the politicians, civic and religious leaders, and influential people in institutions such as the military, academia, the media and the legal and medical professions-to recognize the existence and importance of the issues involved. The research on which it is based will mainly seek to find out why there is a refusal to recognize these issues, and to work out an appropriate way to argue the case.

Protect rights to reduce vulnerability: Like other people, MSM have rights that must be respected. These include the right to information-about risk behavior and how to protect themselves during sex; to services related to HIV prevention and care-including counselling, STD services and other health services; and to the freedom from discrimination on the grounds of sexual orientation. When rights such as these

are not respected, MSM have less control over their behavioral risks and are therefore more vulnerable to HIV infection. On the other hand, protecting such rights greatly increases the likelihood that they will be able to access and use prevention messages, skills and services.

Ending discrimination is thus of great importance for AIDS work, and is something that governments can play a part in, through their legal systems. Among the legal measures that should be considered here is the abolition of laws criminalizing consenting sexual behavior between men. For example, at the end of 1996, the new government of South Africa approved a new Constitution guaranteeing equal rights and outlawing all discrimination against gay men and women—a Constitution that has been hailed as a model for others to follow.

Place male-to-male HIV transmission in national AIDS programs: Once such a recognition has been achieved—or in those countries where it is already generally accepted that sex between men occurs and can be an important factor in HIV transmission—the government should commit its national AIDS program to place the issue of sex between men firmly in its national AIDS program. This involves making MSM issues a component of the national AIDS plan, and giving proper thought to carrying out the MSM projects to achieve set, measurable targets.

Similarly, donor agencies funding AIDS prevention work should include the issue in their funding priorities.

Promote safer sex and risk reduction: Provide condoms and STD treatment. Governments who have accepted the importance of MSM issues and who have made it part of their national AIDS program should organize campaigns to promote safer sex among MSM. Appropriate NGOs should consider carrying out this work—and irrespective of whether their government has accepted the issue. In fact, there are good examples of NGOs conducting successful prevention projects among MSM in places where the authorities continue to ignore the issues. All these campaigns should include the provision of condoms and lubricants (and instructions on proper condom use) and the promotion of alternatives, such as that of non-penetrative sex, to high-risk sexual behavior.

Effective programs to detect and treat STDs in MSM, leading to a reduction of the prevalence of STDs in the MSM population, will reduce the risk of HIV transmission. MSM are often difficult to reach, and careful thought is needed about intervention programs that will find them and be effective.

Methods to reach such men have been developed over the years in several countries; depending on the particular conditions of the society, they include a mix of media campaigns (including

particularly the use of the so-called 'small media' -for example, pamphlets and flyers-whose dissemination is usually more discreet than other forms of media message), peer education and outreach programs.

In outreach work, a mixture of trained professionals and volunteers go out to find men who have sex with men, in a range of places that may include public 'cruising' spots, bars and other social venues, and work places. Peer education uses trained current members of the targeted community-for example, male sex workers. The face-to-face methods used in both approaches provide privacy and confidentiality, and enable the targeted person to ask questions. Outreach programs also provide easy access to high quality condoms and lubricants, and promote safer sex, knowledge of condom use and negotiating skills.

Enough lessons about HIV interventions among MSM have been learnt by now world-wide to know what works and what does not. It must be stressed that programs aimed at men who have sex with men that have proved effective should be maintained. There have been cases where programs have had their funds cut or stopped after the project was pronounced to have been 'successful', or when it was thought that the risk to men engaging in same-sex behavior had declined. As with other forms of AIDS prevention program, the price of continuing freedom from

infection is both eternal vigilance and eternal effort.

It is essential that their peers on HIV risks and prevention methods should educate adolescents and young men. All too frequently lacking access to information on sex between men and thus ignorant of the risks and more vulnerable than others, these young men will tend to listen to their friends.

"We need better interventions for prevention among men who have sex with men, including those who do not identify themselves as homosexual or bisexual. A key strategy is to strengthen emerging gay communities, because they are the ones who can do the best job of prevention education. At the same time, we need to challenge the discrimination that makes people vulnerable." — Dr Peter Piot, Executive Director of UNAIDS.

Working with men who have sex with men is often difficult for governments. However, there are often networks and informal community groups of self-identified gay men, who are interested in carrying out HIV prevention and care activities among men who have sex with men.

Identify and reproduce effective HIV prevention efforts among gay community groups:

Taking this a step further, the amassed experience of gay men's groups world-

wide is now sufficient to start identifying effective types of prevention strategies, and to investigate these to see whether, and in what conditions, they might be replicable elsewhere-thus avoiding having to 'reinvent the wheel' many times over. This is a promising development in extending prevention efforts among men who have sex with men, and one which is being pursued by

UNAIDS in cooperation with groups around the world.

Give strong support to HIV programs for MSM: The more that leading political figures and other influential people in society support-and are seen to support-HIV programs directed at MSM, the more likely it is that such programs will be effective and will be maintained.

*(Ref.: AIDS and Men who have sex with Men, UNAIDS point of view)
UNAIDS: Information Centre.*

AIDS AND MEN

At night in a small village, a man taps his wife's shoulder. Aware of the children sleeping beside them, she silently pulls up her clothing and lets him enter her.

A hundred miles away in a comfortable city apartment, a young woman and her husband make love affectionately.

In a park in the centre of the city, two married men make eye contact. One drops to his knees as the other exposes himself.

Not far away, a woman in her twenties greets her eighth client of the evening, a man 30 years older.

The next afternoon, a teenage girl goes to bed with the businessman who pays for her education.

In the bush, a man in his early twenties molests his seven-year-old nephew. Later that day, his younger brother will persuade his girlfriend to surrender her virginity to him.

That evening in a seaport, an unemployed man returns home drunk and rapes his wife.

Nearby, a young man takes an old syringe, siphons up a bubbling brown paste, injects half into himself and passes the syringe to his friend.

Next door, two men who have known each other for years make love.

A few blocks away, a man negotiates the price of sexual services with a man in woman's clothing.

In the suburbs, a woman in her sixties entices her husband to bed.

The settings and characters may change, but the scenes are universal. The village could be in India, Mali or Bolivia. The apartment might be in Vancouver, Nairobi or Buenos Aires. The park could be in the same city, or in Dhaka, Dakar or Rio de Janeiro. The tourist might be European or North American, Asian, African or Middle Eastern. Such sexual and drug-injecting activity can be found on every continent, in

almost every country, irrespective of law, religion or custom. In each case, if one partner has HIV – the virus which causes AIDS – it may be passed to the other, and in each case transmission could be prevented.

Each scene includes a man because without men there would be no AIDS epidemic. Men are involved in almost every case of sexual transmission; perhaps one in every 10 cases is the result of transmission solely between men. Four of every five drug injectors are men. With more sexual and drug-taking partners than women, men have more opportunity to transmit HIV. More often than not, it is men who determine whether sex takes place and whether a condom is used. In general, women are more liable to contract HIV without passing it on, men more liable both to contract and transmit the virus to others.

Men and women both fall sick and die from AIDS, but in many ways men are less affected by the disease. Worldwide, women are contracting HIV at a faster rate than men. Women with the virus may pass it to their future children. At home and in hospital, women assume greater responsibility of caring for the sick.

Not every man is likely to transmit HIV to others. Perhaps no more than a quarter of men endanger themselves and their female or male partners in this way. Yet, that one in four represents hundreds of millions of men who, it appears, regularly act without thought and leave women to deal with the consequences of their actions.

Those responsible for the AIDS epidemic are also at risk. A man cannot transmit HIV to others unless he contracts it first himself; the same act – unprotected sexual intercourse or drug injection without sterilisation – jeopardises himself as much as his partner. Why do some men regularly risk their own lives, the lives of their loved ones and the lives of acquaintances and strangers? Can men be persuaded to change their behaviour?

Men undoubtedly take risks in relation to HIV. Whether or not they should also take responsibility for transmission of the virus, and how they can do so, are questions that cannot be resolved easily.

(From : AIDS AND MEN – Taking Risks or Taking Responsibility?- PANOS/Zed Books.)

18

PALLIATIVE AND TERMINAL CARE

Dr. Vinay Kulkarni

Definition:

It is the management of patients in whom death is almost certain and not too far off, where the control of symptoms is the prime clinical objective, and (in addition) the emotional and spiritual preparation of both patients and 'family' is given high priority. (European Association of Palliative Medicine, 1989.)

The challenges:

- a. Complexity: Unfamiliar symptoms like uncontrolled diarrhoea, prolonged fevers, etc.
- b. Chronicity: Potentially treatable opportunistic infections requiring prolonged treatment, continuous prophylaxis, and multiple medicines with possible toxicities.
- c. Severity
- d. Unpredictability
- e. Quality of life
- f. Universal fatality.

The recurrent opportunistic infections, which are treatable, either by prophylaxis or maintenance regimens, bring some problems for the physician. It is quite difficult both for doctor and patient to decide when to stop medicines. Discussing this may be the first acknowledgement that the patient is facing death. The issue needs to be handled with pragmatism and sensitivity.

This makes it necessary that there is a very close communication between the physician and the patient and family at all stages of the care.

Some general principles

There are certain misconceptions about the concept of palliation. Many believe that palliation is for one who is 'losing the battle'. Some feel that it is a 'once for all' decision and can not be reversed; and also that once you choose for palliation you shut off choices for therapeutic interventions. All these are myths that need to be broken.

With the advancing disease, there is increasing need to keep a balance between cost and benefit of any intervention, be it diagnostic or therapeutic. In resource poor situations the decisions have to be based on practical grounds and not on emotional and social pressures. Patient's willingness to accept side effects of treatments with doubtful benefits needs to be properly addressed to.

There is a tendency to make certain assumptions about patient's wishes, as it is difficult to understand the complex process of interaction between the illness and person's reactions to it. In addition to the underlying pathology social, psychological and spiritual factors could determine this interaction. The worst feeling a person who is dying may have is that of helplessness.

