



Management of Pediatric HIV

PRAYAS

Initiatives in Health, Science,
Learning and Development

A Physician's Handbook

PRAYAS (Initiatives in Health, Energy, Learning and Parenthood) is a public charitable trust, which was registered in 1994. A group of medical and engineering professionals established this non-government organization (NGO) with a mission to apply their professional knowledge and skills to understand the issues afflicting society and to make efforts to address these issues through appropriate and sensitive strategies especially in the areas of health, energy, resources and livelihood as well as learning and parenthood. The belief behind our efforts is that even the most marginalized people can be empowered to tackle their own problems, if they are provided with sound analysis and appropriate support.

PRAYAS Health group works mainly in the area of HIV/AIDS and sexuality. The group has evolved and expanded along with the HIV epidemic. Our activities include conducting awareness programs, trainings (for community animators, counselors, NGOs, self help groups, health care providers, etc.), resource material development, research (social as well as clinical), and advocacy along with interventions in prevention of mother to child transmission of HIV (PMTCT) and Pediatric HIV. The group also has a clinic which provides quality clinical care, counseling, medicines, and laboratory investigations to people with HIV at subsidized costs. Care is provided at PRAYAS irrespective of the individual's class, caste or economic status.

Management of pediatric HIV: A physician's handbook

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Prayas Health Group
2009

PRAYAS
Initiatives in Health, Energy,
Learning and Parenthood

Management of pediatric HIV: A physician's handbook

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About the cover:

The painting is by a teenage girl. She presented it to us after she was disclosed about her HIV.

There are some open and some closed windows in the wall, yet there are bright colors all around.

The vibrant hue truly depicts her brave and tender perspective.

She is doing extremely well on treatment and is trying her best to lead life with immense enthusiasm.

To,
All our young friends living with HIV.
Their innocent smiles and twinkling eyes have kept us going.

Acknowledgements

We owe a debt of gratitude to many people for their hand in helping this work come to life.

Since pediatric HIV is in itself a newer and developing branch of medicine compared to adult HIV medicine, there was a good deal of want for a ready reckoner- a handbook for the practitioners coming across the patients. We realized this while rendering care and loving support to so many children. We can not thank in words the children and their families for giving us an opportunity to be of a little help as no gratitude is sufficient enough. We could think, try and succeed in writing this book only because of their lovely existence in spite of the predicament they are going through.

After preparing the first draft we involved many experts working in this field for reviewing our work. Drs. Raman Gangakhedkar, Rajan Joshi, Anand Deshpande, Sharad Agarkhedkar, Jitendra Oswal and Aarati Kinikar, all readily agreed to do so. We thank them for their intelligent critique that helped us to sharpen our concepts. Their continued insistence and belief in our work has inspired us a lot.

The book is basically written for family physicians and pediatricians who otherwise do not have to concentrate on HIV related practice. Though India is 3rd in the list of countries with highest number of HIV infected people in the world, our prevalence is quite low. These physicians get an opportunity to treat such patients not so often. To understand their needs as well as understanding the utility of our effort for the intended end users we invited a representative group for their opinions. We thank Drs. Anil Mokashi, Suhas Nene, Sushruta Kulkarni and Marcia Waran for their time, critical feedback and inspiring comments.

The module was then used for training a group of pediatricians who attended a 6 month long training on management of pediatric

HIV. They came from almost 19 districts of Maharashtra to attend two residential contact workshops, participated in on-line case discussions and hands on training at Prayas Amrita clinic. Their feedback has been invaluable to make the contents as simple and practical to understand as possible.

We thank our home-team, especially Dr. Tripti Darak for her dedicated work to edit, fact check and help to improve the manuscript and Ms. Neha Vaidya for her cheerful and effective co-ordination of the whole process.

The cover of this book is a painting done by one of our young friends, a girl who presented it to us a month after she was disclosed regarding her infection. Her braveness and untiring enthusiasm is simply marvelous. We thank her for being with us.

We thank our clinical group and counselors involved in the care of the children. Their inputs and insights have certainly reflected in the book.

We also thank all our support staff, particularly Mr. Abhay Dhamdhare who has typeset the manuscript over and over again and Mr. Ganesh Khambe who is always at hand for all types of support.

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Vinay, Sanjeevani, Ritu and Gayatri

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Structure of HIV

Kwashiorkor

Marasmus

HIV encephalopathy

India Ink Preparation for Cryptococci

Pneumocystis jiroveci pneumonia

Lymphoid Interstitial Pneumonitis - Clubbing

Lymphoid Interstitial Pneumonitis - X-ray-Chest

Pulmonary Tuberculosis

Linear Gingival Erythema

Necrotising ulcerative periodontitis

Oral Hairy Leucoplakia

Aphthous stomatitis

Herpes stomatitis

Esophageal candidiasis

Varicella zoster infection

Herpes zoster

Molluscum contagiosum

Herpes genitalis

Condyloma acuminata (HPV)

Candidial intertrigo

Tinea capitis
 Recurrent bacterial infections
 Cutaneous tuberculosis
 Scabies
 Seborrheic dermatitis
 Pruritic papular eruptions of HIV
 Drug reactions- SJ Syndrome/TEN
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 Toxoplasmosis
 Progressive Multifocal Leukoencephalopathy (PML)

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Foreword

HIV infection posed numerous challenges to the scientists, implementers and policy makers, world over as it transformed itself into a pandemic in a short span of time after its identification in 1981. India had one of the highest numbers of people living with HIV infection among all countries in the world within a few years of identification of the first cluster of HIV infected sex workers in Chennai in 1986. The National AIDS Control Program successfully implemented appropriate strategies for every at risk sub-population and contained the epidemic to a large extent. Recent evidences suggest that the HIV epidemic is reversing in the six high prevalence states in India, perhaps a reflection of effective focused interventions among core groups and bridge populations. Transfusion associated HIV infection has also declined dramatically. The National AIDS Control Organization launched free antiretroviral therapy program in India that has covered almost 3,00,000 people having advanced HIV disease including children.

The management of HIV disease evolved rapidly after 1994 when the three drug combinations came into vogue transforming this potentially fatal infection into a chronic manageable infectious disease. The report of an approach to prevent mother to child transmission of HIV infection using zidovudine in 1994 gave a boost to prevent transmission of HIV infection to babies. With the advent of newer antiretroviral drugs, highly effective regimens for HIV disease management and preventing mother to child transmission (PMTCT) evolved and were adopted for public health practice in the developed countries. The three drug regimen for PMTCT used in the developed countries reduces the risk of transmission to about 1%; limiting the likelihood of emergence of pediatric HIV infection as a major health problem. However, according to the recent estimates of the World Health Organization, almost half of HIV infected pregnant

women receive single dose nevirapine that can reduce the risk of transmission to only about 18% and additionally limits therapeutic options for the mother as well as her HIV infected baby when they develop advanced HIV disease. A change in regimen to prevent parent to child transmission (PPTCT) is being contemplated in India. Until a highly effective regimen to reduce PPTCT is adopted and its coverage is strengthened, pediatric HIV infection will continue to pose a challenge for medical as well as psycho-social management in India.

HIV infection is a new disease. It was not a part of the medical curriculum for a majority of medical practitioners. Additionally, the rapidly advancing frontiers of research, complexities in disease management and low access to new knowledge while practicing are important barriers in providing quality management to HIV infected children. Though free ART program has enhanced access, transportation cost and time to seek consultation for illnesses that occur warrant involvement of pediatricians in providing care to them. However, access to a pediatrician in rural area is also low. It is also known that the proportion of HIV infected individuals living in urban and rural areas is almost becoming equal in India. Hence involvement of family physicians is crucial in management of pediatric HIV infection.

Empowerment of pediatricians and family physicians through training is critical. Their fears and apprehensions need to be addressed appropriately during training. Responding to the needs of these practitioners, PRAYAS started a training program in Maharashtra. It was felt that the practitioners should be provided a simple module to refer.

There are many management guidelines available from different agencies globally. Most of the guidelines in management of pediatric HIV infection deal with different issues separately. For example,

there are guidelines for using antiretrovirals among children and a different set of guidelines for management of opportunistic infections. The practitioner is required to spend time in searching them and also know how to access them. Generally, the guidelines are developed when significant new findings that can impact public health are reported. Revision of guidelines also takes place when significant changes need to be made to the earlier guidelines on any particular issue. Therefore, guidelines for different issues tend to be developed in different time points and sometimes lack updating of minor but from practice perspective important issues. One needs to keep abreast of such small but significant findings by reading scientific journals to which a large majority of practitioners do not have any access.

The book- Management of Pediatric HIV: Physician's Handbook is akin to a one stop shop. It not only takes the best from every available guideline but it takes new information from research studies as well. Additionally, it has a local flavor for burden of diseases that we have. One will always find that the management guidelines from different sources emphasize on issues that are closer to them. The authors have made a laudable attempt to be more local. Importantly, the management approaches do not omit routine pediatric infections nor examination issues as the authors are aiming to involve those who may not be very well-versed with pediatric medicine in to giving quality care. It is likely that the book will serve an additional purpose of refreshing knowledge on managing infectious diseases in children in general as well.

The book addresses issues in a very logical manner that starts from prevention of parent to child transmission to antiretroviral therapy in pediatric HIV infection. It is important to remember that all practical details while handling pediatric HIV infection find a mention in the chapters.

One of heartening features of the book is inclusion of sections on counseling and disclosure of HIV status which is perhaps one of the challenging tasks in managing pediatric HIV infection. The annexure shows a glimpse of cafeteria approach- alternate treatment strategies also find a mention as also the internet based sources to seek more information.

This is a book written by authors who have committed themselves to caring for those who are infected by HIV and preventing pediatric HIV as much as possible. PRAYAS has been working for a long time in both these fields. Therefore this is a book that every physician who provides care to children must have and refer to.

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National AIDS Research Institute, Pune

Preface

Since the recognition of the HIV epidemic in 1981, millions of children have either perished or are living with HIV infection. Many more are affected due to death or illness of their parents and siblings. Unfortunately, only a few among those who are living with HIV are having access to quality care and treatment.

Mother to child transmission is the major mode of infection in children and in fact such transmission can be effectively prevented by appropriate interventions. However, it remains a reality that not all pregnant women have access to prevention of mother to child transmission interventions. Hence unfortunately, every year thousands of children are still being infected worldwide. The global distribution of this burden is grossly skewed, major brunt being borne by middle and low income countries.

In India, it is estimated that approximately 70000 children are living with HIV and more than 20,000 are being newly infected every year.¹ Almost 5000 children progress to AIDS annually. All these children need good pediatric care and proper management of their HIV disease. If provided with good care and proper treatment, we see that HIV infected children do extremely well and lead an almost normal life. However, given the complex nature of HIV disease and its psychosocial complications, this care does not remain restricted to medical management of a sick child. It involves comprehensive care of the family as a unit.

There are several barriers to this, such as difficulties in early diagnosis, denial by parents to test children early, lack of awareness among health care providers about pediatric HIV, lack of access to proper care etc. As the distribution of pediatric cases is far thinner and

scattered as compared to the adult cases, pediatricians tackle them only infrequently. The need to be well informed about management does not really become a 'felt need'.

Being a well known center for comprehensive quality and affordable care for HIV, many children from all over the state of Maharashtra (and some even from outside) avail services at PRAYAS Amrita Clinic. We feel that this was because there was lack of quality pediatric HIV care at local level. As a part of our commitment towards capacity building, we conducted a training program for pediatricians in private sector. The response was so overwhelming that we decided to publish the entire module as a handbook; a handy reference for those who could not attend the training.

The national government and National AIDS control Organization (NACO) with the help of State AIDS Control Society (SACS) are trying their level best to rapidly scale up prevention as well as treatment programs, mainly in public sector but also in private sector through public private partnerships. The training program and this handbook are our humble contributions to this national resolve to control the epidemic.

-
1. National Aids Control Organization, Ministry of Women and Child Health, Government of India and UNICEF Policy framework for Children and AIDS: India, 2007

1.

General Considerations of Pediatric HIV Disease

Pediatric HIV is different from adult HIV disease in many ways. It requires different and specific considerations. One should not treat children as mini-adults.

Epidemiological considerations

In India, and world over, mother to child transmission (MTCT) remains the predominant mode (82%) of incident pediatric HIV infection. Most of the developed countries have almost eliminated MTCT through various preventive measures.

Pediatric epidemic in India still continues to spread. Various factors that adversely influence the epidemic are:

- low coverage of prevention of mother to child transmission programs
- low uptake of available services

- cost of care
- diversity of treatment seeking behaviors and standards of care

There is high morbidity and mortality among children with HIV.

The risk of opportunistic infections (OIs) in infected children is increased due to:

- malnutrition
- poor hygiene due to lack of proper sanitation facilities
- confounding social factors such as poverty
- burden of other infectious diseases etc.

We need to consider pediatric HIV as a different scenario due to following considerations:

Diagnostic considerations

Early diagnosis of HIV infection is crucial for prevention of early morbidity and mortality, but diagnosing HIV infection in children born to HIV-infected mothers is quite challenging.

- Maternal antibodies cross placental barrier, hence serological testing (ELISA) does not have definitive meaning upto 18 months of age. It is possible that child with reactive antibody based test is actually not infected.
- Babies continue to get exposed to the virus during period of breast feeding.
- In case of negative serological reports window period needs to be ruled out.
- The specialized tests such as DNA PCR are essential for early diagnosis but are not widely available and are difficult to afford for people from low socio-economic strata.

Complex clinical profile

- Contrary to adults, children with HIV show two peaks of development of AIDS, some developing AIDS within 2 years of

life and others much later. This is called bimodal distribution of time to progression (measured by age at AIDS diagnosis).

- There is shorter overall survival in children as compared to adults.
- Roughly 25-30% of untreated HIV infected children are rapid progressors and will have severe immune-suppression within first year of life. Annual rate of progression then declines to 3-6% per year in the absence of treatment and 5-25% are long-term survivors.
- Morbidity among children is higher as children have less effective immune control of HIV. Developing organs of children are more prone to direct viral assault (e.g. encephalopathy, cardiomyopathy is more common).
- Recurrent bacterial infections is second most common AIDS defining condition reported such as infections with encapsulated organisms (*Strep. pneumoniae*, *H. influenzae*, and non-typhoid serotypes of *Salmonella* etc.)
- In India, tuberculosis (primary complex) is an important coinfection.
- *Pneumocystis jiroveci* pneumonia (PCP) is the commonest OI in infancy and is associated with high mortality. But it is not easily amenable to definitive diagnosis.

Treatment considerations

Due to the complex clinical profile, management too is complex.

- There is no curative treatment for HIV as on date.
- Availability of anti-retroviral treatment (ART) has altered the outlook but has to be taken life-long.
- ART needs to be initiated comparatively earlier in children than in adults.
- In ART there are limited options for first line and even further limited options for second line treatment.

- Adherence is the key determinant in the success of ART but is more difficult to achieve in children than in adults.
- As survival increases issues of long term toxicities surface, so do co-morbidities requiring treatment and increasing chances of drug-drug interactions.

Ethical considerations

- Pre-treatment counseling and informed consent, which are considered so important in adults, are to be handled differently in case of children.
- In case of such highly stigmatized disease, issues about disclosure of disease status become extremely crucial. Disclosure about the child's infection to him/her is still avoided by majority of parents.
- It is also difficult to maintain confidentiality of the child's sero-status. As children cannot give legal consent, participation of parents and assent of children for testing are some of the questions with no easy answers but definitely need extremely sensitive handling.
- Situation is further complicated by societal attitudes (of which physicians' are also a part) such as this question asked by many, "If we can not assure them normal adult life why at all treat them?" This kind of fatalistic approach influences the care provided.

Social considerations

- Stigma: In spite of being more than 25 years into the epidemic, 'AIDS' still carries a lot of stigma. People with HIV are discriminated against. Thus fear of disclosure may obstruct health and treatment seeking behaviors.
- Lifelong adherence: There are also issues of treatment fatigue and parents may need support to deal with it.

- Adolescents have special problems because it is time for identity seeking, establishment of independence and of rebellion against authority. It is difficult to guess how children would respond to the fact of infection during the period of sexual awakening.

This module is based on a basic premise that HIV infected children also have the same right to life as any other child and we as physicians need to help these children to achieve it (as we would do in case of any other potentially fatal disease).

2.

Mother to Child Transmission of HIV (MTCT) and its Prevention (PMTCT)

There is an old adage, 'Prevention is better than cure'.

Children can get infected with HIV due to the same four modes of transmission of HIV (i.e. unsafe blood transfusions, use of unsafe needles, unsafe sex and mother to child transmission).

- The chances of blood transfusion related transmission have greatly reduced after screening of blood before transfusion became mandatory.
- Though it will be very difficult to estimate the proportion of transmission due to unsafe injections (unfortunately, they are still being used on a very large scale in medical practice), circumstantial experience of those treating children suggests that its proportion is relatively low.
- Unsafe sex can be a significant mode of transmission in post-adolescent children.
- **MTCT remains the most important mode of transmission in our country.**

Effective interventions are available to prevent mother to child transmission and a massive national program called the 'Prevention of Parent to Child Transmission of HIV (PPTCT) is being operated in our country.

Pediatricians definitely have an important role in PMTCT.

Some salient points about MTCT:

- Not every child born to an HIV infected mother is infected. In other terms efficiency of **mother to child transmission** is **NOT 100%**.
- In the absence of any intervention, the overall risk of MTCT of HIV-1 has been reported to be **15 – 45%**, from different parts of the world.
- In India, we estimate it to be around 25-30 %.
- With best of the interventions available, risk of MTCT can be reduced to as low as **1-2%**.

When does MTCT occur?

- MTCT can occur at three stages: during **intrauterine, intrapartum and postpartum** period (due to transmission through breast milk).

Stage	Proportionate Risk
Intrauterine (mainly after 28 weeks)	30 %
Intrapartum	50 %
Breast feeding	7-22 %

(Please note that this proportionate risk is of the overall 15-45% transmission.)

Factors increasing risk of MTCT

1. Maternal factors
 - Stage of maternal HIV disease – The risk of transmission is directly proportional to maternal viral load; thus higher the viral load, higher the risk of transmission.
 - Presence of other sexually transmitted infections.
2. Obstetric factors
 - Prolonged rupture of membranes – The risk increases rapidly after 4 hours of rupture of membranes; by 2% every hour.
 - Obstetric procedures – Any invasive obstetric procedure such as forceps, ventouse or amniocentesis increases the risk.
 - Mode of delivery – Elective cesarean section (E-LSCS) offers some advantage in reducing the risk of transmission as compared to normal delivery, especially if the maternal viral load is high. Recent data suggest that if the woman has received sufficient ante-partum anti retroviral (ARV) prophylaxis (thereby reducing the viral load to less than 1000 copies/ml) the advantage offered by E-LSCS is marginal.
3. Factors associated with breast feeding
 - Duration of breast feeding – Longer the duration (more than 6 months), longer the exposure to the virus and higher the risk of transmission.
 - Mixed feeding is associated with higher risk than exclusive breast-feeding. Mixed feeding is defined as anything other than breast feed (such as honey, animal/tin milk, water, 'gutti' etc) along with breast-feeding. The exact mechanism of higher risk is not known. It is postulated that top feeds alter the gut flora, which probably induces antigen antibody reaction at gut mucosa. The gut mucosa is rich in CD4 cells necessary for entry of HIV present in breast milk; the inflammatory reaction at mucosal surface further facilitates infection. It is further aided by relative achlorhydria in the stomach of the infants. So the virus does not get destroyed in stomach as would happen in adults.

- Cracked nipples, mastitis in mother.
- Oral thrush/mucosal injuries in infant.

MTCT of HIV 2 in India

The prevalence of HIV 2 infection in India is very low (less than 1%). The virus is less pathogenic and has lower transmission efficacy as compared to HIV 1. MTCT of HIV 2 is only 2.6% in breast fed population in the absence of any interventions. Nevirapine as PMTCT prophylaxis is ineffective against HIV 2. Seek expert opinion in such cases.

It is necessary to differentiate between HIV 1 and 2 while making a diagnosis.

The discussion related to PMTCT in this chapter is with respect to HIV1 infection.

Prevention of Mother to Child Transmission of HIV (PMTCT)

With best of the interventions available MTCT risk can be reduced to as low as 1-2%. However it should be noted that in spite of the interventions, some risk of transmission, albeit very small, does exist.

Protocol for PMTCT interventions

Please note that the recommendations keep changing from time to time. Be updated about the current recommendations. **Most recently WHO has issued a rapid advice about PMTCT (December 2009).** Please refer to Annexure 1

1. Anti-retroviral (ARV) prophylaxis

ARV prophylaxis for pregnant woman:

A) Confirm whether the woman is already on ART.

- If the mother is already taking ART as a part of her treatment, there is no need to give additional ARV

medicines to her for PMTCT. Her ART should be continued during pregnancy and after delivery.

B) If not, then decide whether the woman needs antiretroviral treatment (ART) for her own health.

- Assess her CD4 count before considering PMTCT regimen. **If her CD4 count is less than 350/cml**, she must start getting appropriate ART regimen. It is preferable that ART includes Zidovudine (ZDV). The treatment should be continued during and after delivery without interruption.
- Remember that the threshold for starting ART during pregnancy is 350/cml and not 250/cml as for other adults as per current NACO guidelines.¹

C) In case her CD4 count is more than 350/cml, she does not need ART for herself.

WHO (2006) recommends following protocol

- Antepartum ZDV (300 mg) twice a day from 28 weeks
- Intrapartum one combined tablet of ZDV (600 mg) + 3TC (150 mg) in addition to a tablet of ZDV (300 mg) and a single tablet of NVP (200 mg)
- Postpartum combined tablet of ZDV (300 mg) + 3TC (150 mg) twice a day for 7 days to cover the tailing dose of nevirapine.²

(ZDV – zidovudine, 3TC – lamivudine, NVP – nevirapine)

In many resource rich countries, 3 drugs/4 drugs ARV regimen is given to the mother even if she does not require

-
1. Recently WHO has suggested that for all adults irrespective of their clinical staging the CD4 threshold for starting ART should be 350/ c mm.
 2. Nevirapine has relatively longer half life as compared to other drugs. The prolonged presence of suboptimal drug levels has been shown to increase chances of development of permanent resistance to Nevirapine and also to other NNRTIs
-

ART for her own health. It is discontinued after delivery. **This has proven to be the best** intervention for PMTCT. However some studies have demonstrated that if ART is started only for those with CD4 count less than 350/cml and others are provided the WHO suggested regimen there is little difference in efficacy. The 3 or 4 drug regimens are extremely cost intensive, so one must recommend the same only after proper cost analysis and one to one discussion.

- D) In situations **where the woman comes late in pregnancy or in labor** give
- Single dose NVP (200 mg) to mother. The intervention has low protective efficiency.
 - Postpartum: combined tablet of ZDV (300mg) + 3TC (150 mg) twice a day for 7 days to cover the tailing dose of NVP.
- E) **If the mother is detected to be HIV infected after delivery** then there is no role for ARV prophylaxis to the mother.

ARV prophylaxis for baby –

WHO recommends following protocol :

- NVP (single dose, 2 mg/kg) followed by ZDV (4 mg/kg BD). The duration of ZDV differs according to the duration for which the mother has received ARV medicines before delivery.
- **If the mother has received ARVs < 4 weeks, baby should receive ZDV for 4 weeks; if mother has received ARVs for > 4 weeks baby will be given ZDV for 7 days.**
- The dose of NVP can be given maximum up to 72 hours of birth.
- ZDV should be started ideally within first 6 hours of birth, but can be started maximum up to 48 hours.
- If the mother is on ART for her own treatment, then there is no need to give dose of NVP to baby.

2. Mode of Delivery and avoidance of invasive procedures

- Elective cesarean section (E-LSCS) has an advantage especially when the woman has not received any antenatal ARV.
- If the woman has received adequate ARV prophylaxis, the advantage of CS is only marginal. In such case the decision about CS should be based only on obstetric indications. Other factors such as socio-economic condition, availability of adequate and safe services need to be considered.
- In case of normal delivery, avoid forceps and ventouse.
- In case of prolonged rupture of membranes, it would be prudent to hasten the delivery by doing assisted labor or CS.

3. Infant feeding options

The woman should be counseled before delivery during her ANC visits regarding the different feeding options and encouraged to opt for the most appropriate option. As there is some risk of transmission through mother's milk one may feel that breast feeding should not be opted. However it has been documented that if replacement feeds are not given properly there is increase in infant morbidity and mortality. Mixed feeding has been shown to cause maximum breast milk related transmission.

So the options are:

- Exclusive replacement feed (formula/animal milk) if it is **acceptable, feasible, affordable, sustainable and safe (AFASS)**. These criteria must strictly be applied before the decision, otherwise the risks of infant mortality/morbidity due to alternative feeds, may out-way the benefits of reduced HIV transmission.
- Exclusive Breast feeding – This is the best option for those who cannot give replacement feeds. Maintaining exclusivity (only breast milk and nothing else such as honey or gutti) for 6 months is crucial. In our cultural context, this may not be a very easy

practice. It is important that the doctor and/or counselor are aware of this and provide the needed support consistently. The child should be rapidly weaned after 6 months.

- Pasteurization of expressed breast milk – the feasibility of this option for a longer period needs to be evaluated.
- Wet nursing.

The last two have been shown to be unsustainable on programmatic level.

Recent evidence shows that continuation of ARVs in mother till breastfeeding continues or extended ARVs during early infancy to infants can reduce postpartum transmission. (See annexure1)

Remember the following :

- The decision regarding feeding option should ideally be done before delivery.
- Continual counseling support is essential for better compliance to the chosen option.
- Exclusive breast feeding should ideally be given for 6 months. Prolonged breast feeding is associated with increasing chances of transmission.
- Mixed feeding is quite likely after 6 months which increases chance of transmission.
- Abrupt weaning is associated with increased morbidity and mortality among HIV infected children. Therefore weaning should be gradual but spread over not more than a couple of weeks.
- An innovative method of avoiding mixed feeding during weaning has been developed by some African women. At the time of weaning they suggest a stepwise approach. First step is to stop giving night time breast feeds. Then start giving expressed breast milk using spoon and bowl till the child adjusts to the new mode of feeding. As the last step- changing over to animal

milk/formula. The process could be spread over 2-3 weeks and still does not allow mixed feeding. If the child resists while shifting to outside milk, breast milk could be given but never without heating. Heating will make it HIV free.

(Please refer www.who.org for updates on guidelines.)

Critical Concepts

- The efficiency of MTCT is NOT 100%. The risk of MTCT of HIV-1 is 25-45%, even in the absence of any interventions.
- With the best available intervention the risk can be reduced to as low as 1%.
- As the risk of MTCT increases with advanced maternal disease, it is necessary to screen the mother for CD4 counts during pregnancy and choose appropriate ARV protocol.
- If the mother has received adequate antenatal ARV prophylaxis, leading to adequate suppression of viral load, then cesarean section (CS) offers only marginal advantage for reducing the transmission to baby. In such case, the decision about CS should be based only on obstetric indications.
- Exclusive breast feeding for a limited duration (6 months) minimizes the transmission risk through breast feeding significantly.
- Replacement feed (formula/animal milk) should be opted for only if it is **acceptable, feasible, affordable, sustainable and safe (AFASS)**.

3.

Handling HIV Exposed Neonate in Labor Room

While attending deliveries one may or may not be aware of the HIV status of the woman.

A physician should be concerned about two things

- 1. Safety of medical personnel**
- 2. Actions to be taken for the child**

There may be definite concern while handling a case when one knows that the woman is HIV infected. Some may say that it is advisable to know the status so that one can take *extra precautions*. But remember, even if one knows that the woman is not HIV infected, there remains a theoretical possibility that she could be in window period. At times one may not even have time to screen her if she has come in labor. Test reports could only be available next day. So there is not much difference whether one is attending delivery of a known HIV infected woman or with unknown status.

One must follow 'Standard precautions' in each and every case.

If the woman has not been tested in the current pregnancy and her serostatus is unknown; insist on testing even at this stage. Even if the results are available later there still remains a chance to provide PMTCT prophylaxis if required.

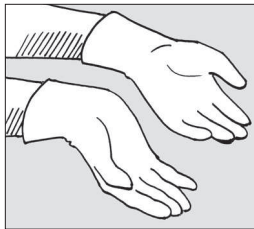
Our safety: Universal precautions:¹

Universal precautions are a standard set of precautions to be taken always, with each patient in every situation appropriately.

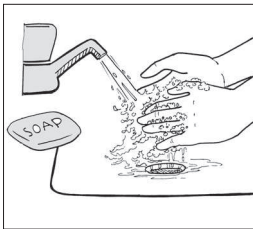
- During labor and delivery you are likely to be exposed to blood, vaginal fluid and amniotic fluid, which are all potentially infective fluids.
- To avoid exposure to these, use proper footwear, plastic gown, gloves, mask and adequate eye protection as per the need.
- Gloves should be worn until all blood and maternal secretions have been washed off.
- If there is accidental exposure of intact skin to these fluids, wash immediately with soap and water. There is no need for post exposure prophylaxis.
- One of the most common reasons for needle stick injuries is trying to recap a used needle. **Never recap a needle.** Destroy used needles or dispose them off in appropriate puncture-proof container containing sodium hypochlorite (liquid bleach) solution.
- Handle sharps carefully.
- Take care while cutting the umbilical cord.
- Dispose off bio-hazardous material appropriately.

1. PRAYAS has prepared a film on infection control measures – ‘Am I at risk?’ available in English and Marathi.

Avoid exposure of skin and mucous membranes to blood and other body fluids.



Risk of contact –
Wear gloves



Always wash hands
before and after
patient contact and
after removing gloves



Risk of splashing
–wear goggles,
mask or gown

Standard Precautions

(Ensure that other people around you in OT or labor room, including the obstetrician, also take these precautions! While other people in the OT or labor room are busy attending labor, they may tend to neglect these precautions. If you observe any such lapses, please provide proper and polite instructions.)

Actions to be taken for the child

Care of newborn at the time of delivery

- Follow standard neonatal care.
- Wipe baby's mouth and nostrils as soon as the head is delivered.
- Clamp cord soon after birth and avoid milking of cord towards baby. Cover the cord with gloved hand and gauze before cutting.
- Handle suction carefully. (Do not use mouth-operated suction for your safety).

- Once the neonate is stable, immediate baby bath is advocated to minimize the exposure of the child with infected fluids. Use warm water with mild soap. Avoid vigorous rubbing.

Once through with attending to the baby: Enquire

- If the mother received any ARV prophylaxis? Or is she taking ART? If yes then how long has she taken these medicines?
- Has the woman been counseled for and has taken any decision regarding infant feeding?

Depending upon the situation :

- Provide appropriate ARV prophylaxis to the infant as per the ARV prophylaxis received by the mother.
- Encourage the mother to start feeding the baby as per her informed choice.
- If things regarding these two questions are not clear, discuss with the obstetrician about who in her family is aware of the situation and is in a position to provide information. Act according to the information available.
 - **As the pediatrician is a new person on the scene s/he should take all the care to avoid uncontrolled disclosure to relatives, which may have dire consequences.**
 - If the woman has opted not to breastfeed then provide proper instructions. One may suppress breast milk. You may be needed to provide valid excuse to the woman's relatives for why she is not breast-feeding. They may not be aware of her HIV status. **Protect and honor her confidentiality, see to it that the woman, you and the obstetrician stick to the same excuse and don't create more confusion and panic.**

Checklist

Before delivery:

- HIV sero-status of the woman
- If unknown – get tested
- If known – whether ARV has been given or not?
- Counseling and decision making regarding infant feeding

During delivery:

- Standard precautions
- ARV prophylaxis to mother

After delivery:

- Infant ARV prophylaxis
- Infant feeding initiated as per decision of the mother

Before leaving delivery room:

- Reconfirm infant feeding decision and guide accordingly
- Reconfirm ARV prophylaxis to both mother and the newborn
- If woman is to be tested – remind to inform you about her reports and take ARV prophylaxis decision accordingly
- Remember to maintain confidentiality and avoid uncontrolled disclosure of woman's serostatus
- Make a note of circumstances and determine plan of action for the week to come

4.

Occupational Exposure and Post-Exposure Prophylaxis (PEP)

In spite of all precautions accidents may, and do occur.

It is possible that in spite of all universal precautions one may get exposed to infected fluids.

In case of accidental exposure :

- If there is contact of infected fluids *with apparently intact skin*, only proper and thorough washing with soap and water is required immediately. There is no need for any anti-retroviral post exposure prophylaxis.
- *If there is accidental injury or needle stick or mucosal exposure*, follow the following protocol for post exposure prophylaxis

A. First aid measures to be taken immediately

- Do not panic.
- Do not squeeze or suck the wound.
- Wash injuries profusely with soap and water.
- Wash splashes to the skin with water and soap.

- Irrigate splashes to the eyes with water or saline, with eyes open. Do not use detergent in the eyes.
- If splashed into the mouth spit out and gargle several times with clean water.
- If blood splashes into the nose, blow the nose and wash with water.

If a glove is found to be torn due to needle stick or other injury:

- Remove the glove immediately and use new gloves as promptly as patient safety permits.
- The needle or instrument involved in the incident should also be removed from the sterile field.

B. HIV status of the source

If HIV status of the source is unknown take immediate steps to determine the same. **Insist on rapid testing.** *If the source case is not infected then there is no need for post exposure prophylaxis (PEP).*

C. It is recommended that the *recipient* too goes for immediate testing to *rule out preexisting infection*. PEP has no role if the recipient is already infected.

D. Risk assessment

If the source is HIV infected, the risk involved is broadly defined as follows:

- Injury with solid bore needle or superficial injury involves **less severe risk**.
- Injury with hollow bore needle, needle used in artery or vein, deep puncture with device with visible blood on it are included under **severe risk**.
- Infection status and the status of ARV exposure of the source also determine the risk of transmission. Symptomatic cases, cases with high viral load and/or low CD4 counts, cases of acute seroconversion are associated with higher risk.

E. Post exposure prophylaxis

Post exposure prophylaxis should ideally be *started as soon as possible, ideally within 2 hours of exposure and maximum within 72 hours*. Expert advice should be sought before starting PEP.

Depending upon the risk assessment, basic (2 drug ARV) regimen for low risk and expanded (3 drug ARV) drug regimen for high risk is recommended for the period of 4 weeks.

Basic regimen

Preferred medicines	Alternative medicines
(Zidovudine 300 mg+Lamivudine (3TC) 150 mg) twice a day	(Stavudine 30 mg+Lamivudine (3TC) 150 mg) twice a day

Expanded regimen

Protease inhibitor (such as lopinavir/ritonavir, indinavir or nelfinavir) is recommended as a third drug. Consult an expert for starting 3rd drug.

NNRTI such as nevirapine/efavirenz should not be used for PEP.

(As the guidelines keep on changing, refer to www.naco.org for updates in guidelines.)

F. Follow up after PEP

- If PEP is started the person should be informed about possible drug interactions and monitored for drug toxicity.
- During this period the person should refrain from donating blood, semen or organ tissue and adapt safe sex practices.
- HIV testing of the recipient to rule out the infection
 - HIV antibody testing is recommended at 6 and 12 weeks post exposure to rule out the infection (considering standard

duration of window period), but can be done only at 12 weeks. If the test at 6 weeks is negative a repeat antibody test at 12 weeks is anyway required. Also, there is hardly any advantage of diagnosing the infection at 6 weeks as far as further HIV treatment is concerned. **So it would be best practice to do the first antibody test directly at 12 weeks.**

- Some recommend **another test at 6 months** based on the assumption that ARVs may delay seroconversion. However there are no data to support the observation.
- The infection can be diagnosed as early as 6 weeks by doing an antigen test (DNA PCR). Though the specificity of the tests is very good, sensitivity is very low during early phase. Sensitivity reaches about 90-95% after 6 weeks. Positive test results need to be confirmed and can be reported immediately but a negative report has to be repeated at least after a month. So while a positive test result would indicate transmission and negative report will not definitively rule out infection. *So routine use of direct viral assay is not advisable.*
- Extended follow up (For 12 months) is required if there is co-infection with HCV in the source case.

5.

Care of HIV Exposed Children

Some definitions :

- A child born to HIV infected mother is called as '**HIV exposed child**' till such time that HIV infection is conclusively ruled out. As early definitive diagnosis of HIV infection in children is not always possible there could be a long delay before the diagnosis is made.
- When, in an HIV exposed child, presence of HIV infection is confirmed, the child is labeled as **HIV infected**.
- Only a small proportion of HIV exposed babies are actually likely to be HIV infected.
- The immediate period after birth is crucial for continuing efforts to prevent transmission in HIV exposed children.

Immediate care of HIV exposed new born (age: 0-7 days)

Following issues require immediate attention :

- **ARV prophylaxis:** As we have seen in the chapter on prevention of mother-to-child transmission (PMTCT), duration of ARV prophylaxis to the baby depends upon how long and what prophylaxis mother has received.

Most babies would receive a combination of single dose Nevirapine (sdNVP) (2 mg/kg) and Zidovudine (ZDV) (4 mg/kg/twice a day either for 7 days OR 4 weeks. (If the mother has received ARVs < 4 weeks baby should receive ZDV for 4 weeks).

- **Infant feeding option:** If the woman has already been counseled during pregnancy and has made her choice regarding the feeding option, enquire and honor her choice.
 - As there is a possibility of transmission of HIV through breast milk, many a time, the mother is forced by health care provider to opt for the replacement feeding. Remember in certain situations complications arising out of replacement feeding may outweigh the risk of HIV infection. To avoid this, ensure that replacement feeding is **Acceptable, Feasible, Affordable, Sustainable and Safe (AFASS)**.
 - If she has opted for exclusive replacement feeding then inform her about
 - clean preparation of a feed
 - use of cup and spoon
 - avoid using nipple- bottle
 - use of boiled water
 - If she has opted for exclusive breast-feeding then emphasize the importance of **exclusiveness of breast-feeding. Ask her to continue it at least for 6 months.** Talk to her about care of nipples. In case of cracked nipples/mastitis, immediate treatment should be provided. Ask her to express and discard the milk from affected breast till it gets cured. Otherwise the lactation may get hampered. During this period continue feeding from unaffected breast.

- If she has opted for replacement feeding ensure that it is **exclusive replacement feeding**.
- **Mixed feeding i.e. anything else given to child - such as gutti, water, animal milk, etc – while the baby is breast feeding is the most risky in the context of HIV transmission. Reinforce messages about avoiding it.**

Ensure that the mother receives medicines for suppression of lactation so that the chances of mixed feeding are completely eliminated.

- **Issues of confidentiality:** While the mother is admitted in the hospital, uncontrolled disclosure of her HIV status is possible. It is necessary to sensitize the hospital staff in this context. In case of decisions, such as not-to-breast feed, which are contrary to the norms in India, it is likely that the doctor will have to provide satisfactory answers to family members' queries. The health care team should be prepared for it and their responses should be consistent. Any uncontrolled disclosure, inadvertently or otherwise should be avoided.
- **Immunization of baby**
 - BCG and first dose of oral polio (live vaccines) should be given as per schedule **except when the child is already symptomatic**.

Care of HIV exposed new born (age: 7 days to 6 weeks)

- **Feeding:** Ensure that there is no mixed feeding and infant feeding practices are followed correctly. Assess nutritional status and adequate weight gain carefully.
- **ARV prophylaxis:** ZDV to be given for 4-6 weeks, if mother has received ARV/ART for less than 4 weeks antepartum. Adjust the dose of ZDV (4mg/kg BD) according to weight of the child.

Weights change rapidly in this period and the mother needs to be educated properly for calibrating the dose. Watch for *anemia*, which is an important side effect of ZDV.

- Watch for signs and symptoms suggestive of HIV infection/disease and treat accordingly.
- Immunization: If the child is symptomatic avoid live vaccines such as oral polio, BCG.

Care of HIV exposed child (age: more than 6 weeks)

Remember – GIFT

Growth monitoring

Immunization

Feeding

TMP-SMX prophylaxis

- **Growth monitoring:**

Monitor child's anthropometry on growth charts. If the child's growth curves are flattening, then intensify assessment for HIV related features and also screen for treatable causes e.g. nutritional deficiency, chronic infections such as respiratory, gastro-intestinal, urinary tract infection and TB. If there is an open case of TB in family (especially parents), the child should be given INH prophylaxis.

- **Immunization:**

We must aim to provide the basic minimum immunization to all HIV exposed/infected children appropriate for the national setting.

There remains some confusion and concern regarding the use of live vaccines in the immune compromised child, due to risk of dissemination of the organisms.

However, most of the immunization schedule is over before the confirmation of infection in a child. We must remember that only a few of HIV exposed children will actually be HIV infected. Of those who are infected, not all would be 'immune compromised' during this period. This situation would be even more common when confirmation of the infection in the infant is delayed till the child is 18 months old. In such a situation it remains our bounden duty to protect all children from preventable diseases, as occurrence of any intercurrent infection is likely to compromise the health of the child.

General rule of thumb: All HIV-exposed children should be immunized according to the routine national immunization schedule.

Exception: Withhold live vaccines (BCG, OPV, measles, MMR) for symptomatic and severely immuno-compromised HIV-infected children.

- **Feeding:**

Ensure continuation of safe infant feeding practices. If the child is breastfed it should not be continued beyond 6 months. **Ensure that there is no mixed feeding.**

Weaning:

Weaning should start at 6 months. Abrupt weaning has been shown to be associated with increased morbidity and mortality in HIV infected children. It should ideally be as rapid as possible to avoid prolonged mixed feeding during the overlapping period. The aim should be **smooth transition** with minimal overlap of mixed feeding. Some reports from African studies suggest an *innovative approach* for the same which is as follows –

- During weaning two things change- taste of milk and method of feeding. Try to change one at a time.

- Initially reduce the frequency of breast feedings during night. Then introduce a few feeds of warmed expressed breast milk given by cup and spoon during day time.
 - Then gradually give all the feeds this way. The child would get accustomed to the new method, while the taste remains same.
 - Breast milk is then replaced completely by alternative feed in a few days.
- **TMP/SMX Chemoprophylaxis:**
Initiate 5/25 mg/kg/day of TMP/SMX (or 150/750 mg/m²/day of TMP/SMX) prophylaxis at age of 6 weeks for prevention of *Pneumocystis jiroveci* pneumonia (PCP) to all HIV exposed children.

It also protects against malaria, bacterial diarrheal disease, pneumonias and toxoplasmosis. Continue it till HIV infection is definitely ruled out.

Reinforce the need for adherence to co-trimoxazole prophylaxis

Keep a watch on signs and symptoms of OIs. Initiate prompt treatment. Inform parents to seek immediate medical advice if the child becomes symptomatic.

Laboratory diagnosis: Advice appropriate diagnostic tests.

- HIV can be diagnosed as early as 6 weeks with antigen based tests such as DNA PCR.
- Antibody tests such as rapid test or ELISA should be used after 18 months. (For more details refer chapter 'Clinical and laboratory diagnosis of HIV in children').

Counseling issues:

- If the child is diagnosed to have HIV, s/he needs closer follow up and monitoring. Very strong counseling support is required for

the parents in such cases. If the child is on breast feeding, ask the mother to continue it.

- But if the HIV infection is conclusively ruled out, it is equally important to inform parents/caregivers accordingly and allay their fears. Parents often remain very apprehensive. A lot of reassurance is required. Continue providing care. Since mother (and in majority of cases) father also is infected, the life of the child is going to be affected by HIV. The term '**HIV affected**', (as against 'infected') is used for such children.

Safe sex and contraceptive advice to the parents:

It is important to provide safe sex and contraceptive advice to parents at this juncture when sexual interactions are likely to restart.

Linking parents to health systems of HIV care:

See that the parents and other siblings are linked to health systems for diagnosis, care and treatment. Comprehensive family oriented care would begin here.

6.

Clinical and Laboratory Diagnosis of HIV in Children

Why is it important to diagnose HIV infection early?

The costs of missed diagnosis are tremendous, both to the individual and to the community. Early diagnosis of HIV is important as it:

- offers better quality of life to the patient due to interventions such as chemoprophylaxis for opportunistic infections and treatment with antiretroviral drugs.
- leads to screening and detection of HIV in parents and siblings, if the child is the first one to get diagnosed in the family (the index case).
- provides an opportunity for preventive counseling, in case of adolescents who are sexually active.
- provides better understanding of the epidemic and helps to design appropriate strategies for the community.

A substantial section of infected children may remain undiagnosed for a long time. It should be our endeavor to diagnose them as early as possible, before they become symptomatic.

Delayed diagnosis can be due to parents being unaware of their own status. In some cases parents are reluctant to test their children in

spite of knowledge about their own HIV status. This reluctance arises out of parental fear and anxiety regarding the ramifications of the child being 'HIV infected'. Lack of suspicion on part of health care providers is one more reason leading to delayed diagnosis.

Parents need consistent and compassionate counseling support regarding getting their children tested. This is easier when assured that support will be available even if the child is detected to be positive.

Pre-test counseling issues

Pre-test counseling issues have a different context in case of children. For very young children the consent of parents is enough. Guidelines suggest taking assent of older children (aged above 6 years). It is very difficult to discuss the issue of HIV (with direct reference) with these children. Generally the assent is for performing the test (i.e. to allow to take the blood sample) and not specifically for HIV testing.

Who to recommend HIV test?

Current recommendations

- Children of HIV infected women
- Children who have received blood/blood product transfusion/s
- Children with sexually transmitted infections
- Children who have been sexually abused
- Clinical scenarios suggesting HIV infection
- Preoperative* (*especially if the surgical condition points towards possibility of HIV associated illness*)

* With a view for protecting oneself, many surgeons routinely advice pre operative HIV testing. Unfortunately most of the times testing is done without informed consent and treatment is denied in case of positive test result. Such a practice is unethical. Preoperative testing should only be done after proper counseling and informed consent of the parents and if positive, care should not be denied.

Could it be HIV?

Clinical scenarios :

1) Strongly suspect HIV infection in any child if:

- Respiratory distress with cyanosis in infancy
- Recurrent oral or vaginal candidiasis
- Recurrent varicella or herpes zoster
- Mycobacterial infections (Tuberculosis, MAC)
- Chronic or recurrent diarrhea
- Recurrent parotid swelling
- Failure to thrive
- Developmental delay or regression of developmental milestones
- Recurrent sinusitis, otitis media, pneumonia, meningitis
- Disseminated non-genital, genital or peri-anal warts
- Papular pruritic eruptions

2) Think of HIV if the child has:

(Make it a point to rule out HIV if any of the following condition occurs in a child in presence of other evidences pointing towards HIV, either clinical or circumstantial)

- Extensive and/or persistent generalized lymphadenopathy
- Extensive molluscum contagiosum
- Purpura and petechial rashes(thrombocytopenia)
- Non-Hodgkin lymphoma
- Unexplained anemia, neutropenia, thrombocytopenia
- Unexplained hilar lymphadenopathy
- Hepato-spleenomegaly
- Unexplained digital clubbing
- Chronic interstitial pneumonia
- Severe refractory non-infectious skin manifestations (such as atopic dermatitis, papular urticaria)
- Unexpectedly severe consequences of common viral infections
- Severe folliculitis
- Seborrheic dermatitis
- Oral hairy leukoplakia

- Findings of chest-x-ray such as hilar lymphadenopathy, chronic interstitial pneumonitis and reticulonodular pattern

Laboratory diagnosis:

Laboratory tests available for diagnosis of HIV in children are:

Antibody tests: ELISA, Rapid tests, Western blot

Antigen tests: DNA PCR test, RNA PCR test (viral load)

Diagnosis of HIV in children below 18 months of age-

Maternal HIV antibodies are passively transferred (trans-placental transfer) during pregnancy. They can persist up to as long as 18 months in children born to HIV infected mothers. Maternal antibodies can not be distinguished from infant's antibodies using tests routinely used for diagnosis. Therefore a positive antibody test such as ELISA does not necessarily suggest presence of infection. Also a negative test result does not rule out infection because the mother may be in window period at the time of delivery or in case of women getting infected while the baby is being breastfed; the baby may continue to get exposed to the virus.

As the interpretation of antibody based test results during first 18 months is inconclusive; antigen based test such as DNA PCR is considered the gold standard for definitive diagnosis of infection during this period.

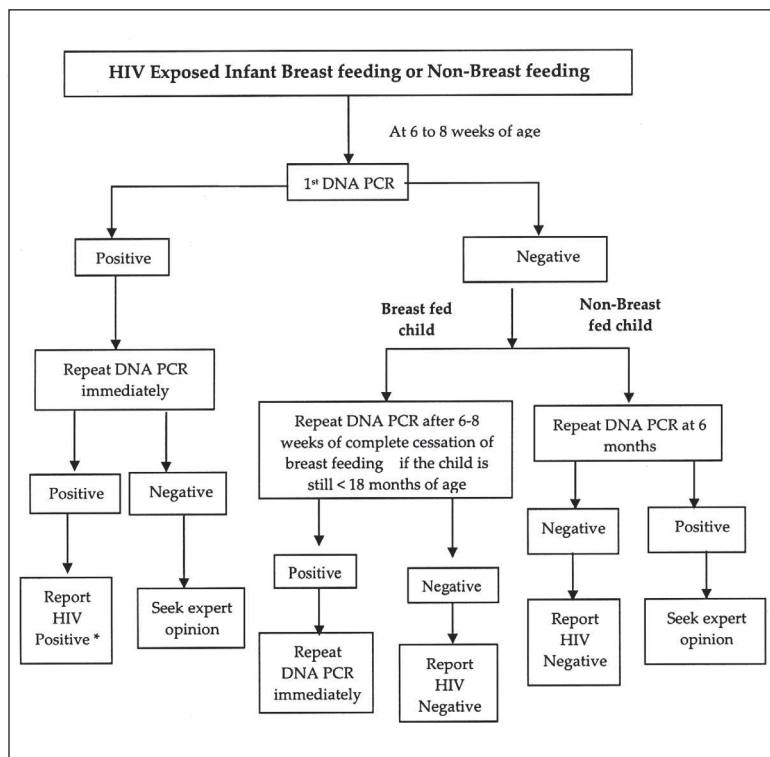
DNA PCR

- Sensitivity of this test is quite low in first few weeks of life, so it is likely that the test may not pick up the infection during this period.
- Sensitivity reaches 98% by the age of 1 month.
- Specificity is high. So, though a positive test may strongly suggest infection, a negative test will not rule it out.

- First DNA PCR is therefore advised at around 6 weeks.
- If positive, it should always be confirmed by repeating the test immediately.
- In case of first report being negative, the second test should be performed after a gap of at least one month.
- These two tests are generally done on either side of the 4th month.
- In order to align these tests with immunization schedules and with starting co-trimoxazole prophylaxis, we may suggest first test at 6 weeks and the second at 4 months.

A. Protocol for diagnosis of HIV in children below 18 months of age:

NACO recommends two PCR tests (at the age of 6 weeks and 6 months respectively) to rule out the infection.



The child especially if symptomatic should be immediately linked to care. (WHO recommends immediate ART to all infants <1 yr of age).

For settings where PCR facilities are costly and not easily accessible, a more cost effective approach has been suggested by WHO. It is based on the observation that though passively acquired maternal antibodies may persist for almost 18 months, almost 74% children lose them by the age of 9 months and almost 95% by the age of 12 months.

In resource challenged situations WHO (2006) suggests:

- Single HIV DNA PCR at 6 weeks
 - If POSITIVE, repeat immediately for confirmation.
 - If NEGATIVE the child is followed up.
- Asymptomatic children are tested with an antibody based test (ELISA) at 9 months. A NEGATIVE test report suggests absence of infection *in non-breast fed children*.
- However, POSITIVE test report at 9 months is not conclusive of diagnosis. The test is repeated at 12 and 18 months. Persistent antibodies even at 18 months of age suggest infection.
- In case of children who become symptomatic, a repeat DNA PCR test is done.