This needs to be approached from various angles. One may be required to go beyond limitations of technological interventions. A multidisciplinary team approach involving a team of physician, nurse, social worker, psychologist, physiotherapist, spiritual/religious clergy, 'self-help' group members, hospice provide-would certainly yield the best results.

We can always help someone who is sick in some little way. Drugs could be used for unconventional indications. e.g. opiates that are used conventionally as analgesic, may be used to ease dyspnoea and control diarrhoea. We must keep on

explaining the rationale behind each of our action, even if the patient says s/he does not want to influence it. We must be honest about the exact prognosis. The prognosis in immediate future, depending upon the stage of the disease, needs to be explained clearly.

A right place where patient can express emotions without embarrassment, has to be chosen for such discussions. Discussions in open wards should be avoided. Inclusion of patients loved ones in the discussion will always be more effective.

We must explain the prognosis using general terms such as better, the same or worse. Also we must keep on telling that something unexpected can still happen.

We must honour patient's wishes, hopes seriously. We should try and set achievable goals. We should allow some freedom to take risks-like travel. We should try to bring some happiness in the lives by showing positive attitudes.

Managing pain

Three broad categories of mechanisms of pain have been described: nociceptive, neuropathic and idiopathic.

Effective management of pain differs between categories. One must still remember that patients present with permutations of all three.

Nociceptive pain ('opioid responsive' pain) is caused by local tissue damage. Nociceptors exist in skin, muscle, connective tissue and viscera. Such pain tends to respond to non-steroidal anti-inflammatory drugs, opiates and the newer analgesics such as ketorolac (an anti-inflammatory with potent, non-opioid analgesic properties).

Neuropathic pain ('non-opioid responsive' pain) is unexplained by continuing tissue injury. It represents discharge arising primarily within the nervous system. Neuropathic pain may follow damage caused by herpes simplex, cytomegalovirus (CMV), HIV, or in the broader context of neuropathic or demyelinating processes. Response to opiates usually requires doses disproportionate to the level of pain experienced.

Idiopathic pain occurs when the level of pain perceived by the patient is disproportionate to the disease present. Psychological or idiopathic pain waxes and wanes with emotionally painful subjects. Idiopathic pain is usually a function of disturbance in the social, psychological or spiritual realm; for example, fear and guilt may be somatised or amplify a relatively minor symptom. Effective management requires one to deal predominantly with understanding the symptomatology and the exacerbating effects of fear, anxiety, sleeplessness, lost future, and of death and its connotations. One should ask

help from a counsellor, psychologist or spiritual healer.

Remember:

- Any pain is a genuine symptom and is disturbing.
- Assume that there is a physical trigger, until proven otherwise
- Majority of patients have combinations of these three categories

Managing the terminal phase

Nutrition

There is a debate about nutrition and fluids in terminal care. However, because of severe anorexia fasting and dehydration generally pose little problem. It is generally seen that many patients want their family members to be less assertive and let them make their own choice.

Oral discomfort

It is common due to debility and dehydration. The skin and mucosa become prone to ulceration. Anticholinergics used for bronchial secretion or bowel control cause local dryness. For local hydration simple measures like oral sponges, frequent saline or water mouthwashes or sucking ice cubes, can be employed. In the extreme, 2% lignocaine may be employed.

Managing pain without drugs

Several techniques could be used to relieve pain without taking drugs or to enhance the effect of pain medication - relaxation, imagery, distraction, and skin stimulation are some of such techniques.

Relaxation: Relaxation relieves pain by easing muscle tension. It can help one feel less tired and anxious and help other pain relieving methods work better.

Imagery: Imagery involves using one's imagination to create mental scenes that use all the senses- sight, sound, touch, smell and taste. Exotic locations, or favourite places could be imagined. Stories and characters could be created to add to the scenes. Imagery can take one's mind off the anxiety, boredom and pain.

Distraction: A distraction is an activity that takes one's mind off one's pain and focuses the attention elsewhere. Doing crafts, reading a book, watching television or listening to music can all help distract mind. Distraction works well when one is waiting for drugs to take effect or if one has brief bouts of pain. Sometimes people can take their mind off their pain for long periods, especially if the pain is mild.

Skin stimulation: Skin stimulation is used to block pain sensation in the nerves. Pressure, massage, hot and cold applications, rubbing and mild electrical current are all ways to stimulate the skin. Skin stimulation can be done at the site of the pain, near it or on the opposite side of the pain. For example, stimulating the left wrist when the right wrist is in pain can actually ease the pain in the right wrist.

Pressure: Using one's entire hand, thumb, knuckles, or both hands one can apply at least 15 seconds of pressure at the point where pain is felt.

Massage: Slow, circular motions of massage on feet, back, neck and scalp could be performed to relieve tension and pain. Some people prefer to apply oils or lotions during the massage. If deep massage is too uncomfortable, one can try stroking. One has to remember that red, raw or broken skin is not to be massaged.

Heat and cold: Some people prefer cold; others prefer heat. One should use whichever works best for oneself. A convenient way to use cold is to use ice cubes. Heat can be applied with a heating pad; hot, moist towel; or a hot water bottle or by taking a hot bath.

Transcutaneous electrical nerve stimulation(TENS): TENS can be used to eliminate or ease pain. A TENS unit is a pocket - sized, battery operated device that provides a mild, continuous electrical current through the skin by the use of two or four electrodes, which are taped onto the skin. It is this mild current that blocks or modifies the pain messages and replaces them with a buzzing, tingling sensation. It is also thought that TENS may stimulate the body to produce endorphin, a natural pain reliever.

(Ref.: AIDS AND HIV INFECTION- Mosby's Clinical Nursing Services.)

Other symptoms

Apart from these there are other symptoms like fever, diarrhoea, breathlessness, etc. which could be disturbing. We must explain that they are now to be managed only symptomatically. We can explain use of simple drugs to the relatives. We should discourage transportation of patients to hospitals for such care, especially if such hospitals are not available locally. Transporting patients to nearby cities is not only costly, but also it unnecessarily puts excess psychosocial pressure on the family.

In the event of death:

It is not always very easy to handle 'death of a near one' in a far off city, without moral and physical help. Carrying a dead body back to the native place or disposal

of the same in an unfriendly place, both could be very demanding.

The decision, whether the patient be allowed to die at home or in a hospital should be taken in consultation with all concerned.

Proper handling of the dead body also needs to be explained. For all practical purposes, we issue only a few instructions: (a) don't delay disposal of the dead body for too long, (b) don't handle the dead body too much, (c) in case of contact with any of the bodily fluids from the dead body wash thoroughly with soap and water, (d) we honour the method of disposal as decided by the family, depending upon their own religious or other considerations.

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INDIGENOUS MEDICINES: ROLE AND PROBLEMS IN THE MANAGEMENT OF HIV

Dr. Deivanayagam

Introduction:

Indian Systems of Medicare consist of

1. The Siddha system, perhaps the most ancient in use in the South of India, for more than 5000 years.
2. Ayurvedic system in use throughout the rest of India and also in Tamilnadu for over 3000 years, popularised by such well known authors like Charaka, Dhanwanthari and others and
3. Unani system practised in areas where the Moghuls had established a presence and is especially popular amongst the Muslim population of India.

Also available are Naturopathy and other related systems of herbal and natural methods of treatment, which include Yoga, Water therapy, Mud therapy, systems of Varma and so on.

The Siddha system of Medicare is based on the notion that Vatha, Pitha and Kapha are found in harmonious relationship to each other and in a very

stable proportion activity and thus any disharmony in this proportion or of these humours will lead to disease or reduced capacity to resist disease. This concept is also similar to the basic concept of Ayurvedic system of Medicare.

Siddha system utilises herbs, other plant products like barks of trees, nuts, roots and gum from trees. It utilises minerals like mercury, sulphur, lead, gold and products of the sea conch, oyster and animal products like the antlers of deer, the horns of Rhinoceros. There are many text-books, many texts and writings in stone tablets and palm leaf-manuscripts which have been translated into modern Tamil and are taught as regular subjects to Siddha Medicine degree and post-graduate courses, in two Siddha Medical Colleges in Tamil Nadu run by the Government of Tamil nadu.

There are thousands of Siddha practitioners who have been registered by the State Government and they practice the traditional Siddha systems of Medicare, with local modifications

that suit local conditions.

The Agathiar Vaidya Valladhi 600, an ancient text for Siddha Practice, published by the Central Council for Research in Ayurveda and Siddha in 1980, contains the description of sufferer which is not different from the cases that we see of advanced AIDS disease now. It is thus likely that the disease was present in perhaps a modified form for more than 2000 years in this country, though the epidemic of HIV infection we see now in this country is new. We are heading towards 1% prevalence of HIV infection in the general population in India. This was unheard of in the ancient days.

The Government of Tamilnadu invited the Siddha Practitioners to work in co-operation with the modern medical (Allopathy) practitioners of the Government Medical Colleges and see whether the team could identify substances that would be of use in HIV infection and disease. Thus the combined Siddha, Allopathy, project for AIDS care and follow-up was started in the year 1993 at Chennai Medical College and Government Hospital of Thoracic Medicine, Chennai.

The Government Hospital of Thoracic Medicine, Tambaram, Chennai is a 65-year old Tuberculosis Sanatorium with 776 beds which began to admit HIV patients with Tuberculosis in the year 1992. So far more than 7000 patients have been investigated at this hospital

for HIV infection and disease. All the patients had HIV infection and disease, the majority of whom were included in the Siddha drugs trial. The two step method, namely screening with ELISA and confirmation with Western Blot testing was utilised.

What drugs have been tested?

More than 40 groups of drugs have been tested in our hospital. All these drugs are traditional remedies prepared by the Siddha practitioners themselves and given to patients in the presence of Superintendent or Medical Officer in charge of the wards. Initially all of these drugs underwent a pilot trial and if found promising with reference to symptoms control and induction of a sense of well-being, they were taken up for either open label comparative study or a double blind controlled study of placebo and Siddha drugs. The Indian Council of Medical Research protocol for such indigenous drug trial was fully adhered to and many promising drugs have been evaluated in the last six years. The original combination of Mahavallathi Lehyam, Thalisdhi Vatagam, Amukkura Choornam and Thoothuvalai Nei was the first group in the double blind studies. Unfortunately the results did not reveal any noticeable improvement in the patient's condition. At the moment, the Siddha drugs which have been useful and have found wide acceptance by the patients include Rasandhi Mezhugu, Amukkura Choornam, and Nellikkai Lehyam, prepared according to an

ancient formula, at the hospital and as well as supplied by the Indian Medical Practitioners Co-operative Pharmacy and Stores, Dr. Muthulakshmi Road, Chennai.

What have been the effects of Rasandhi Mezhugu, Amukkura Choornam and Nellikai Lehyam on Patients?

The following are the observed effects:

1. Improvement in physical condition of patients with control of fever, improved appetite and gain in weight
2. The control of diarrhoea in most patients.
3. An improvement in haemoglobin, reduction in ESR and a stable white blood cell count in all patients.
4. In 72 patients the CD-4 cell count rose by 35 to 175 cells and this improvement in CD-4 count was maintained for nearly in 4¹/₂ months. Further studies were not possible and hence the question whether these drugs if given over intermittent periods of time can maintain high CD-4 level is not resolved.

Are there other drugs that have produced a similar improvement in CD-4 count?

Yes, there are 2 Siddha Practitioners who have been associated with us in conducting drug research, and they were able, on their own, to perform the viral load testing which has shown that their products of Siddha research induced a

fall in a viral load in 5 patients alongwith significant CD-4 cell count improvement. So, it has become very clear that Siddha drugs are in fact able to reduce the viral load and this has been done in the absence of any specified anti-retro virals that are imported now from the West.

What is the next action to be taken by researchers in India and general Practitioners?

The researchers in India have to establish that the continued elevation of CD-4 and reduction of viral load to below measurable levels is maintained over several years, before we begin to think of a permanent control of this disease. It would be ideal to assess the effect of the drugs in the laboratory. In vitro viral cultures can be used, so that we have some idea of the Siddha drugs on the virus in the Laboratory. The General Practitioners have to very carefully evaluate the role of these drugs in combination with Allopathic drugs and see whether the results found in the research hospitals can be reproduced in the field, in the community under their control.

What about Ayurvedic drugs?

Ayurvedic drugs like Kasthuri, Korojanai and other similar drugs have been used in Delhi, Mumbai and Varanasi and we understand that they have been able to increase the CD-4 count but no studies have been undertaken to prove any effect on the viral load so far. We are using

Unani drugs in our hospital from a practitioner of Vamiyambadi in Tamilnadu and the clinical results are very encouraging but we await the results of CD-4 and the viral load tests.

What is the current position with reference to the claims made by Shri Majid of Ernakulam in Kerala?

Shri Majid is not a qualified Ayurvedic or an Herbal doctor. But has been able to give various combination of Herbal drugs in the form of powders and has been able to induce clinical improvement in a large number of patients. But, unfortunately his drugs are given only for a period of 100-days, after which many patients develop symptoms and signs, again and end up by seeking attention from other places including our own hospital. Hence, the claims of Shri Majid of Ernakulam have to be tested in a hospital setting with clear-cut end points, likes CD-4 and viral load tests.

Is it sufficient to give only Siddha drugs to control HIV infection and disease?

No, it is not sufficient at present. In our hospital we have been combining Siddha drugs with Allopathic drugs to control Tuberculosis, various forms of pneumonia including Pneumocystis carinii pneumonia (PCP) and the control of Toxoplasmosis infection of the brain, cryptococcal infection and tuberculosis of the brain in our patients. In the absence of these appropriate drugs the patients do not do well on Siddha drugs alone.

We make it a point to identify the presence of Toxoplasma, Cryptococcus and Tuberculosis meningitis by careful study of the infection through the cerebro spinal fluid (CSF) by carrying out a lumbar puncture of the patients and assessing the level of proteins, sugar and cells in the CSF.

Are you using any drugs for prevention for Tuberculosis, Pneumocystis carinii pneumonia etc., in your patients?

Yes. After completing a 9 months course of treatment with initial four drugs HREZ and later HR for 7 months, we stop the combination treatment and ask the patient to take Isoniazid for the next 12 months, as a secondary prophylactic measure. In USA, a prophylactic treatment with Rifamycin and Pyrazinamide given only for 2 months, has been found to be effective. We also use Cotrimoxazole, one double strength tablet twice daily or once daily for most of the months in a year in patients who have been proved to have Pneumocystis carinii pneumonia. We do not have a big ratio of patients with drugs reaction secondary to cotrimoxazole and the drug is effective also against Toxoplasma gondii and a gut micro organism called Isopora belli.

What is your recommendation for the General Practitioners of India?

The General Practitioners must identify the early symptoms of HIV. Symptoms relating to tuberculosis, pneumonia, diarrhoea, and skin fungi and identify the

disease which recurs after initial apparent improvement following treatment for pneumonia, skin fungus or diarrhoea, and screen the patient with a good ELISA test. The clinically symptomatic and ELISA positive patients should be subjected to confirmation by Western blot testing so that we can categorically tell the patient that he/she has HIV infection or not. (The standard protocol of two ELISA based tests using different kits may be followed. - editors)

When do you advise the starting of Siddha drugs?

The moment the patient is confirmed to have HIV Infection, we start the drugs. We do not wait for the patients to develop prolonged symptoms or the CD-4 count to fall below 200. The CD-4 count itself can only be carried out in a few selected laboratories in the country and the quality of testing varies from place to place. The reason for starting the Siddha drugs so early, is to make sure that Siddha drugs produce beneficial effects on the immune system, instead of waiting for the full symptoms to develop. In the West, many doctors, do wait for the first persistent symptoms to develop or the CD4 Counts fall below 500 or 400 before starting anti-retroviral drugs.

Are the Allopathic drugs combining with Siddha drugs without any reaction?

Yes, they are combining and they can be very safely used together.

Are you able to treat the patients with HIV infection of the brain effectively with Siddha drugs?

No, at the moment the Siddha drugs are not capable of completely eliminating the effects of the viral or fungal brain infections and we are continuing the research to identify the effective anti-viral drugs which will act also in the brain and spinal cord. We do not also have effective drugs for controlling cytomegalo virus (CMV) infection and we are forced to use imported drugs for such infections like cryptococcal disease of the brain is a very major complication of HIV. Amphotericin B and Fluconazole which might have to be continued for life as secondary prophylaxis.

What diet will you advice for patients who are receiving indigenous drugs?

The Siddha practitioners are very keen that the patients should take plenty of fresh fruits, vegetables but avoid tamarind while they are on the Siddha drugs. They are also recommending fair amount of milk, honey and supplemental bananas, during the course of treatment. Using the combination of diet supplementation, Siddha drugs and Allopathic drugs we are able to discharge 60% of our patients within two weeks to carry on with their usual jobs. We also treat a very large number of patients solely as out-patients by giving them monthly Siddha drugs.

Are people from other state taking the Siddha drugs?

YES. We get many patients form Andhra, Kerala, Karnataka, Maharashtra and even from distant parts of the country like Delhi, Kanpur and Jalandhar, who come to take Siddha drugs, because they find them useful supplementation for their modern medical treatment.

HIV/AIDS CARE IN RELATION TO INJECTION DRUG USE IN MANIPUR AND OTHER NORTH-EASTERN STATES OF INDIA

Dr. Samiran Panda

Introduction

Introduction of HIV among injection heroin users of Manipur was noted in 1989. Although it was then thought that spread of HIV in relation to injection drug use would remain restricted to north-east India due to its geographical proximity to large illegal heroin producing country Myanmar, subsequent studies have documented gradually diffusing phenomenon of injection drug use in metropolitan cities like Calcutta, Delhi, Mumbai and Chennai where HIV also made its road in injecting drug users (IDUs). The present chapter intends to highlight the following topics with regard to HIV epidemic among IDUs in North-eastern States of India:

- Brief epidemiology
- HIV disease spectrum
- Issues related to HIV care and management in Manipur

- State AIDS policy in Manipur
- Present scenario

Brief epidemiology

A rapid spread of HIV among injection heroin users of Manipur took place in early 1990s. Extensive sharing of injection equipment and injection paraphernalia was responsible for this spread. Moreover, HIV being asymptomatic during its initial years of infection, did not pose a palpable threat to the injectors as opposed to the prevailing situation now in this State. Unfortunately, as is known from natural history study, the high viral load that persists for weeks immediately following HIV infection also played its role in spreading the virus from one to another without causing any symptom in most of the situations in early '90s. Young adults of Manipur, majority of whom were males, thus became infected with HIV in large number (50% of estimated

15,000 IDUs became HIV positive within 6 months) within a short time. Similar phenomenon was observed in Nagaland and Mizoram, the other two north-eastern States having common border with Myanmar, although IDUs in Mizoram were less affected with HIV compared to those in Manipur and Nagaland. Non-availability of injectable heroin due to stringent law and enforcement activities in Mizoram in 1992 made the injectors switch to injecting dextropropoxyphene after dissolving the content of the capsule in water. It is known that dextropropoxyphene is not a good drug for main line (intravenous) use as it causes venous sclerosis and soft tissue damage within a short period of its use.

In all these three states, IDUs belonged to the age group of 15-30 years; sharing of syringe and needle with drug taking partners was common and some of the injectors even reportedly used the injection equipment available at drug peddling joint, which was used by large number of clients coming to that drug dealing place throughout the day. Although a very high proportion of IDUs had significant knowledge of HIV transmission, situational pressure as peer norms, craving in withdrawal, legal risk of carrying one's own syringe and needle, risk of getting exposed to family members by keeping syringe and needle at home and getting drug by lending syringe forced many of them into sharing of injection equipment.