Availability of DNA PCR

DNA PCR test is yet not available at district level (both in private or public sector). It is likely to be available at some government hospitals in near future.

The cost of the test in private sector ranges from Rs. 1200 to Rs 2000.

Transporting blood to the laboratory –

It is a very sensitive technique and therefore quality control issue is of tremendous importance. The cost and impact of false positive/negative diagnosis is too high. So choose a good quality laboratory.

Standard protocols should be followed while transporting blood to the laboratory. Before you plan to send any samples for this test, ensure that you know the procedures correctly.

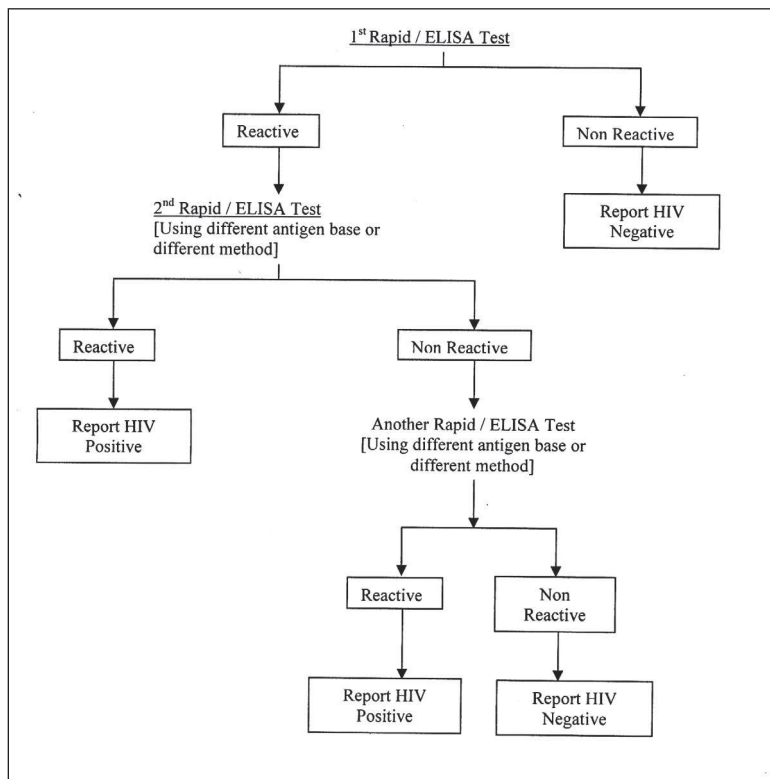
Dried Blood Spots (DBS)

More recently, the use of DBS for both HIV-DNA and HIV-RNA testing has proved more convenient. There are many advantages of DBS, such as:

- does not require venepuncture and can be obtained by a finger-stick or heel-stick.
- easier to train even peripheral health care providers to collect samples.
- carry lesser biohazard risk than liquid samples.
- easier to transport (being stable at room temperature for prolonged periods), thus facilitating centralized laboratory testing.

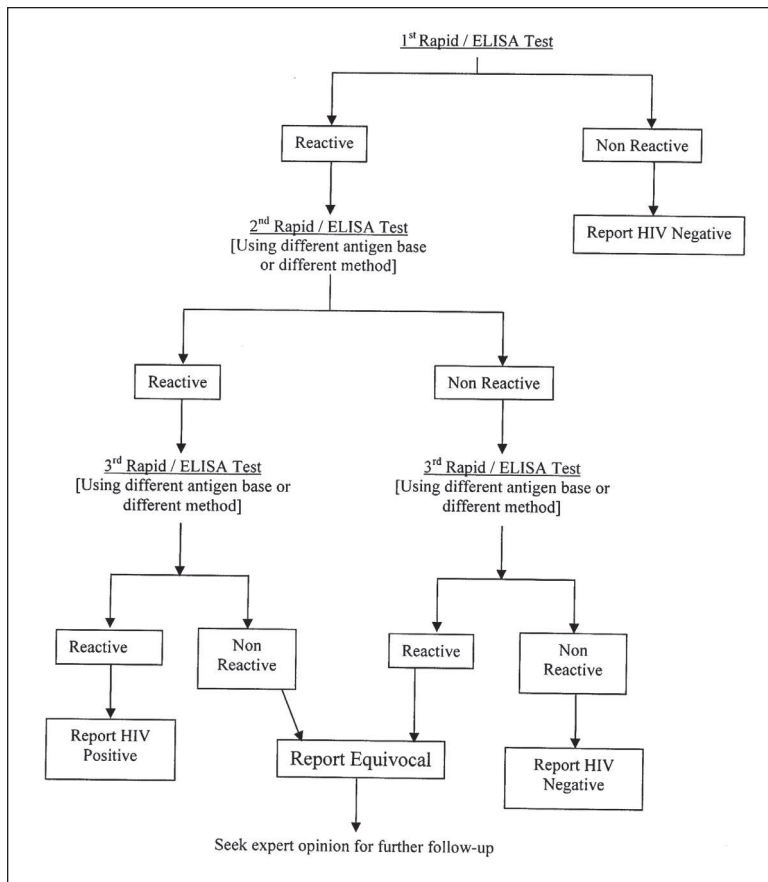
B. Protocol for screening children above 18 months for HIV
(It depends upon whether the child is symptomatic or asymptomatic)

I. HIV testing strategy for *symptomatic* children > 18 months of age



One should rule out window period before advising the test and while interpreting negative test report, rule out breast feeding.

II. HIV testing strategy for *asymptomatic* children > 18 months of age



To summarize: Confirmation of diagnosis in asymptomatic children requires three reactive test results using different test kits (as against two reactive test results in symptomatic children).

Western blot test is also used as confirmatory test. It is costlier and requires expertise. *If above protocols are followed correctly, there is little need for use of western blot.*

Post test counseling:

In case of HIV infected child, breaking the bad news to parents is most difficult and stressful part for the health care provider. Parents tend to go in denial or serious anxiety – depression, which may be tough to handle. The approach of a health care provider ought to be very sensitive and caring. Risk of having to handle such a uncontrollable situation is greatly reduced if the parents are given proper pre-test counseling.

Disclosing status of uninfected child is relatively much easier. But many a time parents are very much apprehensive and require a lot of reassurance.

Critical Concepts

- Early diagnosis in children definitely helps in influencing the course of the disease in children positively.
- Most of the clinical indicators are seen when the disease has fairly advanced. Identifying early disease manifestations would require high index of suspicion on part of health care provider.
- DNA PCR is the standard diagnostic test for children below 18 month. With this test infection can be diagnosed in most children as early as 4-6 weeks of age.
- A reactive antibody based test (such as ELISA / western blot) in a HIV exposed child below 18 months does not necessarily indicate presence of HIV infection.
- For children above 18 months of age, antibody based tests (ELISA / rapid) provide definitive diagnosis. Confirmation of diagnosis in asymptomatic children requires three reactive test results using different test kits (as against two reactive test results in symptomatic children).
- Considering the window period, diagnostic antibody tests in breast fed children above 18 months of age should be carried out 12 weeks after complete cessation of breast feeding. If the child is less than 18 months and is asymptomatic, the diagnostic DNA PCR may be deferred till 12 weeks after complete cessation of breast feeding (at which time the sensitivity of the test has peaked). In case the child is symptomatic the test should be done earlier.

7.

Natural History of Pediatric HIV

The patterns of progression to AIDS in pediatric HIV can be divided into following categories:

Category 1: Rapid progressors:

- 25-30%
- Usually acquire the infection in-utero or during the early perinatal period.
- Develop profound immuno-suppression leading to serious opportunistic infections in the first few months of life.
- Without treatment few of these children survive more than 2 years.

Category 2: Intermediate progressors:

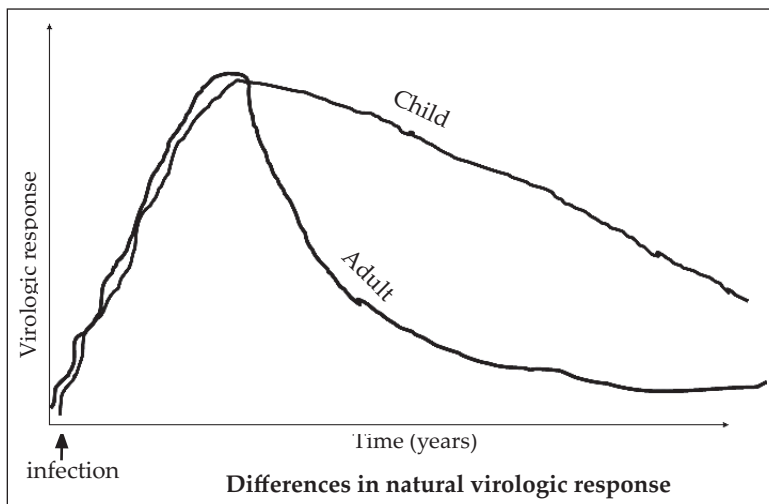
- 50-60%
- Slower progression to AIDS with mean period of 6–9 years.
- Followed by a rapid downhill course and death.

Category 3: Slow progressors:

- 5-25%
- Do not have any symptoms even beyond 8 years of age

Bimodal distribution of progression:

- Though in adults too we see all these categories, the proportion of rapid progressors is very high in children leading to a bimodal distribution. Broadly speaking HIV disease progression in children occurs generally at an accelerated pace as compared with adults.
- This difference is presumably a consequence of the acquisition of infection at a time when immune systems are immature, and/or the availability of increased numbers of susceptible target cells.
- Rapid progression could also be a function of extremely high levels of plasma viremia seen in vertically infected children during first few months of life. They acquire the infection in-utero or during the early perinatal period
- The plasma viral load reduces substantially in first year of life and then more slowly over next several years. The slope of decline is less sharp as compared to that in the adults. This means that



the virus targets developing organ systems for a longer time that may lead to permanent damage.

Factors associated with disease progression

- ***Route of infection and Age at the time of infection:*** Perinatally infected children have much faster progression as compared to those who acquire infection through routes other than MTCT. Children (more than 1 year of age) and adolescents who acquire the disease due to exposure to blood products (eg children with thalassemia or hemophilia) have much slower disease progression than adults.
- ***Socio-economic conditions:*** Risk of opportunistic infections (OIs) is increased due to confounding social factors such as poverty, poor hygiene due to lack of proper sanitation facilities, malnutrition, burden of other infectious diseases etc.
- ***Access to diagnostic services and care:*** Low PMTCT coverage, increase in rate of new infection, similarly low uptake of care and support services due to lack of awareness, stigma, fear of disclosure, high cost of care in private sector etc. increase morbidity and mortality.
- ***Co-morbidities:*** Other factors such as co-infection with TB, hepatitis B or C influence the natural history.

Relationship of plasma viral load, CD4 count and disease progression

- Plasma viremia is an important determinant of child's disease progression.
- Rapid progressors have very high viral loads which do not decline during infancy. However no threshold value of viral load has been identified to differentiate between rapid and slow progressors within first two years of life.

Importance of knowing natural history:

The experience gained over the years strongly suggests that clinical events occurring during course of HIV infection follow a reasonably predictable chronological order. It is possible, on the basis of clinical findings, to make decisions regarding the use of antimicrobial chemoprophylaxis and/or antiretroviral therapy and to predict the patient's prognosis.

- As mortality is very high in first two years, all attempts should be done to detect the infection as early as possible and link the child to care and support services immediately.
- As there is very high chance of pneumocystis pneumonia during first few months, which can be prevented, all HIV exposed children should be put on co-trimoxazole prophylaxis till such time that we know they are not infected.
- Recent evidences also suggest that initiation of early ART in all HIV infected infants below age of 12 months does reduce early mortality at least by 50%.

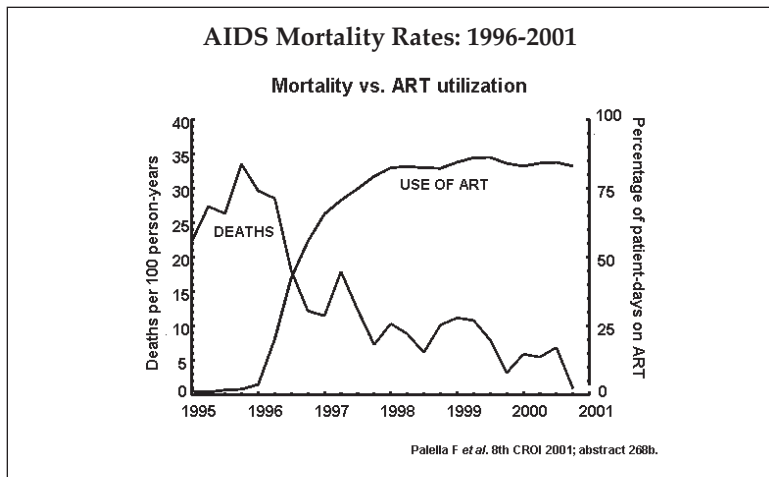
Certain clinical conditions appear to be associated with poor prognosis:

- PCP or encephalopathy at young age
- Enlarged lymph nodes and hepato-splenomegaly at birth
- Growth failure

As against, following conditions are associated with slow progression:

- Generalized lymphadenopathy
- Chronic/recurrent parotid enlargement
- Lymphoid Interstitial Pneumonitis (LIP)

Impact of ART on natural history



Many studies have successfully demonstrated the efficacy of ART in reducing mortality in HIV infected children, both in resource rich and resource poor countries. Progression to AIDS is also significantly reduced with ART.

Critical Concepts

- The natural history of pediatric HIV differs significantly from that of adults.
- It has a bimodal pattern with very high mortality in early years of life.
- Anti-retroviral treatment has significantly influenced the natural history in children reducing both morbidity and mortality.

Clinical Manifestations in children differ from those in adults:

Pediatric HIV	Adult HIV
Primary opportunistic infections (OI)	Reactivation infections due to waning immunity
Bimodal distribution of disease progression	Unimodal distribution
Overall progression more rapid	Relatively slower progression
Immune system more immature with higher CD4 counts	Mature immune system
Prominent effects on growth and neuro-development seen early and are common	Neurological involvement generally late
Peripheral neuropathy (HIV induced or drug induced) is rare	Peripheral neuropathy common
PCP can occur even at higher CD4 counts	PCP seen very rarely before severe immune-deficiency sets in

8.

Clinical and Immunological Staging of Disease in Children with HIV

Need for staging:

Clinical and immunological staging of HIV disease is important for prognostic and treatment purposes.

The decision of starting ART depends on multiple factors including the viral load, CD4 count and clinical stage of disease. In children other factors such as readiness of the care providers and/or child to start the therapy, availability of support systems, availability of pediatric doses etc should also be taken into consideration.

Though viral load could be the prime factor for such decision-making, it is a costly test and majority of our patients cannot afford to do the test regularly. Therefore *immunological and clinical staging* remain the most commonly referred indicators.

Clinical staging

The 4-stage proposed WHO Staging system roughly corresponds to the 4 clinical categories in the 1994 Centers for Disease Control (CDC) Clinical Classification (that classified children into asymptomatic (N),

mildly symptomatic (A), moderately symptomatic (B) and severely symptomatic (C) clinical categories).

WHO Staging System

Clinical Stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy

Clinical Stage 2

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive warts (human papilloma virus infection)
- Extensive molluscum contagiosum
- Recurrent oral ulcerations
- Unexplained persistent parotid enlargement
- Lineal gingival erythema
- Herpes zoster
- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
- Fungal nail infections

Clinical Stage 3

- Unexplained moderate malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)
- Persistent oral candidiasis (after first 6-8 weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis/periodontitis
- Lymph node TB
- Pulmonary TB
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis

- Chronic HIV-associated lung disease including bronchiectasis
- Unexplained anemia ($<8\text{g/dl}$), neutropenia ($<0.5 \times 10^9/\text{L}^3$) or chronic thrombocytopenia ($<50 \times 10^9/\text{L}^3$)

Clinical Stage 4

- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- *Pneumocystis jiroveci* pneumonia (PCP)
- Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
- Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)
- Extra pulmonary TB
- Kaposi sarcoma
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (after one month of life)
- HIV encephalopathy
- Cytomegalovirus infection: retinitis or CMV infection affecting another organ, with onset at age over 1 month
- Extra pulmonary cryptococcosis (including meningitis)
- Disseminated endemic mycosis (extra pulmonary histoplasmosis, coccidiomycosis)
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacteria infection
- Cerebral or B cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Refer Annexure 2 for 'Presumptive and Definitive criteria for Recognizing HIV/AIDS-Related clinical events in infants and children with confirmed HIV infection'.

Recurrent bacterial infections are more commonly diagnosed than opportunistic infections in developing countries. Malignancies are less common than in adults and Kaposi sarcoma is extremely rare. In view of the fact that opportunistic infections are difficult to diagnose even with the best microbiological facilities, several of these illnesses may be diagnosed using presumptive criteria. (Refer Annexure 2)

Immunological staging

When CD4 counts are available, children with HIV infection may be characterized as having mild, advanced or severe immunosuppression based on age-specific CD4 cell counts or percentages.

Proposed WHO Classification of HIV-associated immunodeficiency based on age-related CD4 lymphocyte percentages /counts (November 2006) :

Classification of HIV-associated immune-deficiency	Age-related CD4 cell values			
	< 11 months (%)	12-35 months (%)	36-59 months (%)	> 5 years (cells/mm ³)
Normal	>35	>30	>25	>500
Mild	30-35	25-30	20-25	350-499
Advanced	25-30	20-25	15-20	200-349
Severe	<25% or <1500 cells/mm ³	<20% or <750 cells/mm ³	<15% or <350 cells/mm ³	<15% or <200 cells/ mm ³

- CD4 (absolute count or %) is the best measurement to assess immune deficiency.
- The CD4 count should be used in conjunction with clinical assessment; however, CD4 count allows early detection of worsening of HIV disease, as the CD4 count usually falls before clinical progression takes place.

- CD4 monitoring can aid in the decision to initiate or switch to ART.
- Younger children normally have higher CD4 counts than older children and adults.
- CD4% is the preferred measurement in children <6 years old.
- At ≥ 6 years of age, either CD4% or absolute CD4 count can be used.
- In children <1 year of age, especially those <6 months, the CD4 count is less predictive of mortality and there is a high risk for death even if the CD4% is high.

AIDS-defining conditions include

- All Stage IV illnesses
- Symptomatic LIP (lymphoid interstitial pneumonia)
- Severe immune- deficiency

Critical Concepts

- Clinical and immunological staging are important determinants that guide decision to initiate ART.
- These indicators also determine prognosis of HIV disease.
- In children < 6 yrs of age, % CD4 is preferred over absolute count to assess immune deficiency.
- Presence of any WHO clinical stage 4 condition, symptomatic LIP and/or severe immune-deficiency indicates AIDS in children.

9.

Growth and Nutrition in Children with HIV

Growth is a sensitive indicator of health and well being in childhood.

A child's growth is a composite of weight, height and head growth.

It is affected by many factors including general nutrition, constitution, overall health and nurturing.

HIV and Malnutrition

Malnutrition is the most important reason affecting growth.

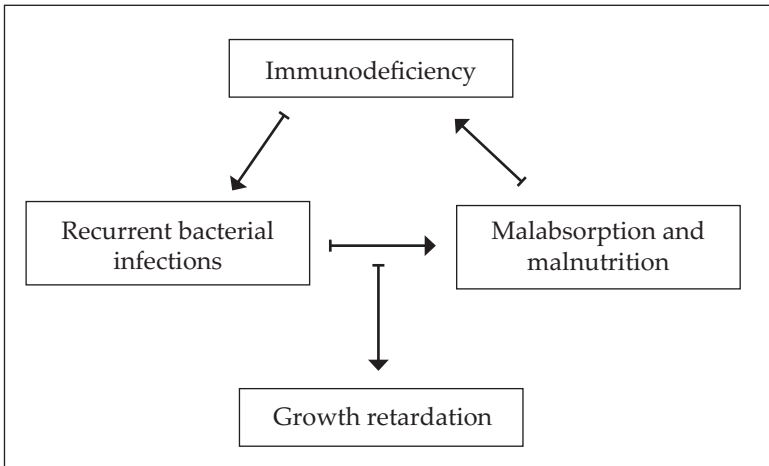
Malnutrition could be a result of

- Decreased intake due to oral lesions causing pain or discomfort while chewing / swallowing.
- Loss of nutrients due to illnesses that cause vomiting or diarrhea.
- Altered absorptive capacity of GI tract due to AIDS enteropathy.
- Increased basal requirements (BMR) due to intermittent infections and fever.

Malnutrition leads to

- Compromised immune function
- Compromised CNS and peripheral nerves maturation
- Compromised physical growth

A vicious cycle of immunodeficiency, enteric infections, malabsorption and malnutrition results in clinical deterioration and growth retardation.



Growth failure

A child is said to be failing to thrive when

- height and weight are less than the 5th percentile for age or
- S/he is crossing 2 or more major centile lines downward on standardized growth curves.

However, growth curve just below but parallel to the fifth percentile can be a normal pattern for a child with intrauterine growth retardation.

There are two main patterns of growth failure in HIV-infected children.

- *Wasting pattern* - Child loses weight or does not gain weight but gains in height. Weight loss greater than 10% of a child's body weight is indicative of wasting.
- *Stunting pattern* - Child's linear growth (height) is delayed. Often weight is maintained, so weight-for-height seems appropriate.

Wasting syndrome is always a sign of severe HIV disease. It is seen in chronically HIV infected children and is diagnosed when the child manifests:

- < 70% of weight for height or -3 SD below the Z score on weight-for-height chart on 2 measurements > 30 days apart, with or without edema of both feet.

Wasting syndrome in the Indian setting could be diagnosed alternatively as -

- when the child's weight is less than 50% of the expected weight for age (protein-energy-malnutrition grade IV) or
- if the child's weight falls below the lowest percentile (usually the 3rd percentile) on the weight-for-age chart.

Growth as a Predictor of Prognosis

- Children with HIV infection grow slower than uninfected children, a difference that becomes more significant with increasing age and immunodeficiency.
- Children with severe illness tend to have poorer growth. Increased levels of postnatal viremia are associated with decreased linear growth.
- ART has a beneficial effect on height and weight.
- Long term ART treatment appears to increase risk of lipodystrophy.

- HIV infected children accumulate bone density at a slower rate than non-infected children and certain ARV medicines (such as tenofovir) may decrease bone density.
- In catch-up growth, weight gets corrected before height.

Assessment of growth

1. Nutritional anthropometry includes
 - Serial height measurement
 - Serial weight measurement
 - Serial head circumference measurement (up to 2 years of life). **Microcephaly may point towards progressive HIV encephalopathy in infants.**
 - Mid-arm circumference and triceps skin fold thickness (up to 5 years) may also be measured.

Regular measurements and close monitoring is essential. Regular plotting of growth charts is a must.¹

2. Nutritional assessment should aim at-
 - systematic evaluation of current nutritional status, diet and nutrition-related symptoms
 - early identification of micro and macro nutrient deficiency

Dietary history should be evaluated every three months as a part of routine follow up.

Specific treatment should be immediately initiated if malnutrition is detected.

3. Age appropriate developmental milestones should be monitored during early years of life and any change in behavior or regression during later years of life.

1. Refer Annexure 3 for Growth monitoring charts.

Interpretation of nutritional assessment

There are various classifications of PEM using varied parameters. A few that will help in diagnosis and management are given below.

Waterloo's Classification

It compares both parameters (height and weight) of the child.

Categorize the child's nutritional status using following three indicators.

	Normal	Wasted	Stunted
Weight/ Age (%)*	100	70	70
Weight/Height (%) **	100	70	100
Height/Age (%)***	100	100	84

*weight/age% = weight of the child/weight of 50th percentile for that age x 100

**Weight/Height% = Weight of the child/Weight of 50th percentile for that height x 100

***Height/Age%=Length or Height of the child/Length or Height of 50th percentile for that age x 100

Interpretation of above Indicators

The table below provides the severity of each category.

Nutritional status	Stunting % of Height/Age	Wasting % of Weight/Height
Normal	>95	>90
Mildly impaired	87.5 – 95	80-90
Moderately impaired	80 - 87.5	70-80
Severely impaired	<80	<70

Severe wasting and severe stunting in a child, which is otherwise unexplained suggests clinical stage 4 HIV disease.

IAP Classification of protein energy malnutrition (PEM)

Nutrition Subcommittee of the Indian Academy of Pediatrics 1972, using the standard value (100%) as 50th percentile of Harvard growth standard, suggested:

Nutritional grade	Percentage of standard weight for age
Normal	More than 80 percent
Grade I (mild)	71-80%
Grade II (moderate)	61-70%
Grade III (severe)	51-60%
Grade IV (severe)	< 50% or less

In this classification, only weight for age criteria is considered. It helps in clinically staging the disease, e.g. unexplained moderate malnutrition suggests clinical stage 3 HIV disease and severe malnutrition suggests clinical stage 4 HIV disease. It also has direct treatment implications. Grade 4 malnutrition may require resuscitation and acute phase management.

Classification Suggested by FAO/WHO Expert Committee

This classification helps in understanding various clinical profiles of malnutrition. (See color atlas)

Nutritional status	Body Weight as % Standard for age	Edema	Deficit in Weight for Height
Under weight	80-60	0	Minimal
Nutritional dwarfism	<60	0	Minimal
Marasmus	<60	0	++
Kwashiorkor	80-60	+ / ++	+ / ++
Marasmic kwashiorkor	<60	+	++

Nutritional rehabilitation:

Remember that prevention is better than cure.

There is increased energy need in chronically HIV infected children.

Even in asymptomatic children, resting energy expenditure is increased by 10%. In children experiencing growth failure, energy needs increase between 50% and 100%.

Hence for all HIV-infected children, a comprehensive nutritional approach is suggested:

- In-depth counseling of mothers and of caregivers/children regarding importance of overall nutrition and hygiene.
- Planning appropriate diet by selecting locally available, affordable, nutritious foods.
- Nutritional counseling for micro- and macro-nutrient deficiency (such as iron deficiency anemia, Vitamin D and calcium deficiency).
- Counseling on selection of specific high-energy foods for children with conditions that interfere with normal ingestion or digestion (e.g. sore throat, oral thrush, diarrhea).
- Ensuring Vitamin A supplementation in cases of diarrhea and measles.
- Treatment of allied conditions.
- De-worming.
- If the child is breast fed, advising to continue the same.

The energy requirement recommended in normal children is 120-150 kcal/kg/day with 2-3 gm/kg/day of proteins of high biological value.

- In asymptomatic children with HIV, increase intake by 10% of the Recommended Daily Allowance (RDA).
- In symptomatic or children recovering from acute infections, NACO recommends increase intake by 20–30% of the RDA.

- Some experts do recommend increase energy and protein intake even upto 50-100% of the RDA in a child experience weight loss.

In any malnourished child, the main goal of treatment is to provide adequate calories and proteins of high biological value. But these should be achieved gradually over a period of few weeks to avoid protein overload syndrome.

Severe malnutrition and ART initiation

First manage malnutrition and then decide about initiation of ART.

Management of severe malnutrition consists of 3 phases.

1. Resuscitation if required
2. Acute phase – correction of dehydration, electrolyte imbalance, treating infection and anemia
3. Rehabilitation – dietary management

In HIV infected children, the response to initial treatment of severe malnutrition may be delayed or very limited.

ART initiation

- Following successful treatment of acute phase of severe malnutrition, the child's clinical condition should be re-evaluated. If the child is clinically stable, ART can be initiated (usually within 2 weeks).
- In children who improve slower to initial treatment of malnutrition, ART may be initiated at 6-8 weeks.
- Dosages of ARVs should be frequently reviewed as children gain weight rapidly after adequate nutritional supplementation.
- The recurrence of severe malnutrition that is not caused by lack of food in children receiving ART may indicate treatment failure and the need to switch therapy.

10.

Neuro-Developmental Assessment of Children with HIV

- HIV infected children are at increased risk of CNS disease characterized by cognitive language, motor and behavioral impairments.
- Approximately 50% children have some problem and approximately 13 to 23% have more severe form called progressive encephalopathy.
- Severity of these manifestations may range from subtle impairments in selective domains to severe deterioration of global developmental skills.
- CNS dysfunction in these children is primarily the result of HIV infection in the brain.
- With the advent of ART the prevalence of severe CNS manifestations has significantly reduced. However CNS acts as a reservoir for persistent HIV-1 infection. Many ARVs do not penetrate CNS well. So HIV infected children on ART may still be at risk of developing CNS manifestations.

Neurodevelopmental assessment is an important aspect of each and every visit in children with HIV. As no single manifestation can predict further development of HIV related CNS disease, identifying early changes is of great importance. Development of HIV related CNS disease indicates need for ART with drugs having good CNS penetration.

Domains of Neuropsychological Impairment

- General cognitive functioning – In frank HIV encephalopathy, general cognitive function will be severely and globally affected while in less advanced disease, it may be preserved with only selective functions being affected.
- Language - HIV infected children frequently exhibit speech and language deficit prior to decline in general cognitive function.
- Attention – Attention deficit in these children may contribute to school and learning problems.
- Memory – Children with HIV CNS compromise exhibit significantly poorer verbal learning and recall and is suggestive of sub-cortical pathology.
- Behavioral functioning – Behavioral abnormality may be the effect of CNS HIV disease and/or psychological stresses of living with chronic illness.
- Motor functioning – Children with HIV encephalopathy exhibit severe motor involvement and may present with regression of motor milestones. Motor dysfunction is highly predictive of late stage disease progression.

Serial assessments are important to evaluate response to treatment and planning appropriate rehabilitation.

Points to be included in serial assessment-

- History regarding developmental milestones and change or abnormality in child's behavior

- Physical and mental milestones achieved and signs and symptoms suggestive of neuroregression
- Detailed neurological examination in case there is any history suggestive of neurological involvement

Recommended neurodevelopmental serial assessment schedule for children with HIV-1 infection at various ages :

Age of child	Serial assessment schedule
< 2 year	Evaluate every 6 months due to higher risk of developing CNS disease
2-8 years	Evaluate every year unless they exhibit neurodevelopmental deficits, in which case they should be assessed every 6 months ^a ; and
> 8 years	Evaluate every 2 years if child exhibits stable functioning in the average range; otherwise, evaluate every year ^a

^a Shorter batteries of individual subtests and specific function tests can be administered between the major evaluations to further decrease the testing burden on children while still monitoring the effects of the disease.

Normal Developmental Milestones - First 24 Months of Life

Age	Psycho-social	Gross Motor	Fine Motor and Visual	Communication and Hearing
1 month	<ul style="list-style-type: none"> Follows faces to the midline 	<ul style="list-style-type: none"> Moves all extremities equally Lifts head when lying on stomach 	<ul style="list-style-type: none"> Opens hands spontaneously 	<ul style="list-style-type: none"> Startled by loud sounds Cries Quiet when fed and comforted
2 months	<ul style="list-style-type: none"> Follows faces past the midline Smiles responsively 	<ul style="list-style-type: none"> Lifts head up 45 degrees when on stomach 	<ul style="list-style-type: none"> Looks at own hand 	<ul style="list-style-type: none"> Makes baby sounds such as cooing, squealing and gurgling
3 months	<ul style="list-style-type: none"> Recognizes mother Smiles responsively (social smile) 	<ul style="list-style-type: none"> Can support head for a few seconds when held upright 	<ul style="list-style-type: none"> Opens hands frequently 	<ul style="list-style-type: none"> Responds to voices Laughs
4 months	<ul style="list-style-type: none"> Follows an object with eyes for 180 degrees Regards own hand 	<ul style="list-style-type: none"> Bears weight on legs Good neck control when pulled to sitting position 	<ul style="list-style-type: none"> Brings hands together in midline (clasps hands) Grabs an object such as a rattle 	<ul style="list-style-type: none"> Turns head to sound

Age	Psycho-social	Gross Motor	Fine Motor and Visual	Communication and Hearing
	<ul style="list-style-type: none"> • Anticipates food on sight 	<ul style="list-style-type: none"> • Lifts chest and supports self on elbows when lying on stomach 	<ul style="list-style-type: none"> • Reaches for objects 	
6 months	<ul style="list-style-type: none"> • Reaches for familiar people 	<ul style="list-style-type: none"> • Rolls from stomach to back or back to stomach • Sits with anterior support 	<ul style="list-style-type: none"> • Plays with hands by touching them together • Sees small objects such as crumbs 	<ul style="list-style-type: none"> • Responds to name • Babbles
9 months	<ul style="list-style-type: none"> • Indicates wants • Waves "bye-bye" • Has stranger anxiety 	<ul style="list-style-type: none"> • Can sit without support • Creeps or crawls on hands and knees 	<ul style="list-style-type: none"> • Looks for a toy when it falls from his/her hand • Takes a toy in each hand • Transfers a toy from one hand to the other 	<ul style="list-style-type: none"> • Responds to soft sounds such as whispers
12 months	<ul style="list-style-type: none"> • Has separation anxiety • Social interactions 	<ul style="list-style-type: none"> • Pulls self up to standing position • Walks with support 	<ul style="list-style-type: none"> • Points at objects with index finger 	<ul style="list-style-type: none"> • Says at least 1 word • Makes "ma-ma" or "da-da" sounds

Age	Psycho-social	Gross Motor	Fine Motor and Visual	Communication and Hearing
	are intentional and goal-directed			<ul style="list-style-type: none"> • Locates sounds by turning head
15 months	<ul style="list-style-type: none"> • Imitates activities • Finds a nearby hidden object 	<ul style="list-style-type: none"> • Can take steps on own • Can get to a sitting position from a lying position 	<ul style="list-style-type: none"> • Can stack one cube on top of another 	<ul style="list-style-type: none"> • Able to say "mama" and "dada" to respective parents (sounds to identify caretakers)
18 months	<ul style="list-style-type: none"> • Initiates interactions by calling to adult 	<ul style="list-style-type: none"> • Walks without help 	<ul style="list-style-type: none"> • Can take off own shoes • Feeds self 	<ul style="list-style-type: none"> • Says at least 3 words
2 years	<ul style="list-style-type: none"> • Does things to please others • Engages in parallel (imitative) play 	<ul style="list-style-type: none"> • Runs without falling 	<ul style="list-style-type: none"> • Looks at pictures in a book • Imitates drawing a vertical line 	<ul style="list-style-type: none"> • Combines 2 different words

The table below enlists age wise developmental problems which should alert the physician.

Developmental Red Flags	
Age	Developmental Problem
Birth to 3 months	<ul style="list-style-type: none">• Failure to alert to environmental stimuli• Rolling over before 2 months (indicative of hypertonia)• Persistent fisting at 3 months
4-6 months	<ul style="list-style-type: none">• Poor head control• Failure to smile• Failure to reach for objects by 5 months
6-12 months	<ul style="list-style-type: none">• No baby sounds or babbling• Inability to localize sounds by 10 months
12-24 months	<ul style="list-style-type: none">• Lack of consonant production• Hand dominance prior to 18 months (indicates contralateral weakness)• No imitation of speech and activities by 16 months
Any age	<ul style="list-style-type: none">• Loss of previously attained milestones

11.

Neurological Manifestations in Children with HIV

- HIV is a neurotropic virus. It has a destructive effect on neuronal tissue of an immature central nervous system leading to impairment of development and growth of CNS in children. The damage could be due to infection of astrocytes, macrophages and microglia with HIV or due to effect of various neurotoxic substances released by the virus and host cells on neurons.
- In contrast to the course of disease in adult population, neurological impairment occurs earlier in children and is not exclusively due to opportunistic infections or neoplasms.
- CNS involvement is manifested as HIV encephalopathy, with developmental delay or loss of developmental milestones (motor, mental and expressive language), microcephaly and pyramidal tract symptoms (e.g., spasticity).

- HIV CNS involvement can occur before significant immunosuppression and is the first AIDS defining illness in approximately 1 in 5 children.
- Highest incidence of HIV-related CNS manifestations is seen in first two years of life.
- Antiretroviral agents may sometimes prevent or reverse the course of neurologic impairment in children.

Common neurological presentations:

A. *Acute presentations*

1. Seizures
2. Altered mental status
3. Raised ICT
4. Paraplegia / Hemi paresis

B. *Chronic presentations*

1. HIV related CNS disease in children - patterns
 - HIV related encephalopathy
 - HIV related CNS compromise
 - Apparently unaffected children
2. SOL (tuberculoma , tumors)

A. *Acute presentations:*

1. *Seizures:*

Seizures could be generalized or focal depending upon the cause. The differential diagnosis of seizure could be guided by the CD4 counts.

- Low CD4 counts – think of infectious causes such as -
 - TB meningitis, bacterial meningitis, HIV encephalopathy, cryptococcal meningitis, HSV, candidal meningitis and tuberculomas

- CD4 counts above the age appropriate definition of immunodeficiency – think of non infectious causes such as
 - cerebrovascular accidents, CNS tumors etc

Immediate Management of Seizures

1. Assess and support ABC's and obtain IV access
2. Treat seizure with Lorazepam 0.05-0.1 mg/kg IV or diazepam 0.1 mg/kg IV (if IV access not available, give diazepam 0.5 mg/kg per rectum)
3. May repeat every 5-10 mins. up to 3 times if seizures not controlled
4. If still not controlled, give phenytoin 15-20 mg/kg IV, slowly. (phosphenytoin in equivalent doses may be given if available)
5. If persists, give phenobarbital 10 mg/kg slowly, watch for respiratory depression, may repeat once)

Once stabilized, put the child on anticonvulsant and antibiotic if required and simultaneously evaluate for the cause.

2. *Altered Mental Status*

Children with CNS infections, malignancies, or cerebrovascular accidents may present with acute alteration in mental status. Differential diagnosis is similar to that considered for HIV infected child with seizures.

3. *Raised ICT*

Typical features of raised intracranial pressure :

- Poorly localized headache often worse at night or early morning, associated with nausea and vomiting

- Associated neurological symptoms such as neck stiffness, altered mentation, photophobia, seizures etc.

Treat this as an emergency.

1. Obtain urgent contrast CT/MRI if possible
2. If it excludes intracranial mass lesion, do lumbar puncture for CSF examination to exclude infectious meningitis and rule out OIs.

4. *Paraparesis*

In advanced disease flaccid weakness with absent reflexes can occur with lesions of peripheral nerves (commonest CMV radiculopathy), or with acute or chronic inflammatory demyelinating polyneuropathy (AIDP/CIDP)- the Guillain-Barre like syndromes seen in HIV disease.

Certain ARVs (stavudine, didanosine) induce peripheral neuropathy. This is commonly seen in adults but is rare in children.

Lower extremity spastic paralysis with increased reflexes is the hallmark of spinal cord involvement- the most common being HIV associated myelopathy (vacuolar myelopathy). Contrast enhanced MRI of whole spine, LP for CSF examination (if possible CMV PCR) should be done.

5. *Hemiparesis*

Common causes are

- Fungal, viral, bacterial (TB) infections.
- Focal brain lesions such as tuberculomas, PML, CNS lymphoma.
- Ischemia or hemorrhagic strokes

Contrast enhanced MRI or CT scan followed by CSF if required to be done wherever possible.

B. Chronic presentations

Following patterns are seen in HIV related CNS disease in children¹

- *HIV related encephalopathy* - Pervasive and severe CNS dysfunction showing global impairments in cognitive, language, motor and social skills. This could be progressive or static.
- *HIV related CNS compromise* - characterized by overall cognitive function within normal limits but with evidence of either significant decline in psychometric test scores or impairment in selective neuro-developmental functions.
- *Apparently unaffected children* - When the neuro-developmental functions are within normal limits and day to day functioning is not affected it is called 'apparently unaffected children'

1. HIV encephalopathy

HIV encephalopathy can manifest as subtle developmental delay to progressive encephalopathy. The child may present with one or more of following :

- Inability to achieve age appropriate developmental milestones
- Loss of achieved milestones (regression)
- Cognitive deterioration
- Acquired microcephaly and symmetric motor dysfunction due to impaired brain growth

Encephalopathy may be static or progressive. Onset can be as early as the first year of life but can occur any time.

Static encephalopathy: Motor dysfunction and other developmental deficits of varying severity which are non-progressive as documented on serial neurological and developmental examination.

1. Please refer to annexure 4 for Specific criteria for classification of HIV related CNS disease in children.

Progressive encephalopathy: There is marked apathy, spasticity, hyperreflexia and gait disturbances with loss of language and motor skills (gross and fine). It may progress intermittently with periods of deterioration followed by transiently stable plateaus. Older children may exhibit behavioural and learning disability.

Presumptive diagnosis - if child has *at least 1 of the following for 2 months in the absence of another causative illness:*

- Failure to attain or loss of developmental milestones or loss of intellectual ability on a standard developmental scale
- Acquired microcephaly on serial HC monitoring or brain atrophy on CT / MRI
- Acquired symmetric motor deficit manifested by 2 or more of: paresis, exaggerated reflexes, ataxia and gait disturbance.

CT / MRI may show cerebral atrophy (see color atlas) in upto 85% children with neurological symptoms, basal ganglion calcifications and leukomalacia.

Being AIDS defining indicator, appropriate ART should be started. ART regimens should include either AZT, DDI or d4T due to their high CNS penetration.

2. CNS infections in pediatric HIV

These manifest in several ways:

- CNS TB is a common manifestation.
- Severe manifestations of common CNS infections such as in bacterial meningitis
- Bacterial CNS infections with uncommon organisms like Atypical mycobacteria, *Listeria monocytogenes* and *Nocardia asteroides*
- OIs
 - CNS OI are rare in children. Seen in severely immunocompromised state
 - They include CMV, JC virus (PML), HSV and cryptococcal meningitis

- CMV may present as subacute/chronic encephalitis/ventriculitis, an acute ascending radiculomyelitis or acute/subacute neuritis
- CNS toxoplasmosis is uncommon in children.

Cryptococcal meningitis

Meningitis is the most common manifestation of cryptococcosis in children with HIV. HIV infected children between 6-12 years of age with severe immunosuppression are prone for this infection.

Clinical features

- Subacute presentation, may evolve over weeks.
- Fever, headache and altered mental status.
- Neck stiffness and focal neurological deficit is rare.

Diagnosis

- Lumbar puncture – direct examination of CSF with India ink preparation is a must. (see color atlas)
- CSF pressure should be measured as CSF cell count, glucose and protein may be virtually normal but opening pressure may be elevated.
- Cryptococcal antigen titers in CSF is helpful in evaluating response to therapy. A CSF titer of > 1:8 after completion of therapy indicate treatment failure or relapse.
- Fungal cultures from CSF or blood may be useful especially for susceptibility testing in patients with refractory disease.

Treatment

Consists of initial treatment for 2 weeks followed by consolidation therapy for 8-10 weeks.

- Initial treatment consists of a combination of amphotericin B (0.7-1.5 mg/kg/day) for a minimum of 2 weeks. Liposomal Amphotericin B (3-5 mg/kg/day) is found to be useful.
- Consolidation therapy with fluconazole (10-12 mg/kg/day IV or orally) for a minimum of 8-10 weeks is recommended.

If fluconazole cannot be given, itraconazole can be used as an alternative (2-5 mg/kg/dose BD). In refractory cryptococcal meningitis, intrathecal or intraventricular amphotericin B can be used.

- For elevated intracranial pressure, serial lumbar punctures to relieve CSF pressure may be required.
- Secondary prophylaxis with fluconazole 3-6 mg/kg/day (life long therapy) is recommended.

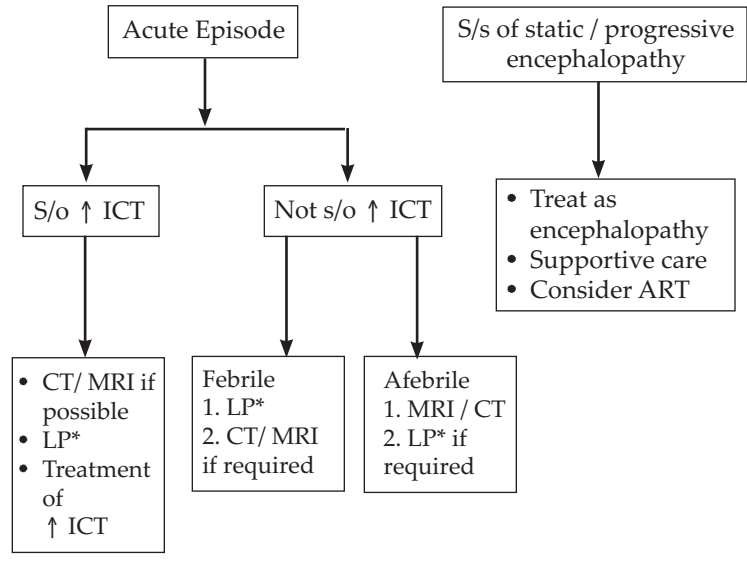
Malignancies in CNS :

Primary CNS lymphoma is the most common cause of CNS mass lesion in children with HIV. These are generally high grade multifocal B cell tumors which present with subacute onset of change in mental status or behavior, headache, seizures and new focal neurological signs. The outcome is poor.

Critical Concepts

1. Central-nervous-system (CNS) abnormalities may result from direct invasion of CNS by HIV or by indirect effects of the virus on the CNS.
2. HIV CNS involvement can occur before significant immunosuppression.
3. HIV encephalopathy is a common presentation seen in HIV infected children.
4. Severely immunosuppressed children are prone to develop opportunistic CNS infections and neoplasms.
5. Prognosis of neurodevelopmental impairment has greatly improved with advent of ART.

Diagnostic Approach to a Child Presenting with CNS Signs / Symptoms



In case of seizure – start anticonvulsant and evaluate further for the cause.

* Examination of the CSF may reveal

- Acute bacterial meningitis: white cell count >100/mm³, Gram-staining and culture of the CSF can show bacteria.
- Cryptococcal meningitis: India ink staining can show yeast. Cryptococcal antigen can be detected in CSF (and serum).
- Fungal meningitis: CSF culture can detect fungal infection like candida, histoplasma etc.

12.

Pulmonary manifestations in Children with HIV

Spectrum of Pulmonary Diseases In HIV Infected Children

1. Conventional respiratory problems in children such as upper and lower respiratory tract infections (URTI, LRTI) reactive airway disease.
2. Opportunistic infections due to viral, bacterial and fungal organisms
3. Pulmonary TB
4. Chronic lung disease
 - a. Lymphoid interstitial pneumonitis (LIP)
 - b. Recurrent LRTI leading to bronchiectasis and cor pulmonale

When to evaluate/investigate further?

Respiratory sign and symptoms are common in HIV infected children. Gauging both, the severity and duration of symptoms is the key for

further evaluation. High grade fever, severe shortness of breath and cough, low-grade fevers but progressive shortness of breath and cough not responding to routine line of treatment would need further investigations.

Erring on the side of caution is advisable; as early diagnosis and prompt initiation of appropriate treatment will result in improved outcomes. This is true especially when there is a case of open TB in the family and the child has not received primary prophylaxis, or if the child is severely immunocompromised.

Common Pulmonary Infections Associated with HIV

A. Infectious pneumonias

Occur at any stage of disease (at any CD4 count). Frequency and severity increases with lowering CD4 count.

I. Bacterial pneumonias

- As such pneumonias are common in children. In HIV infected children, recurrent bacterial pneumonias are more common. Severe complications such as empyema, sepsis may be seen in these children.
- **Recurrent episodes of empyema (two or more episodes within one year)** is one of the AIDS defining conditions.
- HIV infected children are more prone to infections with encapsulated organisms such as *Streptococcus pneumoniae*, *Hemophilus influenzae type B*. Other pathogens include *Streptococcus pyogenus*, *Staphylococcus aureus*, etc.
- Pneumonias caused by *Pseudomonas aeruginosa* and other gram negative organisms appear to be increasing in frequency, especially in patients with chronic lung disease.
- In patients with underlying LIP, superimposed bacterial pneumonia may significantly worsen immune status.
- Recurrent bacterial pneumonias can lead to bullous lung disease and bronchiectasis.

Treatment

- Broad spectrum antibiotic effective against beta lactamase producing pathogens should be the initial choice (such as amoxicillin 40 mg/kg/day + clavulanic acid).
- These children may require extended duration of treatment.
- Addition of aminoglycosides like amikacin should be considered in patients with severe immune suppression, neutropenia or those infected with gram negative bacteria.

Prevention

Vaccination with Hib and pneumococcal conjugate vaccines hold promise regarding reduction of attacks of bacterial pneumonias.

II. Viral pneumonia

- Viral pneumonia is preceded by coryza, may be associated with exanthema and systemic signs /symptoms (such as loose motions). Similar signs /symptoms may be seen in contacts.
- The viruses responsible are same as those causing lower respiratory tract infections in immunocompetent children.
- These viruses cause primary pneumonia or worsen pulmonary pathology in the setting of concurrent opportunistic infection or bacterial pneumonia.
- Pneumonitis associated with viral infections such as measles and chicken pox can be life threatening.
- Treatment is primarily supportive and may require appropriate antibiotics for superadded infections.

III. Fungal pneumonia

- Pulmonary mycoses apart from PCP (which is considered separately) are rare but may be encountered in HIV infected children with severe immunodeficiency.
- Diagnosis of fungal pneumonias is difficult, requires sophisticated investigation; otherwise it is diagnosis of exclusion. Suspect

fungal infection in case of progressive illness not responding to routine treatment.

Treatment

Children should be managed at a tertiary care center. Appropriate antifungal agents such as fluconazole, Amphotericin B, voriconazole need to be used.

IV. *Pneumocystis jiroveci* pneumonia (PCP)

- It is caused by *Pneumocystis jiroveci*.
- It is the most common OI in infants with HIV infection and has high mortality rate of 35%.

Pathogenesis

It infects the alveoli, leads to interstitial edema and may result in progressive hypoxemia and respiratory failure.

Clinical features

Suspect PCP if the child has

- tachypnoea
- dyspnoea
- cyanosis
- non-productive cough

Insidious onset of cough and progressive dyspnea may be seen in older children.

On examination

- Few auscultatory signs as compared to the severity of symptoms.
- There may be bilateral basal crepitations with respiratory distress and hypoxia.

Investigations

- X-ray chest - Bilateral diffuse parenchymal infiltrates with “ground-glass” or reticulo-granular appearance seen in advanced involvement. Mild parenchymal infiltrates, predominantly perihilar and progressing peripherally to reach the apical portion of the lung are often seen. Lobar, cavitary or miliary lesions are rarely seen. Spontaneous pneumothorax or pneumomediastinum are rarely seen.
- Pulse oxymetry (see color atlas) – PaO₂ < 70 mm Hg in room air is highly suggestive of PCP.
- Lactic dehydrogenase (Serum LDH) - LDH is usually increased but is not very specific. However it may be of utility when combined with O₂ saturation arterial blood gas.
- Demonstration of organism by gastric lavage / sputum / bronchoalveolar lavage (BAL)/bronchoscopy with transbronchial biopsy or open lung biopsy. For definitive diagnosis special stains are required.

Treatment

TMP SMX is the drug of choice.

Dose - TMP/SMX - 15-20 mg/kg of TMP IV/orally in 3 to 4 divided doses for 21 days.

Adverse effects

Erythema multiforme, Stevens Johnson syndrome (SJS), bone marrow suppression, hepatitis and interstitial nephritis. For mild rash, TMP/SMX can be temporarily discontinued and restarted when rash resolves. If SJS occurs, it should be discontinued permanently.