Majority of the injectors in Manipur and Nagaland were males (95%) whereas Mizoram comparatively had more female drug injectors (10%). Forty percent of the injectors were married. one fifth of the unmarried injectors reported heterosexual relations either with sex-workers or with friends. Condom use with either regular or non-regular sex partner was negligible.

Within three years of onset of HIV epidemic among injectors in the north-east, female general population, as represented by antenatal mothers, also became infected with HIV. Vertical transmission from mother to baby soon followed. Anecdotal evidence suggested transmission even through blood transfusion. All these events always documented presence of HIV-1 in north-east till 1994 when HIV-2 was detected along with HIV-1 among a group of injectors in Manipur. As HIV-2 was not reported from neighbouring countries of Myanmar and Thailand, it was presumed that movement of injectors from Manipur to outside States, where HIV-2 already gained a foothold, was responsible for this unusual finding. It may be noted here that HIV-2 has mostly been found to spread through heterosexual route.

- **HIV disease spectrum**

Cross sectional study that recruited injectors from different detoxification centres in Manipur during 1992-93 revealed that most of the young injectors

were in the early phases (Stage I, 43%; Stage II, 32%; Stage III, 15% and Stage IV, 9.9%) of the World Health Organization clinical staging of human immunodeficiency virus infection and disease. Herpes zoster, oral candidiasis, pruritic papular eruptions, jaundice and lymphadenopathy had positive predictive values (PPV) of 100%, 100%, 93%, 93% and 88%, respectively for HIV. Cryptosporidial diarrhoea and tuberculosis (pulmonary as well as extra-pulmonary) were also encountered. High PPV of jaundice was probably a reflection of unsafe injecting practices among IDUs that put them also at risk of acquiring HIV.

Subsequently, outbreak of herpes zoster following HIV epidemic among 12-45 year adult males was documented in Manipur. This was the first reported satellite epidemic temporally associated with HIV in India. It was also observed that multidermatomal herpes zoster in young adults could serve as a useful clinical surrogate marker of HIV and raise a clinical suspicion of existence of HIV disease. In the same study, association between role and site of physical trauma with the site of occurrence of zoster (reactivation of latent chicken pox virus) was discounted as in most of the cases, shingles appeared on trunk whereas common site of trauma in injectors was dorsum of the hands, ante-cubital fossa or veins around the ankles where IDUs used to shoot drugs. During mid phase of the epidemic in 1995, home based care team of locally

active non-governmental organizations (NGOs) in Manipur observed advanced spectrum of HIV disease happening in the community. Experiences of the physicians working in the local hospitals or as private practitioners also corroborated this finding. The illnesses observed in this phase included severe weight loss, long continued diarrhoea, hemiparesis, convulsion, palatal palsy and meningitis in considerable number of HIV positive people. Lack of adequate investigation facilities did not allow identification of causative organisms in many instances.

As of 31st December 1996, the number of AIDS cases reported to National AIDS Control Programme (NACO) from Manipur, Mizoram and Nagaland were respectively, 154, 0 and 4. In view of entry of HIV in these States in early 1990s it could be well presumed that AIDS case reporting system was operating in different pace in these three different states and actual picture existing in the community was not being reflected in the Government report.

- **Issues related to HIV care and management in Manipur**

When clinical manifestation of different opportunistic infections in the early phase of HIV epidemic started surfacing in Manipur, NGOs working in the field of drug abuse began seeking help for their clients from research organization, private practitioners and State health authority. But soon it was realized that available and willing human resources

were meagre compared to the gradually expanding needs in this regard. Home based care and orientation of family members in giving care to people with HIV/AIDS appeared then to be a more realistic and preferred goal. Medical management mostly concentrated on treatment of opportunistic infections as anti-retroviral medication was not affordable by many. A remarkable step was taken at this point of time in developing “Continuum of Care Project” in Manipur that envisaged establishing facilities for care at home, at community based clinic as well as at hospitals for people with HIV/AIDS. A home care hand book named “IMUNG” (a Manipur word meaning family) and a resource directory for seeking help with regard to HIV/AIDS care were published by this Project. State AIDS Cell, Medical Directorate, Government of Manipur adopted the publication “Understanding and Living with AIDS” published by the World Health Organization, Regional Office for South East Asia, New Delhi and circulated it for use.

As with time anti-tubercular medicines were needed by many and cost of it was unbearable, “Continuum of Care Project” tried utilizing the facilities available with State Tuberculosis Control Programme. Thus, bridging the gap between NGOs working in the community and Government working at State hospitals for HIV positive people was attempted. NGOs also shared a big portion of care by offering counselling services to family members having

somebody with HIV in the family and widows of HIV positive persons, by establishing 24 hour on-line help service and by addressing the legal and social concerns of people infected with HIV. Issues related to practical nitty gritty like disposal of urine, stool, sputum and cleaning of soiled bed linen were also addressed by home-care team. Suitability of different traditional food of Manipur (e.g. fermented vegetables or spicy pickle prepared from dried fish, chilly and bamboo shoots) in HIV disease state particularly in diarrhoea also had to be addressed.

• State AIDS policy in Manipur

State AIDS policy was published as an official document of “Department of Medical and Health Services, Government of Manipur” Imphal by 3rd October, 1996. This policy adopted by State Government was based on the following principles :

- provision of accurate information and education to make the people aware of and to protect themselves from HIV infection
- voluntary participation of people with HIV/AIDS
- safeguard of confidentiality
- respect for privacy, human dignity and individual human rights
- avoidance of discrimination and stigmatization
- provision of quality medical care
- provision of social benefits and

- social support system for people with HIV/AIDS
- creating a helpful and supportive social environment in the community so that people who suspect themselves to be infected can come forward for voluntary testing and for seeking help so that they can live peacefully with other members of the society
 - avoidance or removal of fear psychosis from the minds of people.

In addition, policy on intervention measures in this document explicitly expressed that harm reduction measures like “Drug Maintenance Therapy”, “Needle Syringe Exchange Programme (NSEP)”, “Bleach and Teach Programme” and “Safer Sex” will be introduced to minimize the risk of spread of HIV infection in the population.

- **Present scenario**

Behavioural modification projects launched in north-eastern States of India have shown that reaching out to injection drug users in the community with the help of outreach workers with drug use background is feasible in a developing country setting. It has also been realized that reaching out to the larger community in general before targeting the IDUs in an area with risk reduction message and material (e.g. stickers with messages, bleach, condom etc.) appears

vital so that the community does not misunderstand the approaches taken up by the intervention projects.

Recent data show that 45% of the spouses of HIV positive IDUs are now HIV positive in Manipur and this has also been known that it’s easier to bring change in injecting behaviour compared to sexual behaviour. This highlights the fact that any intervention programme that intends to modify the risk taking injection practices among IDUs should give adequate attention to promote safer sexual behaviour as well. Understanding the dynamics influencing interface of drug and sex will help in identifying the missing element from the State AIDS Control Programme and will probably help achieve better containment of the epidemic. A strong political will and support appear to be other vital components in this effort of controlling further spread of HIV.

Any physician involved in giving care to people with HIV in the community will certainly be dragged into issues beyond medical management. Getting “burnt out” from this pressure is a reality and one needs to be aware of this phenomenon right from the beginning. One of the several ways of not getting “burnt out” could be formation of HIV care-givers’ association that would have representatives from legal forum, forum of social workers and forum of self-help group so that help in need for different concerns could be obtained from respective technical persons.

Apart from the three north-eastern states highlighted in the present chapter, other four in this region namely Arunachal Pradesh, Tripura, Meghalaya and Assam have not reported HIV as a major problem related to injection drug use. In fact Arunachal Pradesh is the only State in India that has not reported any HIV till date. Researchers feel that

systematic study needs to be conducted to understand the extent of injection drug use problem in these states and role of alcohol as a risk modifier in sexual practices need to be addressed [Personal Communication : Daniel Sunder, Drug Abuse and HIV in Meghalaya, North-east India Drugs and AIDS Care (NEIDAC), Shillong.]



● Dots from top down in the map indicate geographical location of Nagaland, Manipur and Mizoram in order.

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COMONLY USED DRUGS

ACYCLOVIR

Antiviral agent

Clinical information

Uses

In patients with HIV infection, treatment of:

- Severe primary genital herpes
- Herpesviral encephalitis
- Disseminated zoster.

Dosage and administration

Intravenous infusions should be administered slowly over a period of 1 hour to avoid acute impairment of renal function.

Primary genital herpes

5mg/kg i.v. three times daily for 5 days.

Less severe genital infections respond to oral administration of 200 mg five times daily for 7 days.

To prevent recurrence, 400mg may be given orally twice daily, but the optimal

dosage has yet to be determined.

Herpesviral encephalitis

10 mg/kg i.v. three times daily for 10 days.

Disseminated zoster

10 mg/kg i.v. three times daily for 7 days.

Contraindications

Known hypersensitivity to purine nucleoside analogues.

Use in pregnancy

Aciclovir is mutagenic in animal models. Its use in pregnancy must be determined by the physical state of the mother.

Adverse effects

Headache, nausea and vomiting occur commonly after oral administration.

Transient renal impairment may occur during intravenous therapy, possibly as a result of crystallization in the renal tubules. This usually responds rapidly to

dosage reduction or withdrawal of the drug. Acute renal failure has responded to haemodialysis.

AMPHOTERICIN B

Antifungal agent

Clinical information

Uses

In patients with HIV infection, treatment of:

- Cryptococcal meningitis
- Oesophageal and oral candidiasis
- Histoplasmosis and coccidioidomycosis.

Dosage and administration

Amphotericin B is a highly toxic substance that should be used only under experienced medical supervision. Except in the treatment of oral candidiasis, the required dosages should be administered by slow intravenous infusion, when possible via a central venous catheter. An oral dose of 5 mg of hydrocortisone sodium succinate taken 1 hour before infusion of amphotericin B may reduce the severity of chills, fever and vomiting. Infusion fluids should be freshly prepared by dissolving 50 mg in 10ml of water for injection and making up the volume to 500 ml with 5% glucose to give a final concentration of amphotericin B of 100 mg/ml. Solutions containing electrolytes or preservatives are incompatible since they promote precipitation.

Cryptococcal meningitis

0.5-1.0 mg/kg by i.v. infusion daily for at least 6 weeks and until cultures of cerebrospinal fluid have been negative for 4 weeks. Infusions should be continued at weekly intervals indefinitely to prevent relapse.

Oesophageal candidiasis

1 mg/kg by i.v. infusion daily for 10-14 days.

Oral candidiasis

10 mg orally four times daily after food, to be continued indefinitely. Lozenges should be retained as close to major lesions as possible and allowed to dissolve in the mouth.

Histoplasmosis and coccidioidomycosis

0.5-1.0 mg/kg by i.v. infusion daily for at least 6 weeks, up to a maximum total dose of 3g. infusions of 0.5 mg/kg should be continued at weekly intervals indefinitely to prevent relapse.

Contraindications

Known hypersensitivity to amphotericin B.

Precautions

Close medical supervision is required throughout treatment.

Renal function and serum potassium concentrations should be closely

monitored when high doses are administered.

A high fluid intake should be maintained. Potassium supplements may be required to compensate for urinary losses. Dosage must be reduced if renal function deteriorates substantially and particularly if serum creatinine levels rise by over 50%. Infusions of an osmotic diuretic such as mannitol may then be of value. The blood count should be monitored at regular intervals since bone-marrow depression supervenes frequently. Occasionally, blood transfusion is required.

Use in pregnancy

Safe use during pregnancy has not been established. Amphotericin B should be used only when the need of the mother outweighs the risk of harm to the fetus.

Adverse effects

Chills, fever and vomiting are frequent during infusion. Anaphylaxis, flushing, muscle and joint pains, headache and anorexia may also occur. These effects are often most marked in the first days of treatment.

Deterioration of renal function, which may be only partially reversible, must be anticipated.

Progressive normochromic anaemia is indicative of bone-marrow suppression. Selective leukopenia and thrombocytopenia are less common.

Nerve palsies, impaired vision, tinnitus and difficult micturition have also been reported.

Drug interactions

Concomitant administration of other nephrotoxic drugs should be avoided.

BENZYL PENICILLINS

Antimicrobial agent

Clinical information

Uses

Treatment of:

- Primary, secondary and latent syphilis of less than 2 years duration
- Late syphilis, including neurosyphilis and cardiovascular syphilis
- Congenital syphilis.

Dosage and administration

Benzylpenicillin and its repository formulations must be administered parenterally.

Primary, secondary and latent syphilis of less than 2 years duration

Benzathine benzylpenicillin 2.4 million IU i.m. in a single session, or procaine benzylpenicillin 1.2 million IU i.m. daily for 10 consecutive days.

Late syphilis (other than neurosyphilis)

Procaine benzylpenicillin 1.2 million IU i.m. daily for 3 weeks, or benzathine

benzylpenicillin 2.4 million IU i.m. once weekly for 3 weeks.

Neurosyphilis

Benzylpenicillin 4 million IU i.v. every 4 hours for 14 days or, provided that compliance is ensured, procaine benzylpenicillin 1.2 million IU i.m. daily for 2 weeks with oral probenecid 500 mg four times daily.

Early congenital syphilis

Abnormal cerebrospinal fluid: benzylpenicillin 50 000 IU/kg i.m. or i.v. daily in two divided doses for 10 days, or procaine benzylpenicillin 50 000IU/kg i.m. daily for 10 days.

Normal cerebrospinal fluid: benzylpenicillin 50 000 IU/kg i.m. as a single dose.

Congenital syphilis of 2 or more years duration

Benzylpenicillin 200 000-300 000 IU/kg i.v. daily in divided doses for 14 days (maximum 2.4 million IU daily).

Contraindications

Known hypersensitivity to penicillins or cephalosporins.

Precautions

Facilities should be available for treating anaphylaxis whenever penicillins are used. Patients should be questioned carefully about previous allergic

reactions. If a skin rash develops during treatment, the patient should be transferred to a different class of antibiotic.

Use in pregnancy

Benzylpenicillin or its repository for mutations can be used during pregnancy. 'Desensitization' of pregnant women with syphilis who are allergic to penicillins should not be attempted in primary care facilities.

Adverse effects

Hypersensitivity reactions range in severity from skin rashes to immediate anaphylaxis.

Pain and sterile inflammation can occur at the site of intramuscular injection; phlebitis or thrombophlebitis sometimes follows intravenous administration.

Rapid intravenous administration of large doses of benzylpenicillin may cause hyperkalaemia, dysrhythmias and cardiac arrest, particularly in patients with impaired renal function. Accidental intravascular administration of procaine or benzathine penicillin may produce convulsions.

Unduly high concentrations of benzylpenicillin in the brain can result in confusion, convulsions, coma and fatal encephalopathy. The procaine component has been implicated in acute mental disturbances associated with the administration of large single doses.

Interstitial nephritis, neutropenia and thrombocytopenia have been reported.

CALCIUM FOLINAT

Antidote to folinic acid antagonists

Clinical information

Uses

To decrease the haematopoietic toxicity of pyrimethamine and other inhibitors of folic acid metabolism in patients with HIV infection.

Dosage and administration

Adults and children: initially, 3-5 mg orally every third day. Dosage needs to be adjusted in accordance with twice-weekly blood counts and may exceed 15 mg every third day. Much higher doses have been administered without untoward effect.

Precautions

The possibility of pernicious anaemia should always be excluded before starting treatment with calcium folinate. Its use obscures the diagnosis by rectifying the characteristic megaloblastic anaemia but it does not prevent the neurological damage.

Use in pregnancy

Calcium folinate should always be used when pyrimethamine and sulfonamides are administered during pregnancy.

Adverse effects

Rarely, hypersensitivity reactions occur, including urticaria, rash and pruritus.

CEFTRIAXONE

Antimicrobial (cefalosporin) agent

General information

Ceftriaxone is a third-generation cefalosporin. It is highly active against Gram-negative cocci and bacilli.

Clinical information

Uses

Treatment of:

- Gonococcal infections
- Chancroid caused by *Haemophilus ducreyi* that is resistant to β -lactams
- Pelvic inflammatory disease, together with doxycycline.

Dosage and administration

Ceftriaxone must be administered parenterally.

Uncomplicated anogenital and pharyngeal gonococcal infection and gonococcal conjunctivitis in adults

250 mg i.m. as a single dose.

Disseminated gonococcal infection

1 g i.m. or i.v. daily for 7 days.

Neonatal gonococcal conjunctivitis

50 mg/kg i.m. as a single dose (maximum 125 mg).

Chancroid

250 mg i.m. as a single dose.

Pelvic inflammatory disease

For hospitalized patients, 250 mg i.m. twice daily together with doxycycline 100 mg orally or i.v. twice daily for 4 days (or for 48 hours after clinical improvement), followed by doxycycline 100 mg orally twice daily for 10-14 days.

Contraindications

Known hypersensitivity to other b-lactam antibiotics.

Use in pregnancy

There is no evidence that ceftriaxone is teratogenic. It may be used during pregnancy.

Adverse effects

Hypersensitivity reactions are the most common adverse effects. Skin rashes are relatively frequent, while urticaria, bronchospasm and anaphylaxis are uncommon. Nausea, vomiting and diarrhoea have been reported. Rarely, **a n t i b i o t i c - a s s o c i a t e d** pseudomembranous colitis due to *Clostridium difficile* occurs. When this is suspected, treatment should be immediately discontinued.

Reversible cholestatic jaundice has been reported.

CIPROFLOXACIN

Antimicrobial (quinolone) agent

Clinical information

Uses

Treatment of:

- Penicillin-resistant gonorrhoea and gonococcal conjunctivitis in adults
- Chancroid in patients with HIV infection
- Pelvic inflammatory disease, together with doxycycline and metronidazole.

Dosage and administration

Uncomplicated anal and genital gonorrhoea, gonococcal conjunctivitis in adults and chancroid infections:

500 mg as a single dose.

Pelvic inflammatory disease:

For hospitalized patients, 500 mg twice daily together with doxycycline 100 mg orally twice daily for and metronidazole 400-500 mg orally twice daily for 4 days (or for 48 hours after clinical improvement), followed by doxycycline 100 mg orally twice daily for 10-14 days.

Contraindications

- Hypersensitivity to any quinolone.
- Pregnancy, adolescence and childhood, since ciprofloxacin has induced arthropathy in the weight-bearing joints of young animals.

Precautions

Reduced dosage should be considered in patients with hepatic or renal impairment.

Ciprofloxacin should be administered cautiously to patients with epilepsy since seizures may be precipitated.

An adequate fluid intake must be ensured to prevent crystalluria.

Adverse effects

Ciprofloxacin is generally well tolerated. The most frequently reported adverse effects are nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, headache, restlessness, tremor, confusion, hallucinations, dizziness, rash and pruritus. Myalgia, tendinitis, and hepatic and renal disturbances have also been reported.

Drug interactions

Plasma concentrations of theophylline may be raised. A prolonged bleeding time has been reported in patients receiving anticoagulants and ciprofloxacin concurrently.

CODEINE

Antidiarrheal and analgesic agent

Clinical information

Uses

In patients with HIV infection:

- Treatment of mild to moderate pain
- Symptomatic relief of diarrhoea.

Dosage and administration

A dose of 30-60 mg should be taken three or four times daily, as necessary.

Contraindications

- Age less than 1 year
- Exacerbations of bronchial asthma.

Precautions

Prolonged use can result in tolerance. However, the risk of dependence is less than with other opioids.

Use in pregnancy

Codeine should be used during pregnancy only when the need outweighs any possible risk to the fetus. Its use during labour can produce respiratory depression in the infant sufficient to necessitate administration of naloxone, 10mg/kg i.m., upon delivery.