Alternative therapy

1. Primaquin (0.3 mg/kg/day orally) + Clindamycin (10 mg/kg IV every 6 hours) for 21 days.

2. Dapsone 2 mg/kg/day + Trimethoprim 5 mg /kg 3 times a day for 21 days.

Indications for corticosteroids

Early use of corticosteroids decreases need for ventilation, progression to acute respiratory failure and decreases mortality.

It is indicated if there is

- Cyanosis/ $\text{PaO}_2 < 70$ mm Hg in room air or
- Imminent respiratory failure

In the initial critical stage

Dexamethasone - 0.3-0.5 mg/kg 6 hourly for 5 days IV or Methyl Prednisolone should be used, followed by oral steroids.

Prednisolone

- Day 1-5 – 2 mg/kg/day orally
- Day 6-10 – 1 mg/kg/day orally
- Day 11-12 – 0.5 mg/kg/day orally

If the child is not critically ill, one may start with oral prednisolone directly.

If there is no resolution of systemic symptoms within 48 hours of initiation of treatment, the diagnosis of PCP should be reviewed.

Indications for PCP prophylaxis:

1) Primary prophylaxis

- A. For all HIV-exposed children: Starting at 4-6 weeks after birth and maintained until exclusion of HIV infection.
- B. For children with confirmed HIV infection
 - Age < 1 year: all infants regardless of CD4 percent or clinical status.
 - Age 1-5 years:
 - WHO stages 2, 3 & 4 regardless of CD4%
 - Any WHO stage and CD4 <25%

- Age \geq 6 years:
 - Any WHO clinical stage and CD4 < 350 cells/mm³
 - WHO stage 3 or 4 regardless of CD4 count
 - All children being treated for pulmonary tuberculosis
- 2) *Secondary prophylaxis* - All children who have been treated for PCP should receive secondary prophylaxis.

Recommended Drug regimen – 5/25 mg of TMP/SMX /Kg / day

Alternative regimen

- Dapsone 2 mg/kg once daily *or* 4 mg/kg once weekly

When to discontinue secondary prophylaxis?

- Children < 5years: Continue until age 5 years irrespective of clinical and immune response
- Children > 5years: There are different recommendations. NACO recommends lifelong secondary prophylaxis as the safety of discontinuation is not proven. But many authorities do discontinue it if there is good immunological recovery on 2 occasions not less than 3 months apart. If discontinued, it should be restarted if immune decline is detected again.

Important pulmonary conditions in HIV infected children:

Consider following while making a differential diagnosis

1. Signs and symptoms and their severity- The production or non-production of sputum is noteworthy. PCP typically causes dry, non-productive cough; while production of thick, purulent sputum is suggestive of bacterial pneumonia.
2. The onset and duration of symptoms - Bacterial pneumonia classically presents acute picture whereas PCP typically presents with sub-acute, gradual progression of symptoms.

3. Other risk factors

- A prior diagnosis of PCP is a significant risk factor for subsequent PCP infection if not on PCP prophylaxis.
- Contact with open case of TB (parents) increases chances of tuberculosis
- Intravenous drug use (which is common in certain areas) increases the risk of bacterial pneumonia.

Remember steroids used for respiratory distress are likely to mask Lymphoid Interstitial Pneumonia.

4. ART, OI prophylaxis (TMP/SMX) substantially decrease the risk of OIs.
5. Current CD4 count
- Bacterial pneumonia or TB is seen even at higher CD4 counts.
 - With low or very low CD4 counts, one should consider infection with PCP, cryptococcus, CMV, histoplasma etc.
6. Involvement of other systems - Confusion and headache may indicate both neurologic and pulmonary involvement by the fungus such as *Cryptococcus neoformans*. Blurred vision and abdominal pain may indicate concurrent CMV infection.

These observations, however, are generalizations and exceptions to the rule can and do occur. It is important to note that two or more opportunistic infections may present concurrently in the setting of HIV infection, especially with advanced immune suppression.

Any diagnosis based on chest X ray and clinical evaluation should be substantiated with additional investigations such as sputum microscopy, culture etc. if required.

Child not responding to suggested line of treatment and alternative line of treatment should be investigated further to rule out lymphoma.

Comparison of some important differential diagnoses in respiratory system:

Clinical Features	Bacterial Pneumonia	<i>Pneumocystis</i> Pneumonia (PCP)	Tuberculosis
Signs and symptoms	Acute onset, symptoms <1 week Cough with purulent sputum, fever, chills	Gradual onset, symptoms >2 weeks Nonproductive cough, shortness of breath, fever	Gradual onset, symptoms >2 weeks Cough, fever, night sweats, weight loss, swollen lymph nodes
Radiological features	Unilateral, focal, segmental or lobar consolidation Atypical presentations such as multifocal or multilobar involvement and parapneumonic effusions may be seen	Bilateral, reticular/granular opacities (Ground glass appearance) sparing apices. Hilar and perihilar area involvement is common Occasionally normal or minimal findings on X ray	Hilar nodes, paratracheal pneumonic patches, cavitary lesions, miliary lesions, pleural effusion. Atypical pictures are commonly seen with HIV infection and even a normal Xray does not rule out TB

B. Lymphoid Interstitial Pneumonitis (LIP)

It is commonly seen in pediatric HIV disease. The exact etiology of LIP is unknown, however a possible role of Epstein Barr Virus (EBV) or immunological response to EBV is postulated.

LIP is a chronic process with nodular lymphoid hyperplasia in the bronchial epithelium, often leading to progressive alveolar capillary blocks.

Salient features:

- Seen in older children
- There is insidious onset of tachypnoea, cough, mild to moderate hypoxemia with minimal auscultatory findings
- progressive disease is associated with digital clubbing and symptomatic hypoxemia (*see color atlas*)
- chest radiograph shows characteristic diffuse, bilateral, reticulonodular pattern rarely accompanied by hilar lymphadenopathy
- the disease usually resolves with oral corticosteroids

The clinical course of LIP in children is highly variable but is generally benign. **Children with LIP appear to have more indolent course of HIV and prolonged survival.**

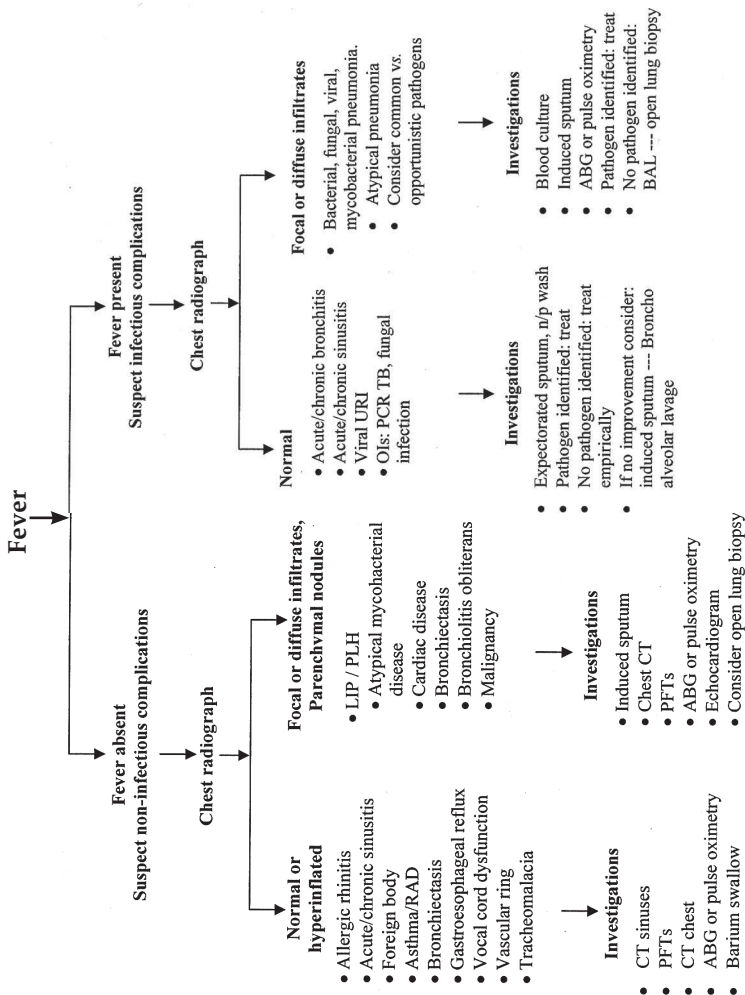
Diagnosis - *presumptive criteria* :

- bilateral reticulonodular pulmonary infiltrates with/without hilar lymphadenopathy present on chest Xray for 2 months or greater
- no response to therapy with antibiotics or antituberculous agents

Treatment – Bronchodilators and intermittent corticosteroids are currently used for mild to moderately symptomatic LIP. Treatment with long term steroids is reserved for severe cases with pulmonary insufficiency.

Approach to HIV infected pediatric patient with pulmonary disease:

Respiratory symptoms such as cough, dyspnea, tachypnea etc.,



Critical Concepts

- Respiratory infections are a major cause of morbidity and mortality especially in young HIV infected children, the frequency decreases with advancing age.
- Recurrent bacterial pneumonia is a good marker to suspect HIV infection in a child. (Recurrent bacterial pneumonias in HIV infected child = Clinical stage 3 disease).
- *Pneumocystis jirovecii* pneumonia (PCP) is common in children with advanced HIV disease, is associated with high mortality and is difficult to diagnose definitively.
- Proper chemo-prophylaxis reduces incidence of PCP.
- Pulmonary TB and bacterial pneumonia are predominant AIDS defining illnesses in India.
- Co-infection with TB leads to immune activation, increased viral replication, decreased CD4 counts, increased risk of OIs and increased risk of death.

13.

Tuberculosis In Children with HIV

HIV epidemic has led to a resurgence of tuberculosis.

Co-infection with HIV and TB is extremely common in developing countries.

TB remains the leading cause of death in HIV infected patients.

Natural history of TB in HIV infected children:

Clinical manifestations at the time of initial infection vary according to the age of the child and immune response:

- In general the clinical features of TB in HIV infected children are very similar to those in HIV negative children although disease is usually more severe.
- TB can occur at any stage of HIV disease irrespective of CD4 counts.
- Clinical features of TB do vary as per with different level of immune suppression.

- In general approximately 25% pediatric TB cases are complicated by extra pulmonary disease. But HIV infected children seem to have even higher rate of extra pulmonary disease, especially TB meningitis. Other forms include TB abdomen, bones, joints and rarely involvement of eye, middle ear, GI tract and kidney.
- In most of the cases, pulmonary involvement is evident subsequently leading to progressive disseminated disease such as meningitis. However in some cases disseminated disease can be seen without obvious pulmonary findings.

Profile of TB in children

1. Asymptomatic Mantoux positive, with normal X ray
2. Symptomatic Mantoux positive, without any manifest TB lesion
3. Pulmonary primary complex
 - a. Nodal
 - b. Parenchymal
 - c. Parenchymal plus nodal
4. TB lymphadenitis with or without pulmonary lesion
5. Progressive primary disease
6. Miliary TB
7. Meningoencephalitic TB (TBM)
8. TB of other organs

General symptoms like persistent low grade fever, unexplained weight loss, poor weight gain and easy fatigability may be associated with any of the above profiles.

Important clinical profiles (See color atlas).

Pulmonary tuberculosis

- Pulmonary involvement occurs in about 75% of all HIV infected children co infected with TB.
- Clinical picture depends on level of immunosuppression. Typical manifestations are frequent in early HIV and atypical manifestations occur (extrapulmonary manifestations) as immunity declines.
- Various pulmonary presentations could range from primary complex, healed primary complex, pneumonias, bronchopneumonia, pleural effusion and endobronchial TB
- Suspect pulmonary TB if
 1. chronic cough, especially pertusoid type, not responding to routine treatment
 2. prolonged pyrexia with no other detectable cause
 3. pneumonia which fails to resolve with routine treatment
 4. persistent wheezing that does not respond to routine treatment (suspect endobronchial TB)
 5. pleural effusion
- Diagnosis will be aided by mantoux test, chest Xray, pleural fluid examination and sputum AFB if possible.
- Treatment includes routine ATT as per standard guidelines.

2. Neurotuberculosis

It is represented by different forms. TB Meningitis (TBM) and tuberculoma are most important. (See color atlas)

A. TB Meningitis (TBM)

- About 1-2% of children with untreated tuberculous infection • develop TBM.
- TBM in children is a serious illness with high rate of neuro-morbidity and mortality.
- Co-infection with HIV further complicates this problem.

Suspect TBM if

- persistent fever
- headache
- vomiting
- altered sensorium.

Following criteria could prove helpful in early diagnosis of TBM in children

Essential features

1. Fever for > 2 weeks
2. Abnormal CSF findings like pleocytosis > 20 cells, predominantly lymphocytes > 60%, and protein > 100 mg%, and sugar less than 60% of corresponding BSL

Plus any two of the following

1. Evidence of extraneural TB
2. Positive family history of exposure to a case of TB
3. Positive tuberculin skin test
4. Abnormal CT findings – (two or more of following)
 - a. basal exudates or exudates in sylvian fissures
 - b. hydrocephalus
 - c. infarcts
 - d. gyral enhancement

Once the child is diagnosed, the disease should be staged using Medical Research Council (MRC) guidelines:

Stage I: (early) conscious, nonspecific symptoms and no neurological signs; 80% recovery, 20% mortality.

Stage II: (intermediate) signs of meningeal irritation with slight or no clouding of sensorium, with or without minor neurological deficit like cranial nerve palsy or limb paresis; 50% recovery, 50% mortality.

Stage III (advanced): severe clouding of sensorium, convulsions, focal neurological deficit and/or involuntary movements; 80% mortality, 20% morbidity.

Treatment

Along with standard ATT, supportive treatment may be needed:

1. Mannitol 20% IV, 5 ml/kg stat followed by 2 ml/kg every 6 hrly for 2 days for raised ICT
2. Antiepileptic drugs if needed
3. IV fluids or Nasogastric feeds if required
4. Steroids are indicated – prednisolone 1-2 mg/kg/day in two divided doses orally for 4-6 weeks and then gradually tapered
5. VP shunts (if indicated) for hydrocephalus

B. Tuberculoma

It is an important cause of space occupying lesion (SOL) in children. Clinical features may vary from raised ICT, focal neurological signs and intractable epilepsy.

- Diagnosis is confirmed on CT / MRI.
- Treatment includes ATT plus oral dexamethasone (0.15 mg/kg/day) 6 hrly for 6-8 weeks tapered over 2 weeks. Surgery is rarely required.

3. Abdominal TB

It continues to be an important differential diagnosis of medical and surgical emergencies of acute abdomen.

Only 15-20% patients of abdominal TB have concomitant pulmonary involvement.

Sites of involvement in abdominal tuberculosis

- Intestine
 - Ulcerative; hypertrophic;
 - Ulcerohypertrophic; miliary
- Peritoneum
 - Exudative (generalized or localized)
 - Dry plastic, fibroblastic, miliary
 - Omental adhesive

- Lymph node
 - Mesenteric, other local nodes;
 - Retroperitoneal

Abdominal TB is of three types

- a. Classic plastic type
- b. Ascitic type
- c. Involvement of mesenteric lymph nodes

Suspect abdominal TB if

- constipation alternating with diarrhoea
- doughy abdomen with hepatosplenomegaly
- ascites
- matted mesenteric lymphadenitis
- subacute intestinal obstruction

Clinical features may vary from

Diarrhoea alternating with constipation, low grade fever, abdominal pain, doughy abdomen, ascites and hepatosplenomegaly.

Definitive diagnosis of abdominal tuberculosis is difficult.

Demonstration of AFB in lesion/ culture and tuberculous granuloma with caseating necrosis from specimens obtained by FNAC, endoscopy, peritoneoscopy, liver biopsy and ascitic fluid.

Supporting factors for diagnosis of abdominal TB

- Identification of contact (adult patient)
- Mantoux test/Tuberculin test
- Radiology (contrast and double contrast meal and enema techniques), chest and abdomen skiagram
- Ultrasound abdomen
- CT scan for nodal involvement
- Adenosine deaminase (ADA) in ascitic fluid
- Serological tests

Management includes routine ATT and symptomatic treatment.

Hepatotoxicity due to drugs should be vigilantly monitored when the child is on ATT.

Diagnosis of TB in children

Diagnosis of TB in children is difficult. It may be aided by following investigations.

1. Mantoux test

HIV-infected individuals often are anergic (nonreactive) to PPD as a consequence of HIV-related impairment of cell-mediated (T-cell) immunity.

In HIV-infected patients, a Mantoux test measuring 5 mm or greater in diameter is considered positive (instead of 10 mm cut off value in case of HIV negative children). Despite using this cut off value, only 50% or less children with HIV and TB co-infection have positive Mantoux test. Hence a negative Mantoux test does not exclude TB.

2. Sputum AFB

It is the standard test for diagnosis of pulmonary TB in adults. But in children as most cases would be non cavitary TB cases, sputum AFB is not useful. Additionally young children can not expectorate sputum. Though gastric aspirate is recommended in children, the test does not give good results.

If there is no sputum production, induced sputum or bronchoscopic lavage fluid can be used as a specimen.

3. Radiology

Radiological investigations as per the system involved e.g. X-ray, CT, MRI etc.

4. DNA PCR

- Limited ability to detect M. Tuberculosis in sputum or gastric aspirate
- More useful in case of CSF
- Costly
- To be used only in cases with confusing picture.

5. Biopsy/FNAC of lymph node: Cytology, histopathology and tissue culture

Biopsy or fine-needle aspirate will reveal necrotizing and non-necrotizing granulomas and may show AFB. One of the differentials for TB lymph node is persistent generalized lymphadenopathy (PGL). Bilaterally symmetrical axillary lymphadenitis is supportive for PGL, while asymmetrical lymphadenopathy should arouse suspicion of lymphoma.

6. Bone marrow smear and culture

In cases of pyrexia of unknown origin, bone marrow culture may yield M. tuberculosis.

A presumptive diagnosis of TB can be made based on a history of contact with an individual with TB, appropriate clinical signs and symptoms, a positive Mantoux tuberculin skin test and contributory findings such CSF examination, typical chest radiographic features etc.

Management of TB

- Children with HIV and TB should be managed as per standard treatment protocol. As such HIV status does not seem to affect child's response to TB treatment. But the duration of ATT may be extended.
- Latent TB is commonly seen in children. It needs to be carefully ruled out before starting ART so as to avoid immune reconstitution inflammatory syndrome (IRIS).

- It is also advisable that all patients with HIV – pulmonary TB co-infection should be provided TMP-SMX prophylaxis.

A. Anti Tubercular Treatment (ATT)¹

In HIV-infected children with TB disease, **the initiation of TB treatment is the priority, even before starting ART.**

a) Directly observed therapy (DOTS)

All patients should receive DOTS regimen as per Revised National TB Control Program (RNTCP) guidelines.

1. Refer Annexure 5 for Anti tuberculosis drugs - dosages, side effects, and drug interactions.

Recommended treatment regimens under RNTCP

Category of treatment	Type of patients	TB Treatment Regimens	
		Intensive Phase	Continuation Phase
Category I	New sputum smear-positive PTB New sputum smear-negative PTB with extensive parenchymal involvement New cases of extrapulmonary TB (more severe forms) Severely ill TB patients with concomitant HIV infection	2 H ₃ R ₃ Z ₃ E ₃ *	4 H ₃ R ₃
Category II	Sputum smear-positive relapse Sputum smear-positive treatment failure Sputum smear-positive treatment after default	2 S ₃ H ₃ R ₃ Z ₃ E ₃ + 1 H ₃ R ₃ Z ₃ E ₃	5 H ₃ R ₃ E ₃

* In patients with TBM on Category 1 treatment, 4 drugs used during the intensive phase should be HRZS (instead of HRZE).

Continuation phase of treatment in TBM and spinal TB with neurological complications should be given for 6-7 months, thus extending the total duration to 8-9 months. Steroids should be used initially in hospitalized cases of TBM and TB pericarditis and reduced gradually over 6 -8 weeks

b) Continuous therapy

Although DOTS is the recommended strategy for treatment of all pediatric TB patients, in some circumstances continuous (daily)

therapy can be used if easily affordable. Adherence should be ensured in such cases.

Poor compliance is the main cause of relapsed or inadequately treated disease. It is estimated that between 10 - 50% of patients treated for tuberculosis do not comply fully with treatment. If there is **any doubt** about potential compliance then treatment should be supervised from the outset. Family physician may be helpful in reaching this decision due to background knowledge of the family.

Assess adherence with

- History of medicine intake (work with the mother as well as the child)
- Pill count if possible
- Urine color

If there is non adherence, ascertain the reasons for the same. If there is any doubt about compliance, then changing to DOT is indicated.

Following points are equally important part of management of TB

- Family screening
- Chemoprophylaxis for other sibling (if open case)

B. Steroids

Steroids are used only in cases of

- TB meningitis
- TB pericardial effusion
- Endobronchial TB
- Adrenal TB
- Miliary TB (maximum for 6-8 weeks).

In HIV- TB co infection they should be used only in life threatening conditions.

Prednisolone 1-2 mg/kg/day in two divided doses orally for 4-6 weeks and gradually tapered over 2 weeks.

C. ART in a child with HIV and TB

Pulmonary TB defines clinical stage 3 disease and Extrapulmonary TB defines clinical stage 4 disease. Indication of starting ART depends on level of immunosuppression. So based on clinical criteria per say all children co infected with TB will need ART.

Recommendations for the timing of ART following initiation of ATT

- All children with TB and clinical stage 4 and 3 HIV disease should be started on ART between 2-8 weeks of ATT.
- If there is mild or no immunodeficiency with clinical stage 3 disease, ART may be deferred till ATT is completed. Clinical response should be monitored closely. If clinical response is not appropriate, start ART earlier.
- There are some data (in adults) which suggest that starting ART simultaneously or after the lag period does not alter morbidity much but has definite impact on mortality. There are no data from pediatric cohort on this.
- Multiple drugs being started simultaneously, complicated nature of regimen and side effects pose major challenges in children. Therefore a phased out approach is preferred by many.

When the child is both on ART and ATT, *possible drug interactions* should be kept in mind and appropriate choice of drug should be made.

- Rifampicin has drug interaction with all NNRTIs (EXCEPT efavirenz.) and almost all PIs.
- Rifampicin lowers NVP drug level by 20-58% and EFV drug level by 25%. In children, there is no information on appropriate dosing of NVP and EFV when used with rifampicin.
- Apart from rifampicin, other anti-TB drugs do not have drug interaction with ART.
- There is no drug interaction between NRTI and rifampicin.
- Both Anti-TB drugs and NNRTI (especially NVP) can cause hepatotoxicity.

- Now that rifabutin is available in India, it can be used as a substitute to rifampicin with NVP/PI based regimens. Dose adjustment is needed with most PIs.

When both ART and ATT need to be given:

1. Rifampicin should be part of ATT especially during the first 2 months of treatment. Consideration to change from rifampicin-based to non-rifampicin-based ATT during the maintenance phase is up to the discretion of the treating physician
2. If ART is to be started in a child on rifampicin containing ATT
 - a. ART should be initiated between 2-8 weeks of ATT in children with clinical stage 3 or 4 disease
 - b. Use efavirenz (2 NRTI + EFV) if the child > 3 yrs and/ > 10 kg
 - c. Following completion of anti TB treatment, it is recommended to change from EFV to NVP after 2 weeks of ATT
 - d. If efavirenz can not be used, consider using abacavir but remember it is not available in pediatric formulation, is costly and 3 NRTI are known to be less efficacious
 - e. As an alternative regimen NVP can be used with rifampicin in the usual dosages and keep a close watch on hepatotoxicity.
 - f. Rifabutin may be used as a substitute for Rifampicin.
3. If the child is already on ART and needs to be put on rifampicin containing ATT
 - a. If the ART regimen contains EFV, continue the same regimen
 - b. If the ART regimen contains NVP, switch to EFV if child is > 3 yrs old and weigh is > 10 kg

Monitoring the child on ATT and ART

- Anti-TB and antiretroviral drugs have overlapping toxicities such as hepato-toxicity caused by NNRTI and rifampicin.
- The large number of drugs involved in treating the two diseases concomitantly poses significant adherence challenges.

D. TMP SMX prophylaxis

Provide TMP-SMX prophylaxis to all HIV infected children co-infected with TB

Clinical Monitoring and evaluation of treatment with ATT

- Clinical improvement is assessed at the end of intensive phase of treatment. Improvement should be judged by absence of fever or cough, decrease in size of lymph nodes and weight gain.
- In sputum positive patients, follow up sputum examination should be performed at the end of intensive phase.
- Radiological improvement is assessed by chest Xray at the end of treatment.

Drug Resistant TB (MDR TB)

Suspect drug resistant TB if

- Lack of clinical improvement at the end of intensive phase
- Deterioration on treatment

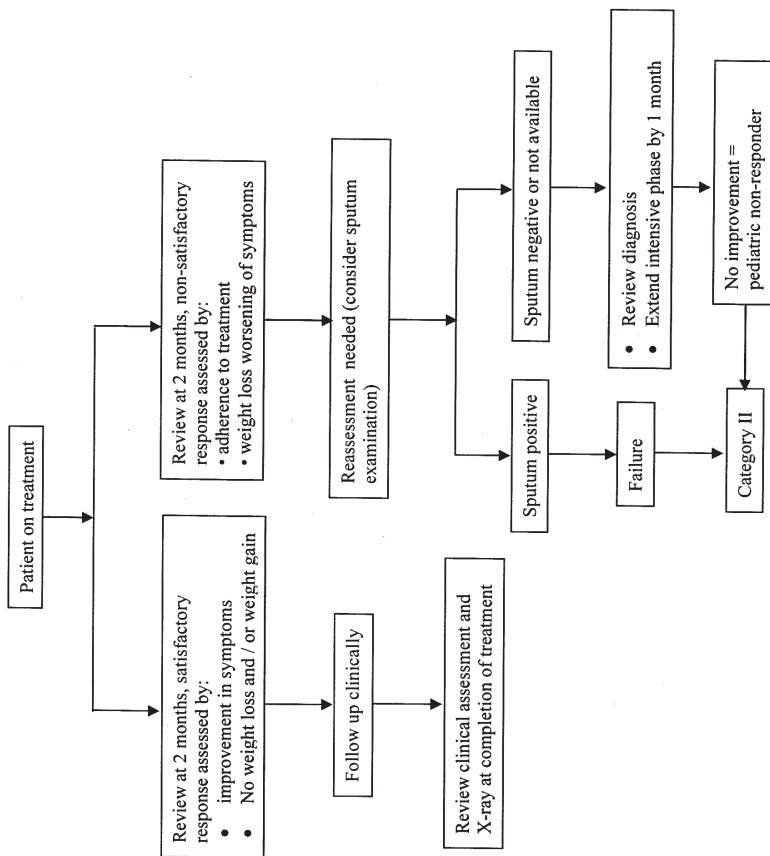
For definitive diagnosis of MDR TB, culture and sensitivity of the isolated AFB is required.