Adverse effects

Dose-related adverse effects include nausea, dizziness and sedation.

Prolonged use can result in intractable constipation and, rarely, in paralytic ileus or toxic megacolon.

Drug interactions

Codeine potentiates the effects of other cerebral depressants.

DOXYCYCLINE

Antimicrobial (tetracycline) agent

Clinical information

Uses

Treatment of:

- Chlamydia trachomatis infections, including lymphogranuloma venereum
- Granuloma inguinale
- Syphilis in non-pregnant patients allergic to penicillin
- Pelvic inflammatory disease, together with other drugs.

Dosage and administration

Chlamydia trachomatis infections

100 mg orally twice daily for 7 days.

Lymphogranuloma venereum and granuloma inguinale

100 mg orally twice daily for 14 days.

Syphilis (excluding neurosyphilis)

100 mg orally twice daily for 15 days. In late syphilis, treatment should be continued for a further 15 days.

Neurosyphilis

200 mg orally twice daily for 30 days.

Pelvic inflammatory disease

For hospitalized patients, 100 mg twice daily for 14-18 days supplemented for the first 4 days by ceftriaxone or by ciprofloxacin plus metronidazole.

Contraindications

Known hypersensitivity.

Precautions

Troublesome oesophagitis may be averted if the patient is propped up while swallowing capsules or tablets and washes them down immediately with a glass of water. Capsules and tablets should not be taken with milk or with magnesium or aluminium salts since these impair the absorption of doxycycline.

Use in pregnancy and early childhood

Doxycycline is generally contraindicated in pregnancy and during early childhood. Because it is deposited in developing teeth and bones and impairs skeletal calcification, it can result in abnormal osteogenesis and permanent staining of teeth, and occasionally causes hypoplasia of dental enamel.

Adverse effects

Gastrointestinal irritation is common and phototoxic reactions and increased

vulnerability to sunburn have been reported.

Transient depression of bone growth is largely reversible, but discoloration of teeth and enamel hypoplasia are permanent.

Drug interactions

The action of oral anticoagulants may be potentiated. Severe renal failure has been reported in patients who have received a halogenated anaesthetic agent while taking doxycycline.

ERYTHROMYCIN

Antimicrobial (macrolide) agent

Clinical information

Uses

Treatment of:

- chancroid
- lymphogranuloma venereum, as an alternative to tetracycline
- other Chlamydial trachomatis infections in patients unable to take tetracycline
- neonatal chlamydial conjunctivitis
- syphilis in pregnant patients and children who are allergic to penicillin.

Dosage and administration

Erythromycin tablets should not be broken in half before administration.

Chancroid

500 mg orally three times daily for 7 days.

Lymphogranuloma venereum

500 mg orally four times daily for 14 days.

Other chlamydial infections

500 mg orally four times daily for 7 days.

Neonatal chlamydial conjunctivitis

50 mg/kg as syrup in four divided doses daily for 2 weeks.

Prevention of ophthalmia neonatorum

A single application of eye ointment should be sufficient.

Syphilis

Adults: 500 mg orally four times daily for 15 days in early syphilis and 30 days in late syphilis.

Children: 7.5-12.5 mg/kg orally four times daily for 30 days.

The effectiveness of erythromycin in syphilis is doubtful and it must be used only as a drug of last resort.

Contraindications

Known hypersensitivity to erythromycin.

Precautions

Hepatic function should be monitored

in patients with a previous history of liver disease.

Use in pregnancy

Erythromycin has not shown to be mutagenic, teratogenic or embryotoxic; it can be used during pregnancy.

Adverse effects

Nausea, vomiting and diarrhoea can occur.

Cholestatic hepatitis that may present with symptoms suggestive of acute cholecystitis, occasionally complicates prolonged courses of treatment. Symptoms resolve rapidly when the drug is withdrawn.

Anaphylaxis and other hypersensitivity reactions are rare.

Drug interactions

Erythromycin, chloramphenicol and clindamycin have a similar bacteriostatic action and tend to be mutually antagonistic when administered together. Erythromycin decreases the rate of metabolism of carbamazepine and warfarin in the liver to a degree that can warrant readjustment of dosage.

FLUCONAZOLE

Antifungal agent

Clinical information

Uses

In patients with HIV infection:

- treatment and prophylaxis of cryptococcal meningitis
- treatment of oesophageal and resistant oropharyngeal candidiasis, vaginal candidiasis, and serious systemic candidal infections, in particular of the urinary tract, peritoneum and lungs.

Dosage and administration

Cryptococcal meningitis

An oral or i.v. dose of 400 mg is effective if taken daily for at least 12 weeks after cultures from the cerebrospinal fluid become negative. Suppressing treatment with a daily dose of 200 mg should then be continued indefinitely.

Oesophageal and resistant oropharyngeal candidiasis

200 mg as an initial loading dose, followed by 100 mg daily for 21 days (i.v. administration for oesophageal candidiasis).

Vaginal candidiasis

150 mg as a single oral dose.

Systemic candidiasis

400 mg orally or i.v. as an initial loading dose, followed by 200 mg daily for at least 4 weeks.

Contraindications

Hypersensitivity to azole derivatives.

Precautions

Dosage should be reduced in accordance with the creatinine clearance rate in patients with renal impairment.

Use in pregnancy

Safe use in pregnancy has not been established. The need for treatment must be determined by the condition the mother.

Adverse effects

Fluconazole is generally well tolerated. Nausea is the most frequently reported adverse effect. Vomiting and abdominal distension and discomfort are also reported.

Elevation of hepatic enzyme levels, which occurs in a small percentage of individuals, is readily reversible in the early stages. Treatment should be discontinued if signs develop that are suggestive of hepatic disease.

Fluconazole should be withdrawn if skin rashes progress during treatment. Exfoliative

Skin disorders have been reported, but a casual association has not been established.

Drug interactions

The hepatic metabolism of other lipid soluble drugs, such as ciclosporin, phenytoin, sulfonyleureas, theophylline and warfarin, is inhibited.

Rifampicin accelerates the clearance of fluconazole.

Concomitant administration of terfenadine should be avoided since it has been associated with serious, sometimes fatal cardiac dysrhythmias.

GANCICLOVIR

Antiretroviral agent

Clinical information

Uses

Treatment of cytomegalovirus infections that threaten life or sight in patients with HIV infection.

Dosage and administration

A dose of 5 mg /kg should be given by slow intravenous infusion every 12 hours for the first 14-21 days. Maintenance treatment with 5 mg/kg daily should then be continued indefinitely.

Contraindications

Known hypersensitivity to purine nucleoside analogues.

Precautions

Dosage should be adjusted in accordance with the creatinine clearance rate in patients with impaired renal function.

The blood count should be monitored every 2 days for the first 14 days. Particular vigilance is required when ganciclovir is administered in combination with other myelosuppressive drugs, such as zidovudin, pentamidine and sulfamethoxazole/trimethoprim.

Use in pregnancy

Because of the urgent need to treat cytomegalovirus infections, ganciclovir should not be withheld during pregnancy.

Adverse effects

The most common severe adverse effects are anaemia, leukopenias (especially neutropenia) and thrombocytopenia. Fever, rash, abnormal liver function tests, raised blood urea concentrations, behavioural changes, psychosis, convulsions and coma sometimes occur.

Drug interactions

Concomitant administration of zidovudin and other myelosuppressive

drugs has been associated with severe haematological abnormalities.

KETONAZOLE

Antifungal agent

Clinical information

Uses

Treatment of oesophageal and resistant oropharyngeal candidiasis in patients with HIV infection.

Dosage and administration

Oesophageal candidiasis

200-400 mg daily until remission is obtained. The need for subsequent maintenance doses of 200 mg daily should be considered.

Resistant oropharyngeal candidiasis

200 mg once daily until remission is obtained.

Children > 2 years:
3-6 mg/kg daily.

Contraindications

- Hypersensitivity to azole derivatives.
- Impaired hepatic function.
- Chronic alcohol dependence.
- Age less than 2 years.

Precautions

Liver function should be assessed before and at monthly intervals throughout

treatment.

Use in pregnancy

Ketoconazole is fetotoxic in animals. Its use in pregnancy must be determined by the physical state of the mother.

Adverse effects

Anaphylactic reactions have been reported following the first dose. Hypersensitivity may also present as pruritus, purpura or urticaria.

Nausea, vomiting abdominal pain, constipation, diarrhoea and transient increases in plasma concentrations of hepatic enzymes are common.

Treatment should be withdrawn immediately if there is evidence of more severe hepatocellular damage.

Drug interactions

Absorption of ketoconazole from the gastrointestinal tract is pH dependent. Concomitant administration of drugs that reduce gastric acid secretion, such as histamine H₂-receptor antagonists, and of other antacids should be avoided whenever possible.

Ketoconazole's extensive binding to plasma proteins and induction of hepatic enzymes are responsible for certain drug interactions. The anti-coagulant effect of coumarin compounds may be enhanced, and use of ketoconazole should not be administered concomitantly with either astemizole or terfenadine, as cardiac

irregularities including prolonged Q-T intervals and ventricular fibrillation may occur.

METRONIDAZOLE

Antiprotozoal agent

Clinical information

Uses

Treatment of:

- Confirmed trichomoniasis in adults
- Trichomoniasis in neonates persisting for more than 4 weeks
- Vaginosis due to *Gardnerella vaginalis*
- Pelvic inflammatory disease, together with ciprofloxacin and doxycycline.

Dosage and administration

Metronidazole should preferably be administered with or immediately after meals.

Trichomoniasis

Adults: 2 g as a single dose, or 400-500 mg twice daily for 7 days.

Infants more than 4 weeks old: 15 mg/kg daily for 5 days in divided doses.

Gardnerella vaginalis infection

Adults: 400-500 mg twice daily for 7 days.