Predictors of drug resistance

- HIV infection in child / adult source case
- History of Previous ATT
- Known contact with MDR TB

Management – Unfortunately little is known about diagnosis and management of MDR TB. Expert opinion should be sought in such cases.

Follow up of the patient on ATT



Antituberculosis drugs used for the treatment of MDR tuberculosis:

Drugs	Average daily dose (mg/kg)/ mode	Toxicity	Type of antimicrobial activity
Aminoglycosides			
Streptomycin	20-40 Injection	Medium	Bactericidal
Kanamycin	15-30 Injection	Medium	Bactericidal
Amikacin	15-30 Injection	Medium	Bactericidal
Capreomycin	15-30 Injection	Medium	Bactericidal
Thionamides			
Ethionamides	10-20 Oral	Medium	Bactericidal
Pyrazinamide	20-30 Oral	Low	Bactericidal at acid pH
Qfloxacin	7.5-15 Oral	Low	Weak bactericidal
Ethambutol	15-20 Oral	Low	Bacteriostatic
Cycloserine	10-20 Oral	High	Bacteriostatic
PAS	10-12 g Oral	Low	Bacteriostatic

Suggested drug regimen for proven drug resistance in relation to HIV status

HIV status	Isoniazid	Rifampicin	Multi-drug
HIV-ve	12RZE	18-24HZE	3 sensitive drugs for 2 years after culture negative
HIV+ve	18RZE or 12 months after culture-ve	18-24HZE or 12 months after culture-ve	3 sensitive drugs for 2 years after culture negative

Preventive Therapy - Chemoprophylaxis for TB

Indication for primary prophylaxis: Asymptomatic children, below 6 years of age, having history of household contacts of smear-positive TB case

Regimen – INH -5 mg/kg daily (max. 300mgs) for 6-9 months

Secondary Prophylaxis for TB is not recommended.

14.

Oral Manifestations in Children with HIV

Oral manifestations are extremely common in HIV disease in general and even more so in children. Some oro-facial manifestations seen in HIV infected children are -

Diagnosis	Features
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Oral mucosal changes

- | | |
|--------------------------------------|---|
| • Candidiasis
(28%–67%) | White patches that rub off, red patches intra orally or redness at corners of mouth |
| • Herpetic
Stomatitis
(3%–5%) | Both primary and recurrent forms may be more dramatic in HIV-infected children |
| • Aphthous
ulcers
(Upto15%) | Ulcers of unknown etiology that can be more severe in HIV-infected children |
| • Hairy
leukoplakia
(up to 2%) | White plaques on the lateral border of the tongue that do not rub off |

Diagnosis	Features
<ul style="list-style-type: none"> Other viral infections (Very rare) Tumors (Very rare) 	<p>CMV, VZV can cause oral changes</p> <p>Kaposi's sarcoma and non-Hodgkin's lymphoma are very rare in this population</p>

Gingival changes

- Gingivitis (>80%) Erythematous gingival changes form plaque on teeth
- Linear gingival erythema (Upto25%) Specific to HIV infection
- HIV-associated periodontitis (Rare) Rapidly advancing periodontal disease

Tooth changes

- Decay (Common) Tooth break down can be obvious. Pain is not normally a presenting complaint
- Abscesses (Fairly common) Can cause fever and pain
- Delayed exfoliation and eruption (Fairly common) Primary teeth maybe retained well into teenage years

Parotid gland enlargement

- Lymphocytic-mediated (2%-11%) Painless enlargements; Clear saliva can be expressed from glands. MRI can be used to confirm presence of cysts.

Diagnosis	Features
<ul style="list-style-type: none"> Bacterial infection 	Pain on palpation; often, pus can be expressed from glands. May or may not be accompanied by fever

Oral Candidiasis (See color atlas)

It is the commonest oral lesion seen in children (28-67%) with HIV disease. Its presence is associated with low or declining CD4 counts.

Classical oral lesions are :

- White creamy plaques on an inflamed base that can be rubbed off easily, involving the palate, buccal mucosa or tongue.
- Spotty or red confluent patches (atrophic type).
- Angular cheilitis* - Erythema and fissuring at the corners of mouth.

Diagnosis is usually clinical. Oral swab or scraping for KOH wet mount or culture can assist diagnosis.

Treatment:

- Maintain good oral hygiene.
- In mild cases, topical antifungal agents like clotrimazole mouth paints, nystatin oral pastes may be used. The standard gentian violet may be used when cost is an issue but it is messy, compliance is poor, and it is not very effective for recurrences, which are frequent.
- Systemic fluconazole (5 mg/kg/day OD 7-14 days) works very well. The drugs may be used till all signs and symptoms have resolved.

Herpes simplex stomatitis (See color atlas)

Herpes simplex infection is commonest among viral infections. It could be more severe and debilitating in presence of severe immunodeficiency due to HIV infection.

Primary herpetic stomatitis is characterized by fever, lymphadenopathy and fluid filled vesicles on gingiva and palate. These vesicles quickly rupture and ulcerate.

After primary infection, virus establishes latent infection in trigeminal ganglion. Typically intraoral recurrent lesions of HSV are found on keratinized tissues of mouth but lesions could be severe and involve any oral mucosal surfaces in children with HIV.

Extra-oral lesions occur on lips and heal in 7-14 days without scarring. Burning and tingling may precede vesicle formation.

In children with advanced immunodeficiency, herpetic infection may present as chronic non-healing ulcers. **In HIV infected individuals, any non-healing ulcer is to be treated as herpetic ulcer unless proved otherwise.**

Intra-oral herpes zoster occurs rarely in children.

Treatment:

- Maintain oral hygiene
- Oral acyclovir 20 mg/kg/dose three times daily *or* Intravenous acyclovir 5-10 mg/kg/dose three times daily for 7-14 days (in case of severe disease)
- 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. But it should be avoided in young children.

Recurrent Aphthous Stomatitis (See color atlas)

- Etiology is unknown. Presence of recurrent aphthous ulcers usually indicates severe immunodeficiency.
- Ulcers are preceded by a prodromal irritation followed by crops of ulcers (1-10 mm diameter). These are usually shallow but may be deep, have yellow slough at the base.

- They can last for a week or even up to a month. They are extremely painful and may take up to 3 months to heal.
- The diagnosis is clinical.
- There may be underlying nutritional deficiencies such as iron, vitamin B 12 and folic acid. It may also be associated with neutropenia.
- Differential diagnosis is ulcers due to HSV, VZV, CMV.

Treatment:

- Maintain good oral hygiene
- Topical treatment
 - Triamcinolone in carboxymethylcellulose 0.1% paste applied in a thin layer q6h daily
 - Betamethasone phosphate: 0.5 mg tablet dissolved in 10 ml mouthwash and rinse q4h or spray on ulcer (1 spray = 100 µg) up to 800 µg
 - Fluocinonide (Lidex) 0.05% ointment q4h
 - Dexamethasone elixir (0.5 mg/5ml) rinse and expectorate
- Systemic treatment in refractory cases
 - Prednisone (1 mg/kg/day) short course with gradual tapering
 - Assess for and correct nutritional deficiency if any

Oral hairy leukoplakia (OHL) (See color atlas)

OHL is rarely seen in children. It is caused by Epstein Barr (EB) virus. The lesions usually occur on the lateral borders of the tongue appearing as white plaques with vertical folds. It may affect the dorsum of the tongue, as well. The diagnosis is usually clinical. No treatment is required, as it is asymptomatic.

Intra-oral warts

Intra-oral warts are caused by Human Papilloma Virus (HPV). Both verruca vulgaris and condyloma acuminata are found intra-orally.

Treatment: Topical:

- Podophyllin resin 25% applications,
- Surgical excision
- Laser ablation
- Cryotherapy

Dental Caries and eruption problems

Decay is frequently seen in children with HIV infection and at levels higher than the general population. Its prevalence increases as HIV advances. It may present as early childhood caries, in which decay occurs on smooth surfaces normally not prone to caries.

- Prevention is important as restorative treatment in children is difficult
 - Good oral hygiene is imperative for its prevention.
 - Control of dietary sugars, bottle-feeding would be valuable additions in prevention efforts.
 - These issues should be regularly discussed with parents / care providers.
- The child should be assessed for presence of caries at each visit and treatment should be instituted promptly.

Delay in eruption and exfoliation of primary teeth and permanent teeth have been noted in HIV infected symptomatic children.

HIV-Associated Periodontal Disease (See color atlas)

It is characterized by

- bleeding gums
- bad breath
- pain/discomfort
- loosening of teeth
- sores (sometimes)

Left untreated, HIV associated periodontal disease may progress to life threatening infections, such as Ludwig's angina and noma (Cancrum oris), especially in malnourished children.

Management and control of HIV associated periodontal disease begin with good daily oral hygiene. Treatment includes frequent dental cleaning, use of antibacterial oral rinses and antibiotic therapy.

Various manifestations:

Linear gingival erythema (LGE) is characterized by the presence of a 2-3 mm red band along the marginal gingiva, associated with diffuse erythema on the attached gingiva and oral mucosa.(see color atlas)

Necrotizing ulcerative gingivitis (NUG) is more common in adults than in children. It is characterized by the presence of ulceration, sloughing, and necrosis of one or more interdental papillae, accompanied by pain, bleeding, and fetid halitosis.

Necrotizing ulcerative periodontitis (NUP) is characterized by the extensive and rapid loss of soft tissue and teeth.

Necrotizing stomatitis is thought to be a consequence of severe, untreated NUP. It is characterized by acute and painful ulceronecrotic lesions on the oral mucosa that expose underlying alveolar bone.

Noma, also known as *Cancrum oris*, is a gangrenous condition that primarily affects children. The most important risk factors are poverty, chronic malnutrition, poor oral hygiene, and severe immunosuppression. Noma has a case-fatality rate of 70-90 percent if left untreated. Treatment includes local wound care, penicillin and metronidazole.

Salivary gland pathology

Salivary gland enlargement can be due to

- Lymphocyte infiltrates of the salivary gland presenting as unilateral or bilateral swelling with xerostomia and pain. Clear saliva can be milked from gland.

- Bacterial infection with purulent discharge at duct opening when massaged. It usually occurs because of retrograde infection of oral flora. Treatment with penicillin, clindamycin or second generation cephalosporins is indicated.
- Mumps and salivary gland tumors are the other differential diagnoses. Suspect tumor if glands continue to enlarge. For definitive diagnosis FNAC or biopsy is indicated

Disorders of mucosal pigmentation

Platelet deficiency can lead to purpuric lesions anywhere on the body including the oral cavity. Areas of black or brown pigmentation can also be found in all parts of the oral cavity as part of HIV disease. Treatment with zidovudine has also been documented to cause brown patches.

Neoplasms associated with HIV in oral cavity are rarely found in children.

Kaposi's sarcoma (KS) is a neoplasm of the endothelial cells with early lesions presenting as red, purple or brown patches and later becoming nodular, enlarged and ulcerated. However, KS is extremely rare in India.

Conditions which indicate advanced HIV disease are –

- severe/recurrent aphthous ulcerations
- severe periodontal disease
- acute necrotizing ulcerative gingivitis or stomatitis
- acute necrotizing ulcerative periodontitis
- chronic orolabial herpes simplex, oral candidiasis
- oral hairy leukoplakia

In the presence of such conditions further evaluation to assess the need for ART should be promptly undertaken.

Critical Concepts

- Oral manifestations are common clinical findings in children with HIV infection
- Maintaining oral hygiene is extremely crucial as it prevents many of the common ailments seen in HIV infected children. It is necessary that we discuss this issue with parents / care providers
- Oral lesions are likely to impact adversely on food intake because of pain leading malnutrition. So while managing oral lesions equal attention needs to be given to issues related to nutrition, along with treatment of specific ailments. .
- If oral lesions are present, advise the parents / care providers to avoid giving spicy, hot food. Soft, bland food and plenty of liquids would be more suitable.

15.

Gastro-Intestinal Manifestations in Children with HIV

Acute diarrhea is the most common gastrointestinal manifestation in HIV-infected patients. Others are vomiting, malabsorption, jaundice. Weight loss and failure to thrive could be secondary to gastrointestinal problems. Esophagitis is less common in children as compared to adults.

A. Diarrhea

Acute diarrhea is one of the most common cause of morbidity and mortality in the first year of life. It tends to be prolonged and can be complicated by dehydration and malnutrition. One must also keep it in mind that diarrhea is also common in HIV exposed uninfected children whose mothers are sick or are dead, or also following early weaning.

HIV and diarrhea

- Early HIV disease – may present with recurrent acute episodes of diarrhea.
- Late HIV disease –
 - AIDS enteropathy can develop. It is characterized by villous atrophy and leads to malabsorption and malnutrition.
 - Recurrent parasitic, viral, fungal and bacterial infections are seen.
 - Opportunistic AIDS-defining diarrheal illnesses include chronic cryptosporidium (lasting more than one month), CMV disease, histoplasmosis, isosporiasis, MAC.
 - Chronic cryptosporidiosis / isosporiasis suggest clinical stage 4 HIV disease.
 - Higher risk of developing invasive disease due to salmonella (salmonella septicemia) and other enteric organisms. Therefore any sign of systemic illness should raise the concern of bacteremia

Other causes of diarrhea include medications, such as antiretrovirals. Many antibiotics also cause loose stools due to their effect on normal flora, and *C. difficile* infection may occur in the setting of recent broad-spectrum antibiotic therapy.

The basic approach remains the same as that for a child with diarrhea without HIV infection.

Clinical types of diarrhea

1. Acute watery diarrhea,
2. Dysentery/acute bloody diarrhea,
3. Chronic/persistent diarrhea

1. Acute watery diarrhea

- Large-volume watery diarrhea due to a predominant small-bowel infection. Commonly caused by agents such as rotavirus, norwalk virus, enteroviruses, *Vibrio cholerae*, enterotoxigenic *E. coli*, giardia.
- Viral diarrhea is commonly associated with vomiting.
- Measles infection followed by diarrhea is associated with increased morbidity and mortality and therefore should be treated vigilantly.

2. Dysentery/acute bloody diarrhea

- Blood with mucus due to predominant colonic (lower GI) infection.
- Dysentery may be accompanied by systemic symptoms such as fever and an elevated white-blood cell count.
- Commonly caused by shigella, typhoid and non-typhoid salmonella, yersinia, campylobacter, *Clostridium difficile*, enterohemorrhagic and enteroinvasive *E. coli*, and the parasite *Entamoeba histolytica*.
- In advanced HIV disease, one must also keep *Mycobacterium Avium* Complex (MAC) in mind.

3. Chronic/persistent diarrhea

- It is defined as diarrhoea with or without blood, which begins acutely and lasts at least 14 days.
- In HIV disease, chronic diarrhea belongs to clinical stage III disease.
- It leads to weight loss and failure to thrive.

- Common causes are *Candida albicans* and parasites such as cryptosporidium and isospora.
- Apart from infectious causes, non-infectious causes such as malabsorption syndrome, lactose intolerance, cow milk allergy should also be considered.
- Prolonged use of antibiotics and certain antiretroviral drugs (nelfinavir, ritonavir) can cause persistent diarrhea.

Management of acute diarrhea in HIV infected child:

Management remains same as any other child with diarrhea.

- Rapid and adequate rehydration is the mainstay of the treatment
- ***Adsorbents, anti-motility drugs are not indicated in children.***
- Antisecretory agents (such as Racecadotril) have shown good results. _
- Antibiotic treatment is not required for routine treatment of acute viral diarrhea.
- Antibiotic treatment is recommended in cases of
 - bloody diarrhea
 - suspected cases of bacterial diarrhea
 - diarrhea associated with other serious infections like pneumonia, septicemia, meningitis.

Antibiotics such as oral norfloxacin (10 mg/kg BD) for 5 days or ofloxacin 15 mg/kg/day in 2 divided doses for 5 days may be used.

Consider oral cefixime 8 mg/kg/day or ceftriaxone 50-100 mg/kg/day IM/IV OD if there is systemic involvement.

In case of amoebic dysentery, treat with metronidazole 10 mg/kg/day for 3-5 days.

- Administer vit A if history of recent measles.
- Zinc supplementation is recommended (*Dose:* 10 mg/day for infants below 6 months of age, 20 mg/day for > 6 months of age for 10-14 days).

The child is referred for hospitalization or kept under observation if :

- initially dehydrated (grade 2 / 3) or in shock
- has decreased urine output and abnormal mental status

Management of chronic diarrhea

1. Obtain detailed history including diet and medication
2. Most recent CD4 counts
3. Send Stool sample for smear (oval/parasitic evaluation, RBCs, leukocytes, modified (Kenyon) AFB stain, special stain for cryptosporidium if available), bacterial culture etc.
4. If needed blood culture should be done.

If no pathogen detected, empiric antibiotic treatment with norfloxacin/ofloxacin is indicated. If systemic symptoms are present, antibiotics like cefixime or ceftriaxone should be given. Add metronidazole if there is no response.

Cryptosporidial infection may not be treated in immune-competent children but it needs treatment in children with HIV infection.

Hospitalization in chronic diarrhea is indicated in

- cases which are associated with serious systemic infection
- have signs of dehydration
- in infants below 4 months age

Every child with persistent diarrhea should be examined for non-intestinal infections such as: pneumonia, sepsis, urinary tract infection or otitis media.

Antibiotic treatment for Diarrhoea

Etiology	Treatment
BACTERIA	
<i>Salmonella</i> (non-typhoidal)	Ciprofloxacin* 10–15 mg/kg 2 times a day for 5 days
<i>Shigella</i>	Ciprofloxacin* 10–15 mg/kg 2 times a day for 5 days
<i>Escherichia coli</i>	No antibiotic
<i>Campylobacter jejuni</i>	Erythromycin 12.5 mg/kg 4 times a day for 5 days Oral ciprofloxacin* 10–15 mg/kg 2 times a day for 5 days.
<i>Mycobacterium avium complex</i>	Clarithromycin 15 mg/kg/day 2 times a day plus Ethambutol 15–25 mg/kg 4 times a day (plus rifabutin** 6 mg/kg once daily) for at least 12 months
<i>M. tuberculosis</i>	Standard treatment for tuberculosis
<i>Yersinia enterocolitica</i>	TMP–SMX: TMP 4 mg/kg + SMX 20 mg/kg 2 times a day for 5 days

VIRUS

<i>Cytomegalovirus</i>	Supportive treatment as the internationally recommended treatment with ganciclovir is very expensive
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* Use is not licensed for use in infants and children less than 5 years of age. Quinolones taken by mouth have been shown to cause bone problems in very young animals and caution is advised in children.

** Rifabutin is currently not available in south-east Asia.

Etiology	Treatment
<i>Rotavirus</i>	Supportive treatment

PROTOZOA

<i>Cryptosporidium</i>	No therapy proven efficacious, Nitazoxanide: For 1-3 yrs 100 mg BD and for 4-11 yrs 200 mg BD or Azithromycin 10 mg/kg on day 1 and 5 mg/kg on day 2-10 may be used, spontaneous resolution may occur after antiretroviral therapy
<i>Isospora belli</i>	TMP-SMX TMP 4 mg/kg + SMX 20 mg/kg 4 times a day for 10 days then 2 times a day for 10 days. Maintenance therapy may be considered
<i>Giardia lamblia</i>	Metronidazole 5 mg/kg 3 times a day for 5 days
<i>Entamoeba histolytica</i>	Metronidazole 10 mg/kg 3 times a day for 10 days
<i>Microsporidia</i>	Albendazole 10 mg/kg 2 times a day for 4 weeks (maximum 400 mg/dose)

PARASITE

<i>Strongyloides</i>	Albendazole 10 mg/kg once daily for 3 days (maximum 400 mg/dose)
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YEAST

<i>Candida albicans</i>	Nystatin 100,000 IU orally tid for 5-7 days for mild cases Alternative: ketoconazole 5 mg/kg/dose once daily or 2 times a day or fluconazole 3-6 mg/kg once daily (also for moderate -to-severe cases)
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Prevention of recurrent diarrhea

- Treat current episode of diarrhea using it as a window of opportunity to pass on messages for prevention of more such episodes.
- Discuss with care providers issues of safe drinking water and food, maintaining proper hygiene etc.

B. Anorexia

- Causes of anorexia most often remain the same as in other children.
- Perceived anorexia arises more out of care provider's anxiety rather than due to any pathological cause. In such cases there is no failure to thrive and the child does not look sick.

Reasons of anorexia considered in case of HIV infected children:

- hepatitis
- sepsis
- meningitis
- pancreatitis
- increased intracranial pressure

C. Nausea and vomiting can be due to medications, such as antiretroviral agents, drugs used to treat or prevent opportunistic infections (OIs) and antineoplastic (anti-cancer) drugs.

D. Odynophagia / Dysphagia

It is almost always related to esophageal ulcers that could be due to:

- a. Candida esophagitis: Commonly associated with oral lesions but may not always be so.
- b. CMV esophagitis: discrete ulcers with well demarcated borders seen only in very advanced disease
- c. Herpetic esophagitis: small vesicles with superficial ulcerations or diffuse hemorrhagic appearing esophageal mucosa

- d. Tubercular ulcers: large, often circumferential ulcers causing narrowing due to scarring
- e. Rarely *Histoplasma capsulatum* and *Cryptococcus neoformans* can cause painful ulcerations in oropharynx
- f. Drugs can cause injury to mouth or esophagus if not cleared rapidly into the stomach (NSAIDS, ZDV)
- h. Tumors such as Kaposi's sarcoma or lymphoma are quite rare.

Diagnosis

- Endoscopy and biopsy remains the mainstay for diagnosis of esophageal ulcers so need to be managed in higher centers.
- Dysphagia more for liquids than solids suggests esophageal ulcers.
- Give a trial of oral fluconazole 5 mg/kg OD for 7 days; if child improves continue it for 14 additional days and if not refer to higher centers.

Oesophageal candidiasis (see color atlas)

- Esophageal candidiasis is seen in children with low CD4 cell count, high viral load and neutropenia and those with concomitant oropharyngeal candidiasis. It is an AIDS defining condition.
- The presenting complaints include odynophagia (pain during swallowing), dysphagia, retrosternal pain, nausea and vomiting.
- Diagnosis
It should be suspected in a child with oral candidiasis who has refusal to feeds, swallowing difficulty especially to solids, drooling, hoarse voice or stridor.
 - Barium swallow - Classic cobblestoning appearance.
 - Endoscopy - white raised plaques with extensive ulceration and biopsy will prove candida on KOH preparation.

- Endoscopy is required in resistant cases to rule out other infections such as HSV, CMV, MAC and azole resistant candida.
- Presumptively diagnosis is based on:
 - Oral candidiasis and
 - Recent onset of retrosternal pain on swallowing.

Treatment

Fluconazole, at the dose of 3 -6 mg/kg/day IV for 21 days changing to oral route once the child starts tolerating food.

Itraconazole capsule is not useful for treatment of esophageal candidiasis, however oral solution may be given for 14-21 days.

E. Abdominal pain

Persistent abdominal pain should be evaluated appropriately

1. Children with HIV can experience crampy abdominal pain due to infection with enteric pathogens.
2. Infected mesenteric lymph nodes - Mycobacterium avium, often infects lymph nodes before infecting mucosa. Infected lymph nodes cause abdominal pain earlier while diarrhea may ensue months later. The exact mechanism of pain is not known but role of partial intussusception due to enlarged lymph nodes is suspected. USG abdomen may be useful for early diagnosis.
3. Pancreatitis – may be caused by CMV, Cryptococcus could be drug induced (didanosine, stavudine). In children lamivudine can cause pancreatitis (though uncommon in adults). If pancreatitis is suspected, test serum amylase, lipase. Withhold 3TC, d4T, ddI. Treatment remains often supportive.
4. TB abdomen – is commonly seen in HIV infected children. Treatment is standard anti TB regimen. (Refer to chapter on Tuberculosis for more details).

F. Hepatomegaly

Although hepatomegaly and mildly elevated liver function tests are common findings in HIV infected children, chronic and progressive liver disease is unusual. They are mostly associated with nutritional deficiencies.

Hepatomegaly is often associated with splenomegaly. Isolated hepatomegaly is uncommon and suggests primary liver disorder.

Other causes include hepatitis B, hepatitis C, EBV, MAC infection, CMV and drug toxicity (rifampicin, INH, fluconazole, TMP SMX, Nevirapine, Lamivudine, stavudine etc).

Although hepatitis B co-infection is more frequently seen, it does not usually cause hepatocellular injury.

Infants born to mothers who are co-infected with hepatitis C and HIV are at significantly higher risk of developing hepatitis C. They develop slow progressive disease and hepatocellular carcinoma may not be evident until adulthood.

Jaundice

- Common cause of jaundice is hepatitis A, E or B.
- Also consider bile duct obstruction due to gallstones, fibrosis, inflammation of biliary tract.
- Cryptosporidium or CMV are two common pathogens causing acalculous cholecystitis in HIV infected children.
- Drug induced hepatic injury should be ruled out in the presence of progressive liver disease.