Pelvic inflammatory disease

For hospitalized patients, 400-500 mg twice daily together with ciprofloxacin 500mg orally twice daily and doxycycline 100 mg orally twice daily for 4 days (or for 48 hours after clinical improvement), followed by doxycycline 100 mg orally twice daily for 10-14 days.

Contraindications

- Known hypersensitivity.
- Early pregnancy.
- Chronic alcohol dependence.

Precautions

Patients should be warned not to take any alcohol during treatment since disulfiram-like reactions can occur.

Use in pregnancy and lactation

Metronidazole should not be used to treat trichomoniasis during early pregnancy. For symptomatic relief, clotrimazole 100 mg may be given as a vaginal suppository daily for 7 days. Breast-feeding should be interrupted until 24 hours after cessation of treatment since metronidazole is excreted in milk.

Adverse effects

In general, metronidazole is well tolerated, but mild symptoms of headache, gastrointestinal irritation and a persistent metallic taste are common.

Less frequently, drowsiness, rashes and darkening of urine occur.

More serious reactions are rare and usually occur only during extended courses of treatment. They include stomatitis and candidiasis, reversible leukopenia, and sensory peripheral neuropathy, which is usually mild and rapidly reversible.

Ataxia and epileptiform seizures have been reported among patients receiving dosages considerably higher than those currently recommended.

Drug interactions

The action of oral anticoagulants is potentiated. Alcohol may induce abdominal pain, vomiting, flushing and headache.

Phenobarbitol and corticosteroids lower plasma levels of metronidazole, whereas cimetidine raises them.

MICONAZOLE

Antifungal agent

Clinical information

Uses

Treatment of vaginal candidiasis.

Dosage and administration

A dose of 10 ml (200 mg) of cream should be inserted high into the vagina on 3 consecutive nights.

Contraindications

- Known hypersensitivity to miconazole.
- Severe liver impairment.

Precautions

Treatment should be discontinued if irritation or sensitivity occurs.

Miconazole should not come in contact with the eyes.

Use in pregnancy

Topically applied miconazole is not systemically absorbed and can be used safely during pregnancy and lactation.

Adverse effects

Isolated cases of sensitization have been reported, characterized by irritation and burning and necessitating discontinuation of treatment.

NYSTATIN

Antifungal agent

Clinical information

Uses

- Treatment of vaginal candidiasis
- Treatment and prevention of oral candidiasis in patients with HIV infection.

Dosage and administration

Vaginal candidiasis

100 000-1000 000 IU as pessaries inserted high into the vagina nightly for at least 2 weeks.

Administration should be continued for 48 hours after clinical cure. Higher dosages and a longer period of treatment may be necessary in immunocompromised patients.

Oral candidiasis in patients with HIV infection

Treatment: one tablet four times daily; tablets should be sucked, not swallowed, and retained in the mouth for as long as possible. Therapy should be continued for at least 48 hours after symptoms have resolved.

Prophylaxis: two tablets daily, to be continued indefinitely.

Contraindications and precautions

Treatment should be discontinued if symptoms of irritation or sensitization occur.

Use in pregnancy

Safe use in pregnancy has not been established. The need for treatment must be determined by the condition of the mother.

Adverse effects

Mild and transient nausea, vomiting and diarrhoea may occur after oral administration. Irritation rarely occurs after topical application.

PENTAMIDINE

Antiprotozoal agent

Clinical information

Uses

Treatment and prophylaxis of pneumonia due to *Pneumocystis carinii* in patients with HIV infection.

Dosage and administration

Treatment:

4 mg/kg by i.v. infusion over at least 60 minutes, daily for at least 3 weeks.

For patients with severe renal failure, infusions should be administered on alternate days.

Prophylaxis:

300 mg in 6 ml by oral inhalation as a single dose every 4 weeks, to be continued indefinitely. The nebulizer should provide a particle size of less than 5 µm.

Contraindications

Known hypersensitivity to pentamidine.

Precautions

Because of the risk of hypotension and syncope all patients should remain supine

and under observation for at least 30 minutes after each injection.

The risk of death during the first few days of treatment can be substantially reduced if a corticosteroid is administered as soon as therapy is started, if the patient's arterial oxygen tension is less than 70 mmHg (9.33kPa).

Blood pressure, blood count and serum creatinine and blood glucose concentrations should be monitored daily throughout treatment.

Interruptions or discontinuation of treatment may need to be considered should acute deterioration of bone marrow, renal or pancreatic function occur.

Use in pregnancy

Use in pregnancy can induce abortion. However, pneumonia due to *Pneumocystis carinii* must always be treated without delay.

Adverse effects

Mild nephrotoxicity is frequent and usually completely reversible.

Rapid intravenous infusion can induce acute hypotension and syncope. Oral inhalation can precipitate bronchospasm. Pancreatic damage firstly induces hypoglycaemia due to excessive insulin release. Hyperglycaemia due to insulin insufficiency and pancreatitis may occur subsequently.

Other adverse effects include hypocalcaemia, gastrointestinal effects, confusion, hallucination, cardiac dysrhythmias, local induration and, occasionally, sterile abscess formation.

Rarely, thrombocytopenia, leukopenia, abnormal hepatic function tests and erythema multiforme (Stevens-Johnson syndrome) have been reported.

PODOPHYLLUM RESIN

Keratolytic agent

Clinical information

Uses

Topical treatment of genital warts (condylomata acuminata).

Dosage and administration

A 10-25% solution should be applied to the affected area. Care must be taken to avoid contact with normal tissue. The solution should be thoroughly rinsed off after 1-4 hours.

Therapy may be repeated at weekly intervals up to a maximum of four applications.

The active ingredient podophyllotoxin (0.5%) is available in some countries. It is less corrosive and may be applied without medical supervision.

Contraindications

Podophyllum resin should not be applied to large areas of skin, nor should it be

used in the treatment of cervical, urethral, anorectal or oral warts.

Treatment is contraindicated during pregnancy since podophyllum resin is both teratogenic and fetotoxic.

Precautions

Preparations of podophyllum resin should be used only under close medical supervision because potentially serious local and systemic toxic effects can result from prolonged or excessive applications. Systemic absorption is enhanced when applications are made to friable, bleeding warts.

Adverse effects

The systemic effects of excessive cutaneous absorption include nausea, vomiting abdominal pain and diarrhoea.

Transient leukopenia and thrombocytopenia sometimes occur, providing evidence of bone-marrow depression.

Gross over application can result in serious neurotoxicity. The signs are characteristically delayed in onset and slow to resolve. They include visual and auditory hallucinations, delusions, disorientation, confusion and delirium.

PYRIMETHAMINE

Antiprotozoal agent

Clinical information

Uses

Treatment of toxoplasmic encephalitis and other manifestations of active toxoplasmosis in patients with HIV infection.

Dosage and administration

A total of 200 mg in divided doses on the first day, followed by 75-100 mg daily for at least 6 weeks. Suppressive treatment with a daily dose of 25-50 mg should then be continued indefinitely.

Pyrimethamine at this dosage must always be taken together with sulphadiazine.

Pyrimethamine has been administered alone to patients who are hypersensitive to sulphonamides at dosages some four times those suggested here. However, such regimens are associated with a greater risk of bone-marrow depression.

Contraindications

- Known hypersensitivity to pyrimethamine.
- Severe hepatic or renal dysfunction.
- Pregnancy during the first trimester, except when the mother's health is seriously endangered.

Precautions

All patients should receive calcium folinate concurrently to prevent folinic acid deficiency resulting from high daily doses of pyrimethamine.

Use in pregnancy

Pyrimethamine is normally contraindicated during the first trimester, but administration should not be delayed when the mother's health is seriously endangered. It should always be given thereafter to reduce the risk of congenital transmission.

Adverse effects

Anorexia, abdominal cramps, vomiting, ataxia, tremors and seizures have been reported.

As the high dosages required for the treatment of toxoplasmosis, pyrimethamine may induce thrombocytopenia, granulocytopenia and megaloblastic anaemia due to folinic acid deficiency.

Drug interactions

Various other drugs, including all sulphonimides, trimethoprim and methotrexate, act synergistically with pyrimethamine to inhibit folic acid metabolism. Coadministration (other than planned use of sulfadiazine) should be avoided.

SPECTINOMYCIN

Antimicrobial agent

Clinical information

Uses

Treatment of:

- Uncomplicated anogenital and disseminated gonorrhoea
- Adult and neonatal gonococcal conjunctivitis
- Chancroid, as alternative to erythromycin.

Dosage and administration

Uncomplicated anogenital gonorrhoea:
2 g i.m. as a single dose.

Contraindications

Known hypersensitivity.

Precautions

In patients with renal impairment, spectinomycin should be used only when alternative therapies are inappropriate.

Use in pregnancy

Since safety in pregnancy has not been established, spectinomycin should be used in pregnant women only if the need outweighs any possible risk to the fetus.

Adverse effects

Hypersensitivity reactions occur rarely. Pain at the injection site, nausea, fever, dizziness and urticaria have been reported.

SULFADIAZINE

Antimicrobial agent

Clinical information

Uses

Treatment of:

- Toxoplasmic encephalitis and other manifestations of active toxoplasmosis in patients with HIV infection
- Lymphogranuloma venereum.

Dosage and administration

Toxoplasmosis in patients with HIV infection

A total of 6-8 g orally or i.v. in four divided doses daily for at least 6 weeks, followed by a suppressive dose of 2-4 g daily, to be continued indefinitely.

For the treatment of toxoplasmosis, sulfadiazine must always be administered in combination with pyrimethamine.

Lymphogranuloma venereum

1 g orally four times daily for 7 days.

Contraindications

- Known hypersensitivity to sulfonamides.
- Pregnancy during the first trimester, except when the mother's health is seriously endangered.
- Severe hepatic or renal dysfunction.

Precautions

Patients with HIV infection receiving sulfadiazine and pyrimethamine treatment for toxoplasmosis should be given calcium folinate concurrently to prevent folinic acid deficiency.