Critical Concepts

- Common GI manifestations in children with HIV include recurrent diarrhea, abdominal pain and asymptomatic hepatomegaly.
- Management of acute diarrhea is same as seen in HIV uninfected children. Rehydration remains the mainstay of treatment.
- In advanced HIV disease oesophageal candidiasis, AIDS enteropathy, chronic cryptosporidiosis / isosporiasis are common .

16.

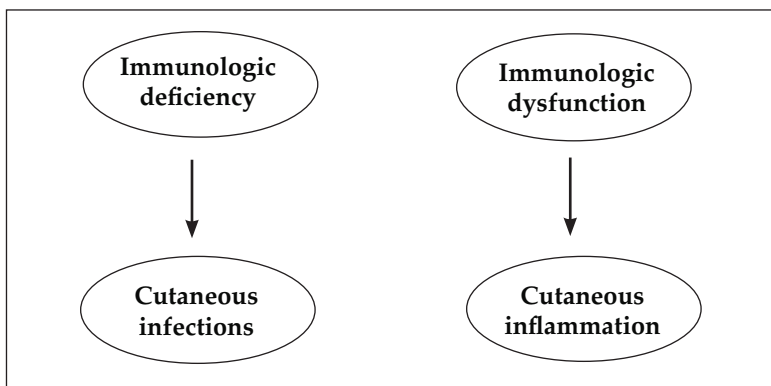
Cutaneous Manifestations in Children with HIV

Skin is a major target organ for infections, inflammatory disorders and neoplastic processes in HIV infected individuals.

Importance of Cutaneous lesions

- a) Some skin lesions occur early in the disease and may alert the physician to suspect the diagnosis of HIV for the first time. e.g. herpes zoster.
- b) Certain skin lesions occur later and may act as AIDS indicator conditions. e.g. cutaneous cryptococcosis, histoplasmosis.
- c) Most skin lesions become more aggressive and florid as immunity declines and CD4 counts fall. Thus they may act as surrogate markers of CD4 counts, viral load and mean survival time. e.g. HPV infection, molluscum contagiosum.
- d) Some skin diseases, though common, may present with such atypical or florid manifestations that their diagnosis and treatment becomes challenging e.g. seborrheic dermatitis.
- e) Certain diseases may not be life threatening, but are so persistent or disfiguring that they greatly add to the morbidity of HIV infection e.g. molluscum contagiosum.

- f) Rarely, serious systemic opportunistic infections or malignancies may have skin manifestations, which help in their diagnosis e.g. cryptococcosis, lymphoma.
- g) With the advent of ART, the scenario of skin lesions has changed. Infective lesions are waning; drug reactions are increasing; inflammatory conditions still persist and some lesions relapse during the IRIS (Immune Reconstitution Inflammatory Syndrome).



Essentials for dermatological examination:

1. Well-lit room.
2. Parent or guardian to assist examination.
3. **No need to wear gloves for routine examination** (except when contact with potentially infectious fluid/agent is possible).
4. Complete examination of skin and mucus membranes including nails, scalp, oral mucosa, genitals and feet.
5. Whenever in doubt, refer for consultation. Do not treat empirically.

Cutaneous Manifestations

I. Infective disorders:

A. Viral Infections

1. *Varicella (chicken pox)*

- Primary VZ infection is chicken pox (varicella) i.e. caused by varicella zoster (VZ) virus infection. Common presentation is centripetally distributed vesicular rash, occurring in crops accompanied with fever.
- **In children with HIV, varicella can be severe, even fatal.** Patients should be closely monitored for systemic illness including pneumonia, central nervous system involvement, hepatitis, pancreatitis and secondary bacterial infection. After the primary infection, the virus remains dormant in sensory dorsal root ganglia.
- Treatment – All children with HIV with VZV infection should be treated with acyclovir. Oral acyclovir 20 mg/kg/five times daily (max. 800 mg/dose) for 7 days.

2. *Herpes Zoster (HZ) (see color atlas)*

It is due to a reactivation of the latent VZV infection. It mostly occurs as a painful, grouped vesicular eruption, along a single nerve segment (dermatomal distribution).

- The incidence of HZ is higher in HIV infected, as compared to non infected children
- With declining immunity and low CD4 counts, HZ can manifest with certain atypical features or complications such as :
 - Multidermatomal involvement
 - Disseminated lesions, which may mimic varicella (chicken pox)

- Ulcerative and necrotic painful persistent lesions healing with scar formation
- Verrucous or hypertrophic lesions which may persist
- Severe post herpetic neuralgia.
- Ophthalmic herpes zoster may be complicated by retinal necrosis, optic neuritis and encephalitis.
- Recurrent episodes in the same or different dermatome.

Management consists of:

- Aggressive antiviral therapy, pain relief and antibiotics for secondary infection.
- *Antivirals* : Acyclovir or valacyclovir or famciclovir.
Acyclovir : Oral acyclovir 20 mg/kg/five times daily (max. 800 mg/ dose) for 7 days
- Alternatively valacyclovir, famciclovir can be given. They have better GI absorption, patient compliance and less pill burden.
- Ophthalmic herpes zoster, disseminated herpes zoster or herpes zoster in advanced immunodeficiency (CD4 < 50) are best treated with I.V. acyclovir (10 mg/kg/twice daily) till clinical remission.

There is no role for topical acyclovir ointment except for ophthalmic drops/ointment in case of ophthalmic zoster.

Key points

- A child with herpes zoster must be screened for HIV.
- Ophthalmic zoster is the most dangerous, and needs aggressive management to prevent long term morbidity.

3. *Molluscum contagiosum* (see color atlas)

- Very commonly seen even in normal children.
- May be self limiting.

- Pearly white dome shaped lesions with an umbilicated center.
- Giant mollusci can become confluent and have a 'cluster of grapes' appearance.
- Secondary infection and necrotic lesions are atypical manifestations.
- Differential diagnosis: cutaneous cryptococcal lesions.

Management:

- Chemical cautery, electrodesiccation, cryo-freezing.
- Recurrences are common.
- Topical imiquimod cream.
- Institution of HAART can induce resolution of mollusci.

It is very difficult to decide which child with molluscum contagiosum should be screened for HIV and which not. It would depend upon the number, rapidity of spread, size, site and other situational factors (infected parents/orphan child etc.) etc.

4. *Herpes simplex* - (see color atlas)

HSV Type 1 - herpes labialis

HSV Type 2 - herpes genitalis

- Primary herpetic gingivostomatitis is fairly common in children and is particularly severe in immune compromised children. Children present with painful ulceration of lip, tongue, palate and buccal mucosa.
- Recurrent lesions occur anywhere irrespective of type of virus.
- Acute lesions present as painful grouped vesicles. Chronic lesions erode progressing to deep ulcers, which are painful and persistent.
- HSV co-activates HIV and may lead to accelerated progression of HIV.

Management

- Acyclovir : oral acyclovir 20 mg/kg/dose three times daily for 5-7 days.

Any persistent painful ulcer should be treated as herpetic unless proved otherwise.

5. *Human Papilloma Virus infection* - (see color atlas)

- Causes warts. Hands, feet and face are commonly involved.
- Consider sexual abuse if there are genital or perianal warts.
- Oncogenic HPV types transmitted sexually are rare in children.

Management:

- Electrocautery, radiofrequency, CO2 laser or cryosurgery.
- 25% Podophyllin: for genital warts.
- Imiquimod: Immune enhancer.

6. *Oral hairy leukoplakia(OHL)* - (see color atlas)

OHL is due to infection of the oral epithelium by the EBV virus. It presents as white colored verrucous or corrugated plaques on the lateral aspect of the tongue. It is asymptomatic. It is rare in children.

7. *Kaposi's sarcoma (KS)* is associated with Human herpesvirus (HSV8). It is **rarely seen in India** and is extremely rare among children with HIV.

B. Fungal Infections

1. *Candidiasis (thrush)* - (see color atlas for oral thrush and candidial intertrigo)

- Mucocutaneous candidiasis is the commonest dermatologic manifestation of HIV in children. Oral candidiasis presents

in children as friable white plaques on oral mucosa (For details refer to chapter on 'Oral manifestations in children with HIV').

- On the skin, intertriginous and diaper areas are commonly affected; lesions appear as ill-defined erythematous plaques with satellite pustules.
- In children (age - 2 to 6), candidial paronychia with secondary nail dystrophy may occur.
- Persistent or recurrent mucocutaneous candidiasis indicates severe HIV disease.

Management:

- Local application of Clotrimazole/Nystatin
- Fluconazole 3-6 mg/kg OD x 7-10 days OR
- Itraconazole 2-5 mg/kg twice daily x 7-10 days OR
- Ketoconazole 5-10 mg/kg OD for 7-10 days
- IV Amphotericin B 0.3 -0.5 mg/kg/daily in disseminated or recalcitrant cases.

2. *Dermatophytosis* - (see color atlas for tinea capitis)

- Commonly seen in children, often after 2 years of age.
- Scalp, feet and nails are usually affected.
- In the scalp, lesions appear as non inflammatory scaly plaques with secondary alopecia. Typical kerion formation is not common in children with HIV.
- Lesions of feet and other skin surfaces appear as annular plaque with scales on the advancing borders.
- In the nails, infection may occur beneath the nail plate (subungual onychomycosis) or within the superficial nail plate (white superficial onychomycosis); the latter indicates severe underlying immunodeficiency.

Management

- Ketoconazole 3-6 mg/kg/day /Itraconazole (> 12 yrs old) 200-400 mg/day for 2-3 weeks OR

- Terbinafine 4-5 mg/kg/day for 2-3 weeks.

3. *Disseminated fungal skin infection*

- Disseminated cryptococcosis and histoplasmosis may occur rarely.
- Cutaneous cryptococcosis may present as molluscum like lesions or nodules, cellulitis, abscess, ulcers.
- Cutaneous histoplasmosis can present as acneiform papules, pustules, macules and plaques often involving face.
- Disseminated fungal infections have high mortality rates.
- Request special stains with routine histopathology if fungal infections are suspected.
- *Penicillium marneffe*, endemic in south-east Asia, appear as papules (with central umbilication) on face and extremities. It is seen more commonly in eastern India.

Management

- IV Amphotericin-B – 1mg/kg/day (ambisome (liposomal) – 1-3 mg/kg/day) for 2-3 weeks OR
- Fluconazole 3-6 mg/kg/day for 2-3 weeks.

C. **Bacterial infections**

Only gram positive bacteria (*Staphylococcus aureus* and *streptococcus*) cause primary skin infections.

1. *Bacterial infection in HIV (see color atlas)*

- Violent necrotic or recurrent bacterial infections are a feature especially of paediatric HIV disease.
- *Staph. aureus* remains the most important pathogen.
- Recurrent furuncles resulting in necrotic ulcerations are common.
- Extensive folliculitis and widespread impetigo and ichthyma may occur.
- Secondary infection with mixed organisms (gram negative organisms (*pseudomonas*) and anaerobes) may result in

gangrenous lesions (ecthyma gangrenosum) and culture sensitivity studies may be needed to guide the choice of antibiotics.

- Infections from IV lines and catheters may cause septicemia.

Treatment

- Commonly used drugs: ampicillin 100-200 mg/kg/day, macrolides - Azithromycin 10mg/kg/day on first day, followed by 5mg/kg/day for 5-7 days.
- MRSA (Methicillin Resistant Staph Aureus) may complicate therapy - Antibiotic therapy must be dictated by culture and sensitivity studies.

2. *Mycobacterium tuberculosis* : (see color atlas)

- Though pulmonary tuberculosis is the commonest infection associated with HIV, paradoxically cutaneous tuberculosis is rare.
- Lupus vulgaris and scrofuloderma arising from tubercular lymphadenitis may be encountered.
- BCG vaccination in HIV infected and immunocompromised / symptomatic child may lead to systemic disease and hence avoided.

3. *Mycobacterium Avium Complex (MAC)*

- Non-tuberculous mycobacteria (M. avium, M. intracellulare, M. paratuberculosis).
- Very low CD4 counts (< 50cells/cmm) is an important risk factor.
- Isolated lymphadenopathy, occasional skin lesions may be present.

Management

- Clarithromycin 7.5 mg/kg/dose (max 500 mg) twice daily plus ethambutol 15 mg/kg/dose (max 800 mg) daily for at least 12 months.

- Alternatively Azithromycin 5 mg/kg/dose (max 250 mg) plus ethambutol 15 mg/kg/dose (max 800 mg) daily for at least 12 months could be used.

D. Diseases caused by arthropods:

1. *Scabies* (see color atlas)

- The usual clinical picture may be replaced in HIV by a widespread eruption of itchy, eczematous, infected lesions which may also involve the scalp and the face. This may be easily mistaken for atopic or seborrheic dermatitis, both of which are common in HIV.
- 'Crusted scabies', a rare variety of scabies may occur in AIDS in which heavy population of mites on the skin may be seen. Patient is highly infectious. May closely resemble psoriasis or exfoliative dermatitis.

Management

- 1% BHC lotion applied all over body below neck or 5% permethrin applied all over body only once. May be repeated after a week.
 - Ivermectin (0.2 mg/kg) as a single dose orally, repeated after a week.
2. Exaggerated response to mosquitoes and other insect bites is commonly seen in HIV infected children. Grouped erythematous papules (with surrounding excoriation) on distal extremities should arouse suspicion. Chronic scratching of the lesions may lead to nodular lesions.

II. Non Infectious Complications

1. Drug reactions

- HIV infected individuals have a higher (10-20 fold) risk of developing drug reactions, which could range from extremely mild to severe life threatening.
- Immune dysregulation and concomitant viral infections (EBV and CMV) may be pathogenetic factors.

Various types of drug reactions and common incriminating drugs are as follows:

A. Stevens- Johnson Syndrome/Toxic Epidermal Necrolysis (SJS-TEN): (*see color atlas*)

The most severe type of drug reaction with high mortality (60-70 %.)

Characterized by severe ulceration of mucous membranes (eyes, mouth, genitals) and blisters and erosions involving >30% of the skin.

Drugs : TMP/SMX, Nevirapine, pyrimethamine, sulphadiazine, dapsone, thiacetazone, rifampicin, ethambutol, phenytoin, carbamazepine, ibuprofen and other NSAIDs.

B. Erythroderma : Generalised scaling, erythema with fever and chills

Drugs : Ant-tubercular drugs, Dapsone, NSAIDs, Abacavir, Indinavir.

C. Urticaria-Angioedema : Acute eruption of wheals and swelling of lips and eyes

Drugs : Penicillin, TMP/SMX, Aspirin, Lamivudine, Nelfinavir.

D. Fixed drug eruptions: Recurrent eruption of red to violaceous macules especially on lips and genitals.

Drugs : TMP/SMX, Sulphonamides, Pyrimethamine, Dapsone, Tetracycline, NSAIDs.

E. Generalized maculopapular rash: The commonest variety of drug rash

Drugs : Ampicillin, TMP/SMX, NSAIDS.

G. DRESS Syndrome (*Drug* Rash with Eosinophilia and Systemic Signs and Symptoms) - Generalized maculopapular rash, conjunctivitis and facial edema, high grade fever, lymphadenopathy associated rarely with hepatitis and nephritis.

Drugs : Dapsone, anticonvulsants (phenytoin, carbamazepine), Abacavir.

F. Vasculitis: Purpuric lesions

Drugs: AZT, Lamivudine, Efavirenz.

Management of adverse drug reaction:

- Removal of offending drug is foremost treatment. It also depends upon severity and may require hospitalization as well as barrier nursing.
- Good antibiotic cover, management of fluid and electrolyte balance, care of mucosae, nutritional support and general supportive care are needed for severe SJS or TEN.
- Role of steroids is debated but many would use it in the course of evolution till new lesions stop appearing.
- Emollients help soothing exfoliating skin.
- Antihistamines can be used judiciously.

2. Itchy lesions in HIV

Chronic intractable “maddening pruritis” is one of the commonest and most distressing problems in HIV medicine. Several dermatoses are responsible for these itchy lesions.

a. Eosinophilic folliculitis:

A chronic eruption of itchy papules, pustules or urticarial plaques (RED BUMP DISEASE). Lesions are mostly on the upper torso and face.

- Postulated to be an abnormal reaction to commensal yeasts or bacteria in the hair follicles.
- Occurs early in the HIV disease.

b. Papular Pruritic Eruption of AIDS: (see color atlas)

- Extremely itchy excoriated papular lesions.
- Lesions mostly on hands and legs and may look like ‘insect bites’.
- Prurigo simplex or lichenoid lesions may also be present.
- Occurs in advanced HIV disease.

Management (EF and PPE)

- Extremely recalcitrant to treatment - various modalities have to be tried:
 - Potent topical steroids
 - High dose antihistaminics
 - Systemic itraconazole
 - UVB phototherapy
- Anti retroviral treatment leads to rapid resolution of lesions.

Key points (EF and PPE)

- Itchy lesions not responding to routine therapy may be one of the first clinical signs of HIV.
- The D/D of generalized pruritus in HIV is diverse. Apart from EF and PPE, scabies, atopic dermatitis, xerosis and metabolic causes (renal and hepatic disease) have to be considered.

Treatment of EF and PPE is problematic but with the advent of HAART these lesions have become manageable.

c. Seborrheic dermatitis - (*see color atlas*)

- Disease may occur as scaly plaque involving scalp and diaper areas in infants or as scaly greasy plaques involving nasolabial folds, eyebrows and scalp in older children.
- Fungal infection, psoriasis and drug rash should be ruled out

Management:

- Local steroids and Ketoconazole shampoo may help induce remission.
- In severe cases systemic therapy with ketoconazole or itraconazole may help.

d. Atopic dermatitis

- May be particularly severe in HIV infected children.
- Severe pruritis and secondary bacterial infections are common complications.
- Lesions appear as poorly demarcated, erythematous, lichenified, scaly plaques in flexural areas.

e. Diaper dermatitis

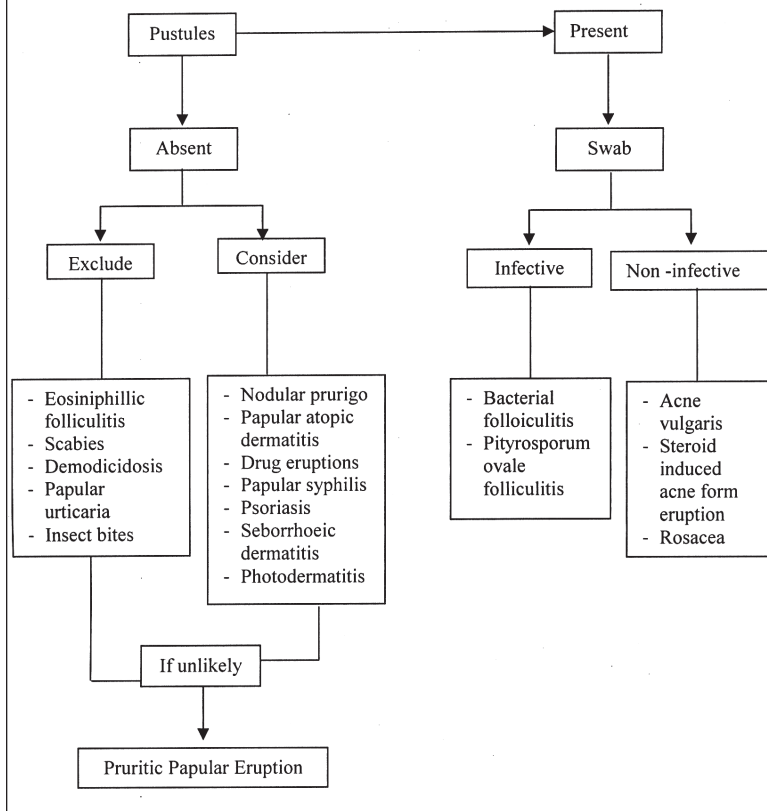
- May be particularly severe in HIV infected infants.
- Rule out and treat candidiasis and dermatitis if present.
- Proper control of concomitant diarrhea.
- Rule out underlying nutritional deficiency (especially zinc).

Cutaneous lesions rarely encountered in Indian individuals with HIV

a) Kaposi's sarcoma:

- A neoplasm of vascular endothelium.
- Presents either bluish red or brown nodules or plaques on legs, mucosa.
- Management: Chemotherapy (vincristine, vinblastine) or radiotherapy.
- HAART may induce remission.

Itchy papular or pustular eruptions in HIV



b) Bacillary angiomatosis:

- Angioma like vascular lesions on skin mucosa and internal organs.
- Caused by *Bartonella henselae*, a gram negative bacillus
- Occurs only in HIV and in no other immunodeficiency.

c) Other malignancies:

- Invasive Squamous cell carcinomas of cervix, vulva , penis arising from genital warts
- Cutaneous metastasis from lymphomas or leukemia.

‘Red Alert’ to suspect HIV - In a new patient presenting with:

- Herpes Zoster
- Genital Molluscum
- Herpes Simplex
- Oral Candidiasis
- Recurrent Itchy lesions

‘Red Alert’ for AIDS; In a known case of HIV infection:

- Multi dermatomal or recurrent Herpes zoster
- Persistent painful perianal ulcer of Herpes simplex
- Pharyngeal/oesophageal candidiasis
- Cryptococcosis: ‘Molluscum like lesions’

ART has benefited most skin lesions but some may recur during Immune Reconstitution Inflammatory Syndrome (IRIS).

IRIS and skin manifestation

Exacerbation of inflammatory lesions, worsening of existing infectious lesions or unmasking of latent cutaneous infections may be seen after starting ART.

Management:

- Continue ART.
- Treat any infection appropriately.
- Oral steroids may be needed for reducing the inflammation.
- Only in very severe /recalcitrant cases, one would be required to stop ART for a while.

17.

Other Systemic Manifestations in Children with HIV

In severely immuno-compromised children, almost any organ system may be attacked by HIV infection or opportunistic infections. Here we describe some miscellaneous common and serious manifestations.

Otitis Media and Sinusitis

As such otitis media and sinusitis are common childhood bacterial infections even in immune competent children. Episodes of sinusitis occur more frequently in HIV infected children.

Clinical manifestations, diagnosis, microbiology and management of episodes of acute otitis media (AOM), chronic recurrent otitis media and bacterial sinusitis in HIV infected and HIV uninfected children are similar.

Diagnosis of AOM

- Acute onset of fever, pain and ear discharge
- Presence of middle ear effusion (on otoscopy)

Treatment of AOM

- Amoxycillin – 45-90 mg/kg/day for 7-10 days or

- Amoxycillin/clavulanate potassium 45 / 6.5 – 90/6.5 mg/kg/day for 7-10 days
- Symptomatic management for pain and fever.

Refer to ENT specialist in case of chronic ear discharge or any other complication such as tympanic membrane perforation, mastoiditis, intracranial suppuration, cholesteatoma etc.

Ophthalmic manifestations:

- Ophthalmic disease occurs in upto 75% patients over the course of disease.
- As children rarely complain of ocular symptoms, diagnosis of serious complications (e.g. CMV retinitis) may be delayed.
- The posterior segment (vitreous, retina, choroids) is affected most commonly.
- Molluscum contagiosum on lids and conjunctiva, herpes simplex keratitis, herpes zoster ophthalmicus are common.
- In severely immune compromised children, fungi such as aspergillosis, mucor mycosis, parasites (toxoplasma gondii) and other bacteria may invade orbital organs.
- Neoplasms are rare.
- Drugs such as didanosine, ethambutol, rifabutin may cause ocular toxicity.
- CMV retinitis, immune recovery uveitis, progressive outer retinal necrosis are rare but serious manifestations and may compromise vision.

CMV retinitis

- A serious ocular infection related with HIV disease.
- Usually associated with very low CD4 counts.
- With advent of ART, occurrence of CMV retinopathy has dramatically reduced.
- Child may present with floaters and decreased vision or may

have very few visual complaints despite advanced retinitis. Therefore high index of suspicion is necessary.

- Vitreous hemorrhage, advancing retinitis and sometimes retinal detachment are serious sequel.
- Treatment - systemic ganciclovir (IV 5 mg/kg BD) – initial induction for 2-3 weeks followed by maintenance therapy (IV 5 mg/kg OD). Oral ganciclovir has been approved only for adults. Oral valganciclovir can be used instead of ganciclovir.
- All children with CMV retinitis should be given life long CMV prophylaxis with oral ganciclovir but should be monitored for adverse effects, especially bone marrow suppression. (See chapter on OI prophylaxis)

Hematological manifestations

Most HIV infected children and adolescents have abnormalities of their peripheral blood and/or haemostatic system like anemia, thrombocytopenia, neutropenia.

These could be due to

- Direct/indirect effect of HIV on hemopoiesis
- Secondary infection
 - TB
 - MAC
 - CMV
 - Histoplasma
- Dietary deficiencies
 - Iron
 - Folate
 - Cobalamin
- Drug toxicities
 - ZDV
 - Ganciclovir
 - Acyclovir
 - TMP-SMX

- Primaquine
 - Dapsone
- Immune aberrations

Anemia

- Occurs in 20-70% HIV infected children.
- Commonest causes are – chronic infection, poor nutrition and adverse effect of ARVs such as zidovudine.
- Iron deficiency is the commonest type and should be treated promptly.
- Dimorphic anemia – commonly seen in children on zidovudine.

Neutropenia

- Occurs in one third of untreated HIV infected children.
- Antineutrophil antibodies are the cause; treatment with IVIG is successful.
- Drug induced neutropenia is seen with TMP-SMX and zidovudine.

Thrombocytopenia

- Occurs in 10-20% of patients.
- Etiology could be immunologic or due to drug toxicity. ART may reverse thrombocytopenia.
- Platelet transfusion is used only to treat clinical bleeding.
- Immunosuppressants such as Azathioprine are used but should be closely supervised.

Serious hematological manifestations need to be managed in consultation with a hematologist.

Renal Disease in children with HIV

Fluid and electrolyte disorders (water, sodium, potassium), acid base disorders are fairly common especially in hospitalized children. Other manifestations are rare but may be life threatening.