In these patients, the blood count should be monitored twice weekly throughout therapy to detect signs of bone-marrow depression. Administration should be discontinued immediately should presumptive signs of hypersensitivity occur, such as skin rashes, dark urine and purpura.

Sulfadiazine is less soluble in urine than many other sulfonamides. A high output of alkaline urine must be maintained during treatment of toxoplasmosis to avoid crystallization.

In all patients, concomitant administration of other drugs that interfere with folic acid metabolism (apart from pyrimethamine) should be avoided whenever possible.

Use in pregnancy

Administration of sulfonamides during pregnancy can induce severe hypersensitivity reactions in the mother. Their action in displacing bilirubin from protein binding sites has given rise to concern, based on data derived from premature neonates, that they may promote kernicterus. Although sulfonimides readily cross the placental barrier there is no conclusive evidence

that the fetus is at risk. Nevertheless, sulfadiazine should not be administered during the first trimester, except when the mother's health is seriously endangered.

Adverse effects

Nausea, vomiting, diarrhoea, and headache sometimes occur.

Sulfonamide-induced hypersensitivity reactions can be severe. They include rare life threatening cutaneous reactions such as erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis.

Crystalluria may result in dysuria, renal colic, haematuria and acute renal obstruction.

Other infrequent reactions include granulocytopenia, thrombocytopenic purpura, agranulocytosis, aplastic anaemia and toxic hepatitis. Haemolysis occasionally occurs in individuals deficient in glucose-6-phosphate dehydrogenase.

S U L F A M E T H O X A Z O L E / TRIMETHOPRIM

Antimicrobial agent

Clinical information

Uses

- Treatment of granuloma inguinale.
- Treatment of chancroid (as an alternative to erythromycin) and

gonorrhoea in areas where strains remain sensitive and regular monitoring can be carried out.

- Treatment and prophylaxis of pneumonia due to *Pneumocystis carinii* in patients with HIV infection.

Dosage and administration

Granuloma inguinale

Sulfamethoxazole 800 mg+trimethoprim 160 mg orally twice daily for 14 days.

Chancroid

Sulfamethoxazole 800 mg+trimethoprim 160 mg orally twice daily for 7 days.

Gonorrhoea

Sulfamethoxazole 4000 mg + trimethoprim 800 mg orally as a single dose once daily for 3 days.

Pneumonia due to *Pneumocystis carinii* in patients with HIV infection

Treatment

Oral administration: sulfamethoxazole 100 mg/kg+trimethoprim 20 mg/kg in two to four divided doses daily for at least 3 weeks.

Intravenous infusion for severely ill patients: sulfamethoxazole 75 mg/kg+ trimethoprim 15 mg/kg daily in four divided doses, each administered in a 5% glucose solution in water over 60 minutes. Oral dosage forms should be substituted as soon as they can be injected.

Prophylaxis

Sulfamethoxazole 25 mg/kg in two divided doses daily on 3 consecutive days each week for as long as immunosuppression persists.

Contraindications

- Known hypersensitivity.
 - Severe hepatic or renal dysfunction.
- Precautions

In HIV infected patients with pneumonia due to *Pneumocystis carinii* whose arterial oxygen tension is less than 70 mmHg (9.33kPa), the risk of death during the first few days of treatment can be substantially reduced if a corticosteroid is administered as soon as therapy is started.

Treatment should be suspended immediately should a rash or any other manifestation of sulfonamide hypersensitivity occur.

The risk of sulfonamide crystalluria is decreased by maintaining a daily urinary output of at least 1.5 litres. Whenever possible, plasma sulfonamide concentrations should be determined periodically.

Patients must be advised to seek medical advice should they develop sore throat or fever during treatment. This advice can be of greater value than routine monitoring of the white cell count.

Since elderly patients may be more susceptible to severe adverse reactions

especially blood dyscrasias, their treatment should not be unnecessarily prolonged.

Patients deficient in folate may require supplementary calcium folinate to prevent megaloblastic anaemia.

Use in pregnancy

The combination of sulphamethoxazole and trimethoprim is best avoided in pregnancy as it may give rise to kernicterus of the new-born. However, treatment of patients with *Pneumocystis carinii* pneumonia, which is life threatening, should in no circumstance be delayed.

Adverse effects

Nausea, vomiting, glossitis and skin rashes are common. In patients with HIV infection receiving sulphamethoxazole/trimethoprim for *Pneumocystis carinii* pneumonia, recurrent fever, neutropenia, thrombocytopenia and increases in serum transaminase levels also occur frequently.

Trimethoprim may induce a megaloblastic anaemia responsive to calcium folinate.

Sulfonamide-induced hypersensitivity reactions can be severe. They include life threatening cutaneous reactions such as erythema multiforme (Stevens - Johnson syndrome) and toxic epidermal necrolysis.

Other reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura, and toxic hepatitis. Haemolysis occasionally, occurs in individuals deficient in glucose-6-phosphate dehydrogenase.

Drug interactions

Maintenance requirements for sulfonylureas and coumarin anticoagulants are often reduced as a result of their displacement from plasma proteins by sulfamethoxazole.

Concomitant use of other inhibitors of folate metabolism (such as pyrimethamine, methotrexate and certain anticonvulsants) increases the risk of megaloblastic anaemia.

Overdosage

Symptoms of acute overdosage include vomiting, dizziness and confusion followed by visual disturbances, petechiae, purpura and jaundice. Crystalluria, haematuria and anuria may also occur.

Emesis or gastric lavage may be of value within a few hours of ingestion. Provided urinary output is satisfactory, a high fluid intake should be maintained. Haemodialysis may be of value in eliminating some of the drug. Otherwise, treatment is symptomatic and supportive.

TETRACYCLINE

Antimicrobial (tetracycline) agent

Clinical information

Uses

Treatment of:

- Chlamydia trachomatis infections, including lymphogranuloma venereum
- Granuloma inguinale
- Syphilis in non-pregnant patients allergic to penicillin.

Prevention and (when systemic treatment is not available) treatment of conjunctivitis of the new-born due to *Neisseria gonorrhoea* and *chlamydia trachomatis*.

Dosage and administration

Chlamydia trachomatis infection

500 mg orally four times daily for 7 days.

Lymphogranuloma venereum and granuloma inguinale

500 mg orally four times daily for 14 days.

Syphilis

500 mg orally four times daily for 15 days. In neurosyphilis and late syphilis, treatment should be continued for a further 15 days.

Ophthalmia neonatorum

Prevention: a single application of the ointment should be sufficient.

Treatment: ointment should be instilled into each eye hourly pending referral of the infant.

Contraindications

- Known hypersensitivity.
- Severe renal impairment.
- Pregnancy and early childhood (except for topical use to prevent or treat ophthalmia neonatorum).

Precautions

Troublesome oesophagitis may be averted if the patient is propped up while swallowing capsules or tablets and washes them down immediately with a glass of water. Capsules and tablets should not be taken with milk or with magnesium or aluminium salts since these impair the absorption of tetracycline.

Time-expired capsules and tablets should be discarded. Degraded tetracycline has been reported to induce renal dysfunction indistinguishable from the Fanconi syndrome and skin lesions similar to those of systemic lupus erythematosus.

Use in pregnancy and early childhood

Tetracycline is generally contraindicated in pregnancy and during early childhood.

Because it is deposited in developing teeth, and bones and impairs skeletal calcification, it can result in abnormal osteogenesis and permanent staining of teeth, and occasionally causes hypoplasia of dental enamel.

Adverse effects

Gastrointestinal irritation is common, as is depletion of the normal bowel flora, permitting overgrowth of resistant organisms. Irritative diarrhoea should be differentiated from enteritis due to suprainfection, particularly with coagulase-positive staphylococci, and from pseudomembranous colitis due to *Clostridium difficile*.

Phototoxic reactions occasionally result in porphyria like skin changes and pigmentation of the nails.

Hypersensitivity reactions are rare. Morbilliform rashes, urticaria, fixed drug eruptions, exfoliative dermatitis, cheilosis, glossitis, pruritus and vaginitis have been reported, as have angioedema, anaphylaxis and pseudotumour cerebri.

Drug interactions

The action of oral anticoagulants may be potentiated. Severe renal failure has been reported in patients who have received a halogenated anaesthetic agent while taking tetracyclines.

(WHO Model Prescribing Information: Drugs used in Sexually Transmitted Diseases and HIV Infection)

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HIV grows very fast in it.

About PRAYAS

PRAYAS's main interest areas are Health, Energy Learning and Parenthood.

The Health Cell deals mainly with the problem of HIV/AIDS.

We conduct awareness programs for different groups; train animators to conduct awareness programs; publish articles, booklets and prepare software in the form of slides, posters, flip charts, etc., for spreading the message; provide counselling services to HIV infected individuals and their families; provide care and treatment for the sick. We also co-operate in and conduct research in sexual behaviour, contributing to better planning of effective intervention strategies. We are also a part of different advocacy groups striving to create an environment conducive to containment the epidemic. We have established an "AIDS networking and Information Centre" for collection, collation and distribution of HIV/AIDS related information. We have prepared a slide set and handbook for AIDS awareness programmes. The slide sets are available in Marathi, Hindi and English. These have also been translated in other regional languages.

Our selected publications

1. '*AIDS vishayee he mala mahit have!*' (Marathi)
2. Children and AIDS (an English compilation)
3. Handbook for Animators to conduct awareness programs (Marathi)
4. A Slide and Poster Set, Flip Charts for AIDS Awareness Programs
5. '*Madhyamanshi Maitree*' (Marathi)
6. '*HIV/AIDS Mhanaje Ahe Tari Kay?*' Awareness booklet for Media personnel (Marathi)
7. '*Chandrapurchya Janglat*' a video film
8. '*Pudhe Kay?*' a booklet for HIV infected individuals and their family members (Marathi)
9. HIV/ AIDS Diagnosis and Management: A Physician's Handbook