Acute renal failure could be due to several reasons:

Prerenal

- Intravascular volume depletion (vomiting, diarrhea, glucocorticoid deficiency)
- Capillary leak (sepsis, hypoalbuminemia, therapy with interleukin-2, interferon- α , or interferon- γ)
- Hypotension (sepsis, HIV cardiomyopathy)
- Decreased renal blood flow (non-steroidal anti-inflammatory drugs)

Renal

- Acute tubular necrosis (ischemia, sepsis, antimicrobials, radiographic contrast, rhabdomyolysis)
- Interstitial nephritis (penicillins, ciprofloxacin, non-steroidal anti-inflammatory drugs, adenovirus, cytomegalovirus, polyomavirus, microsporidia, *Mycobacteria*)
- Rapidly progressive glomerulonephritis (immune complex glomerulonephritis, thrombotic thrombocytopenic purpura)

Postrenal

- Tubular obstruction (sulfadiazine, acyclovir, tumor lysis)
- Extrinsic ureteral and pelvic obstruction (e.g. lymphoma or massive lymphadenopathy)
- Intrinsic ureteral obstruction (e.g. stone, fungus ball due to *Candida*, blood clot, sloughed papilla, indinavir crystals)

HIV is associated with diverse range of renal disease including

- HIV associated nephropathy (HIVAN). ART is supposed to improve it.
- Complications due to infections associated with HIV
- Complications of therapy (e.g. Indinavir leading to renal calculi, tenofovir causing nephrotoxicity)

Renal manifestations should be managed in consultation with a nephrologist.

Neoplastic disease in pediatric HIV disease

Malignancies are uncommon in children

Following malignancies contribute to AIDS defining diagnosis:

- Non-Hodgkin's lymphoma (NHL) is most common of the malignancies seen with advanced disease. It should be managed in consultation with an expert.
- Cervical cancers (Ca-Cx) are rarely seen in adolescent/post adolescent girls.
- Kaposi's sarcoma is extremely rare in India.

18.

Common Opportunistic Infections (OIs) in Children with HIV

As we have seen, AIDS is characterized by opportunistic infections and certain malignancies occurring in immune compromised persons infected with HIV.

Prophylaxis (chemoprophylaxis and immunizations), early diagnosis and aggressive management of OIs as a part of HIV management have contributed to improved survival and reduced morbidity, even before ART became available.

Some important aspects with respect to pediatric HIV are:

- OIs in children often reflect primary infection rather than reactivation.
- OIs in children occur at a time when their immune system is immature.
- HIV-infected family members are often the source of horizontal transmission (e.g. TB).
- HIV-infected women co-infected with OI (e.g. CMV, HCV) are more likely to transmit infections to newborns.

It is often difficult to diagnose OIs in children because of

- their inability to describe symptoms.
- confounding of antibody-based tests by maternal transfer of antibodies.
- difficulties in diagnosis of tuberculosis as samples cannot be obtained without invasive procedures.

Many of the OIs have been described in detail in previous chapters on specific systems. The following table gives a summary of clinical manifestations and management of common OIs. (Adapted from 2006 NACO guidelines for HIV care and treatment in infants and children)

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
Mycobacterium avium complex (MAC)	<p>Fever, night sweats, weight loss, fatigue, chronic diarrhea and abdominal pain</p> <p>Laboratory findings: neutropenia, raised alkaline phosphatase or lactate dehydrogenase (LDH)</p> <p>Isolation from stool or respiratory</p>	<p>Definitive diagnosis: isolation of organism from blood, bone marrow, lymph node or specimen from normally sterile sites</p> <p>Histology demonstrating macrophage-containing acid-fast bacilli is suggestive</p>	<p>ART should be provided to restore immune function</p> <p>Treatment with at least 2 drugs: clarithromycin 7.5-15 mg/kg twice daily (max 500 mg/dose) plus ethambutol 15-25 mg/kg/day once daily (max 1 g/dose)</p> <p>Consider adding a third drug,</p>

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
	specimen does not necessarily indicate invasive disease	Culture is essential for differentiating from TB	e.g. amikacin or ciprofloxacin in severe cases Duration of treatment: at least 12 months Lifelong suppressive therapy required after initial treatment Consider delaying ART by 1-2 weeks to prevent IRIS
Pneumocystis jiroveci pneumonia (PCP)	Dry cough, tachypnoea, dyspnoea, cyanosis	Chest X-ray: bilateral diffuse parenchymal infiltrates with “ground-glass” or reticulo-granular appearance Associated with a high level of LDH Microscopy of sputum induced by bronchoalveolar lavage (BAL):	TMP/SMX 15-20 mg/kg/day of TMP in 3-4 divided doses for 21 days

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
		Gram stain — stains cyst wall brown or black; Wright stain — stains the trophozoites and intracystic sporozoites pale blue	
Candidiasis	<p>Oral candidiasis: creamy-white, curd-like patches that can easily be scraped off showing an inflamed underlying mucosa</p> <p>Esophageal candidiasis: odynophagia, dysphagia, or retrosternal pain</p> <p>Disseminated candidiasis – fever, endophthalmitis and</p>	<p>Oral candidiasis: KOH preparation demonstrates budding yeast cells</p> <p>Esophageal candidiasis: Barium swallow shows cobblestone appearance,</p> <p>Endoscopy shows small white raised plaques to elevated confluent plaques with</p>	<p>Oral candidiasis: Clotrimazole oral troches 10 g, or Nystatin 400,000-600,000 units 5 times daily for 7-14 days, or oral Fluconazole 3-6 mg/kg once daily for 7-14 days</p> <p>Esophageal candidiasis: Oral fluconazole 3-6 mg/kg IV once daily for 14-21 days, changing to oral route once the</p>

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
	cutaneous lesions	hyperaemia and extensive ulceration Disseminated infection – isolation of organism from blood culture, biopsy from skin lesion:	child starts tolerating food.
Histoplasma capsulatum	Recurrent fever, weight loss, malaise, respiratory symptoms, hepatosplenomegaly, lymphadenopathy	X-ray chest may show variety of patterns including reticulonodular, lobar or military lesions Microscopic examination of fluid/tissue sample or culture For disseminated lesions–blood culture and bone marrow	Treatment - Amphotericin B (0.5-1 mg/kg/day IV) for 3-10days followed by Itraconazol 5-12 mg/kg/day orally/IV for 12 weeks <i>For meningitis:</i> Amphotericin B for 12-16 wks followed by Itraconazole as maintenance therapy

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
		biopsy and culture Antigen detection in serum and urine	
Toxoplasmosis (Rare in children but may be seen in adolescents)	CNS toxoplasmosis may present as headache, fever, changes in mental status, seizures, psychosis and focal neurological deficits. (see color atlas) Isolated ocular toxoplasmosis is rare and is usually associated with CNS infection.	A presumptive diagnosis of CNS toxoplasmosis is done with correlating clinical symptoms, presence of toxoplasma specific IgG and presence of space occupying lesion on imaging studies of the brain especially ring-enhancing lesions in the basal ganglia and cerebral cortico-medullary junction.	Pyrimethamine-2mg /kg/day x 3 days followed by 1 mg/kg/day x 6 weeks. Sulphadiazine-25-50 mg/kg/dose 4 times daily. <i>Secondary prophylaxis-</i> Sulphadiazine (80-100 mg/kg/day in 2-4 divided doses) + pyrimethamine (1 mg/kg/day PO) + folinic acid (5 mg PO alternate day)

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
		Definitive diagnosis requires histologic or cytologic confirmation by brain biopsy	
Cryptococcosis	<p>Manifestations of meningo-encephalitis: fever, headache, altered mental status, nuchal rigidity</p> <p>Manifestations of disseminated disease: persistent fever with translucent umbilicated papules on skin which may resemble molluscum contagiosum.</p>	<p>Raised intracranial pressure, elevated cerebrospinal fluid (CSF) protein and mononuclear pleocytosis.</p> <p>India ink staining of CSF shows budding yeasts.</p> <p>Cryptococcal antigen can be detected in the CSF or serum by the latex agglutination test</p> <p>Wright stain of skin scraping</p>	<p>Induction therapy: Amphotericin B (0.7-1.5 mg/kg/day) for 2 weeks</p> <p>Consolidation therapy: Fluconazole 5-6 mg/kg/dose twice daily for 8 weeks</p> <p>Maintenance therapy: Secondary prophylaxis: Fluconazole 3-6 mg/kg/day</p>

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
		shows budding yeast	
Herpes simplex virus (HSV)	<p>HSV gingivostomatitis: fever, irritability, superficial painful ulcers in the gingival and perioral areas, and oral mucosa</p> <p>HSV encephalitis: fever, alteration of consciousness, abnormal behaviour</p>	<p>HSV gingivostomatitis is diagnosed by clinical evaluation</p> <p>HSV encephalitis is diagnosed by detection of HSV DNA in the CSF</p>	<p>HSV gingivostomatitis: oral acyclovir 20 mg/kg/dose three times daily or intravenous acyclovir 5-10 mg/kg/dose three times daily for 7-14 days</p> <p>Disseminated HSV or encephalitis: intravenous acyclovir 10 mg/kg/dose or 500 mg/m²/dose three times daily for 21 days</p>
Herpes zoster virus (HZV)	Primary varicella infection: generalized pruritic vesicular rash	<p>Use clinical features for diagnosis</p> <p>If on clinical examination</p>	Primary varicella infection: intravenous acyclovir 10 mg/kg/dose or 500 mg/m ² /

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
	Herper zoster: painful rash with fluid-filled blisters, dermatomal distribution	<p>the diagnosis is not clear then Giemsa staining (Tzanck preparation) of cell scrapings from the lesions can be done.</p> <p>These show multinucleated giant cells suggestive of Varicella zoster virus (VZV). (Note that this is also seen in HSV infection.)</p>	<p>dose three times daily for 7 days in children with moderate to severe immuno-suppression. Oral formulation should be used only in a child with mild immuno-suppression.</p> <p>Herper zoster: Oral acyclovir 20 mg/kg/dose four times daily (max 800 mg/dose) for 7 days</p>
CMV infection	CMV retinitis: young HIV-infected children are frequently asymptomatic and the infection is discovered on routine examination.	Diagnosis of CMV retinitis is based on the clinical appearance — white and yellow retinal infiltrates and associated	Intravenous ganciclovir 5 mg/kg/dose twice daily for 14-21 days followed by lifelong maintenance therapy

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
	Older children present with floaters or loss of vision	retinal haemorrhages	Oral ganciclovir 30 mg/kg every 8 hours as maintenance
	Extraocular CMV disease; e.g. CMV colitis, CMV esophagitis, CMV pneumonitis, CMV hepatitis	Extraocular CMV disease: recovery of the virus from tissues or histopathological examination of specimens demonstrates characteristic “owl’s eye” intranuclear inclusion bodies or positive staining of biopsy specimens with CMV monoclonal antibodies	therapy Valaganciclovir can be used as an alternative to IV ganciclovir
Cryptosporidiosis	Subacute or chronic watery diarrhoea often associated with cramps, nausea	Modified Kinyoun acid-fast stain of stool: small oocyst	Effective ART is the only treatment that controls persistent

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
	and vomiting Can cause cholecystitis and cholangitis	(4-6 μm in diameter) At least 3 stool samples should be examined as oocyte excretion can be intermittent	cryptosporidiosis. Supportive care includes hydration, correction of electrolyte abnormalities and nutritional supplementation Nitazoxanide is approved for treatment (age 1-3 years: 100 mg twice daily, age 4-11 years: 200 mg twice daily) or Azithromycin – Day1:10 mg/kg, Day2to10:5mg/kg
Penicilliosis	Persistent fever, anemia, hepatomegaly, generalized lymphadenopathy and translucent umbilicated papules which may resemble molluscum	Definitive diagnosis: isolation of organism from blood, bone marrow aspirate or specimens from normally	Induction therapy: Amphotericin B (0.7-1.5 mg/kg /day) for 2 weeks Consolidation therapy: Itraconazole

Opportunistic infections	Clinical and laboratory manifestations	Diagnosis	Treatment
	contagiosum. Laboratory findings: anemia, and/or thrombocytopenia	sterile sites Wright stain of skin scraping shows basophilic, spherical or oval yeast-like organisms with clear central septation (diameter 3-8 μm)	5-6 mg/ kg/ dose twice daily for 8 weeks. Maintenance therapy: Itraconazole 3-6 mg/ kg/day

19.

Fever in Children with HIV

Fever is the most common presenting complaint among HIV infected children.

It could be of infectious or non-infectious origin.

Infectious causes

Endemic infections such as malaria, typhoid fever, dengue, seasonal influenza etc. or newer concurrent epidemics such as H1N1 virus¹.

- Invasive bacterial infections –
 - Otitis media, sinusitis
 - Pneumonia
 - Meningitis
 - Urinary Tract Infection
 - Osteomyelitis, abscesses of internal organs
- Viral infections
 - Severe consequences of common viral infections such as measles and mumps.

-
1. *Currently many parts of the world including our country are in the midst of a raging H1N1 or swine origin influenza virus epidemic. One must keep such scenarios in mind and act according to the guidelines issued by the public health authorities.*

- Disseminated infections with agents such as respiratory syncytial virus, varicella, rubella.
- Pneumocystis jiroveci Pneumonia
- Tuberculosis
- OIs such as cryptococcosis, histoplasmosis, MAC
- Manifestation of advanced HIV disease

Non - Infectious causes

- Immune Reconstitution Inflammatory Syndrome
- Neoplasms

Regarding infectious causes there could be 3 patterns of presentations.

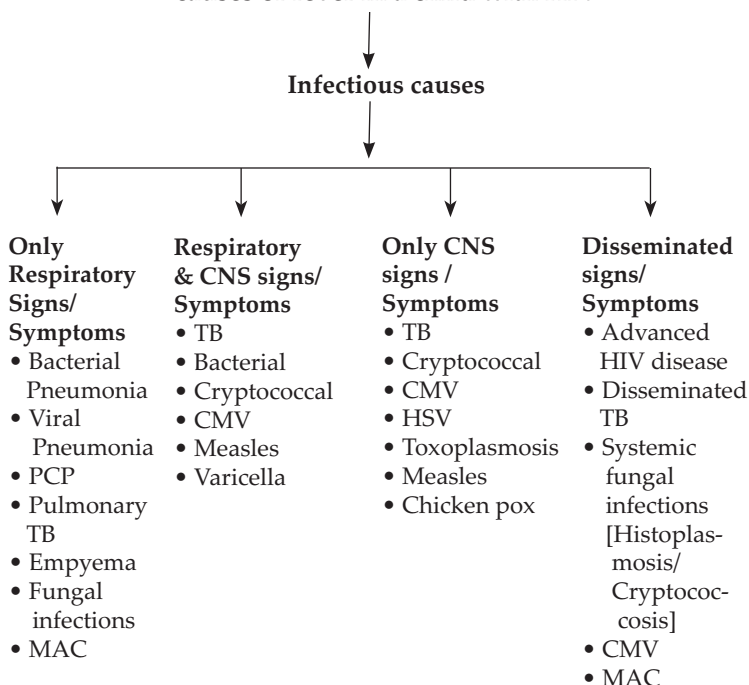
1. Common infections presenting with common manifestations – in immunocompetent HIV infected children, routine childhood infections are seen e.g. URTI/sinusitis.
2. Common infections with uncommon/severe manifestations – e.g. measles in immunocompromised children can present as aseptic meningitis.
3. Uncommon infections seen commonly in immunocompromised children e.g. PCP

Keep in mind the current epidemiological trends and situations in the community.

Following factors would guide the differential diagnosis :

1. Latest CD4 count – In case of low CD4 counts, suspect OIs.
2. If child on OI prophylaxis – Assess adherence to prophylaxis
3. If child on ART
 - i. Suspect IRIS.
 - ii. It may be drug fever.
 - iii. Assess treatment compliance to rule out treatment failure.

System wise differential diagnosis of infectious causes of fever in a child with HIV



Evaluation of a febrile child

Targeted history and thorough physical examination should be carried out.

Appropriate investigations should be done.

Apart from routine investigation, remember -

- In CNS infections, there may be persistent or recurrent fever without abnormal neurological signs. Perform lumbar puncture in case meningitis is suspected. A cranial ultrasound and/or CT scan might be beneficial.
- For finding other foci of infection, bone marrow examination and culture may give a better yield of pathogens than routine blood culture. Mycobacteraemia can be detected by bone marrow culture.

Management

- Symptomatic treatment with antipyretics (avoid use of Aspirin in children below 18 yrs [Reyes Syndrome])
- If infectious cause is suspected, put the child on broad spectrum antibiotics till such time that specific diagnosis is made.
- In case of febrile child with respiratory distress and hypoxia, start empirical PCP treatment.
- Treat specific cause once diagnosed and omit empirically prescribed medicines.

Indications for hospital admission in a febrile child

- Toxic appearance (lethargy, unexplained tachycardia or tachypnoea, hypotension)
- Increased WBC count/increases band cells on PBS
- Previous episodes of serious invasive bacterial disease or OI
- Presence of indwelling venous device

20.

Overview of Care of HIV Infected Children

Important aspects of routine care of HIV infected children include general medical care, monitoring of HIV disease progression or response to treatment, anti-retroviral treatment (ART), prophylaxis and treatment of opportunistic infections and counseling support for the child and family.

Initial evaluation

Initial evaluation is actually the beginning of a long-term dialogue and relationship between health care provider/s and the child and his/her family.

A detailed clinical history and medical examination is necessary to understand disease staging and need for prophylactic or therapeutic treatment. Initial history should also attempt the assessment of other psychosocial needs of the child and caregiver.

Key components of initial visit

- History
- Physical examination
- Laboratory evaluation
- Assessment and Plan
- Counseling

History

- Current symptoms
- Child's past medical history
 - Gestational age and birth weight
 - Infant feeding history
 - Immunization history
 - Growth and developmental history
 - Scholastic and behavioral history
 - Recurrent symptoms, serious illnesses, hospitalizations (history s/o OIs)
 - Receipt of antiretroviral drugs by the child
 - Current and past OI prophylaxis
 - Co-existing other medical conditions
 - Age of puberty and sexual history (in case of adolescents)
 - History of menstruation and pregnancy (in case of adolescent girls)
- Mother's medical history
 - Her own HIV status, disease stage and h/o ART
 - Any current OIs (especially TB)
 - H/o PMTCT interventions (prophylactic ARV, mode of delivery)
- Family history
 - The primary care provider
 - HIV status of family members including father, siblings, their disease status and history of ART
 - Family history of illness including TB
 - Foster care and adoption history if appropriate

- Social history
 - Socio-economic status of the family
 - Other care takers in the family
 - Disclosure of child's status in the family

Physical examination

Sequence in such a way that more invasive examinations are done at the end.

A complete examination of all systems with *special emphasis* on following points -

- Nutritional and growth status – *wasting*
- Developmental assessment – *developmental delay*
- Neurological examination - *Hypertonia, hyperreflexia, spasticity, rigidity*
- Detailed general physical examination
 - cutaneous manifestations - *Papular urticaria, recurrent scabies, extensive molluscum contagiosum, bruising or petechiae*
 - *unexplained clubbing and lymphadenopathy*
- Oral and ENT examination – *dental caries, stomatitis, candidiasis, angular cheilitis, otitis media, parotitis*
- Rule out active tuberculosis
- Fundoscopy if required
- Examination of genito-urinary tract (in adolescents, to rule out STI)

Laboratory evaluation

- Confirmatory testing for HIV (if necessary)
- Complete Blood Count (CBC)
- CD4-absolute, % and CD4/CD8 ratio
- LFTs, RFTs, Hepatitis B titers and VDRL
- Viral load (baseline if feasible)
- X-ray chest, ultra sonography of abdomen and imaging studies

Follow up visit protocol

A. In case of children not on ART

- I. *For children less than 2 years* - Ideally every month
 - Assess weight and development of milestones
 - Measure head circumference
 - Assess for presence of OIs - As CD4 count and viral load do not help much in identifying the rapid progressors, we have to rely on clinical indicators for the same.
 - Evaluate and counsel for adherence to TMP-SMX prophylaxis

The gap between follow ups could be extended for an asymptomatic child more than 1 year old and who has growth parameters within normal range.

- II. *For children older than 2 years :*
Follow up visit at every 3 months for an asymptomatic child with normal growth and development parameters is sufficient.

During these visits, child should be assessed for:

- Presence / history of any OI
- Weight gain and developmental milestones
- Need for TMP-SMX prophylaxis.

Laboratory investigations

- CD4/CD8 count every 6 months (If the child develops symptoms may be repeated more often)
- Other tests (CBC, biochemistry, etc.) as per the symptoms.

B. Children on ART

For initial few months of ART, monthly follow up is necessary.

Encourage care-givers to bring in the child if s/he is sick and especially during the first few months of ART, as the child may experience ART side effects, intolerance as well as may develop IRIS. Once the child is stable, the frequency of visits could be reduced.

During clinical assessment following points should be carefully evaluated:

- Worsening of existing symptoms – it may be due to treatment failure or Immune Reconstitution Inflammatory Syndrome (IRIS)
- Development of new symptoms / OI
- ARV side effects
- Need for TMP SMX prophylaxis
- Weight gain – You may have to adjust dose of ART as per the changes in the weight
- ART adherence – performing pill count is time consuming but better tool to assess and ensure adherence
- Any possible drug interactions if the child is taking any other medicine
- Do keep in mind that adolescents could be sexually active, provide safe sex counseling if required.

Laboratory investigations

- CD4/CD8 every 6 months. In case IRIS (immune reconstitution syndrome) is suspected, repeat earlier.
- CBC , LFT, RFT done every year
 - in case of specific sign and symptoms repeat earlier
 - Hb and CBC may be done more frequently in initial months of starting ZDV based ART
- Closely monitor following patients for hepatotoxicity if
 - co-infected with hepatitis B or C
 - patients who are initiated on NVP based regimens especially adolescent girls with higher CD4 counts
 - children on ATT
- Viral load – Recommended every 6 months. However in resource constrained setting, it can be done initially at 6 months after commencement of ART to document undetectable viral load.
- Pregnancy test may be required for certain girls, especially those who are going to start EFV based ART.

Family based care in pediatric HIV

As MTCT is the most common mode of transmission of infection to children, it is almost certain that mother is infected (unless child is infected by some other way). In Indian context, in majority of cases it is seen that the father is also infected. There is probability that sibling/s too are infected. If the child happens to be the index case in the family, ensure that parents and siblings are encouraged to get tested. A comprehensive family based model seems appropriate in such situation.

The burden of more than one person in the family being HIV infected is quite high. It is not only physical but also financial, psychological and social. The situation is more complicated in case one or both parents are dead. The disease is so much feared and stigmatized that relatives may be unwilling to care for infected and orphaned child. All these issues have direct or indirect implications on treatment uptake and disease progression. Health care provider must be aware of all these issues. Addressing these issues has to be a part of care and support.

As pediatric HIV is a chronic multi-systemic disease, there would be need for referrals to other sub-specialties and psychosocial services. Issues regarding shared confidentiality as well as of stigma and discrimination must be considered before such referrals.

Many children if provided with proper and timely treatment would have a long and healthy childhood and adolescence. Considering this it would be prudent to involve the child in treatment seeking right from the beginning. A child friendly clinic directed towards making the children feel comfortable is the first step in this direction.

Having said this there will be many children orphaned due to HIV. They would need to be taken care by the community, including institutions. For such institutionalized kids issues of timely nutrition and adherence to treatment are generally very nicely taken care of. However attending to their psychological needs is a huge challenge.

21.

Immunization in Children with HIV

The standard immunization schedules vary from place to place.

We must aim to provide the basic minimum immunization to HIV infected children appropriate for the national setting.

1. **General rule of thumb:** All HIV infected children should be immunized according to the routine national immunization schedule.
2. **Exception:** Withhold live vaccines (BCG, OPV, measles, MMR) for symptomatic and severely immuno-compromised children. Inactivated Polio vaccine (IPV) is available in India and should be preferred over OPV in children with HIV, although there is no evidence that routine OPV has lead to any major complications.
3. Hib vaccine is recommended to all children who are confirmed to be HIV-infected.
4. Because *Streptococcus pneumoniae* is a common cause of respiratory disease and as there is increasing resistance to antibiotics, pneumococcal vaccine is advocated.
5. Additional vaccines such as varicella, hepatitis A, influenza virus etc. may be given.

6. In general, immune-compromised children tend to have poor immunologic response to vaccines, and the same also decreases further as the disease advances. So, appropriate passive immunization should be considered if the child is directly exposed to infections such as varicella, measles or tetanus.
7. Yellow fever vaccine is a live vaccine, but is not contraindicated in HIV infected children. There is a theoretical risk of encephalitis in immune-compromised children.
8. Typhoid vaccine can be given.
9. Japanese encephalitis vaccine can be safely given, however immunological response is less in immune compromised children.
10. Vitamin A supplementation should be as per the Universal Immunization Program (UIP) schedule.

Immunization chart for children living with HIV

Age	Vaccine recommended
Birth	BCG OPV0 HepB 1
6 weeks	DTWP1/DTaP1 OPV1*/OPV1 +IPV1 Hib1 HepB2
10 weeks	DTWP2/DTaP2 OPV2/OPV2 + IPV2 Hib2
14 weeks	DTWP3/DTaP3 OPV3/OPV3 + IPV3

Age	Vaccine recommended
	Hib3 HepB3**
9 months	Measles
15-18 months	DTWP B1/DTaP B1 OPV4/OPV4 + IPV B1 Hib B1 MMR1
2 years	Typhoid [#]
5 years	DTWP B2/DTaP B2 OPV5 MMR2 ^{\$}
10 years	Tdap HPV***

* OPV alone if IPV cannot be given

** The third dose of hepatitis B can be given at 6 months

Revaccination every 3 years

\$ The second dose of MMR vaccine can be given at any time 8 weeks after the first dose

*** Only females, three doses at 0, 1-2 and 6 months

(From: GOI and IAP recommendations on immunization- 2008)

Vaccines to be given after one to one discussion with parents

Age	Vaccine
≥ 6 weeks	Rotavirus vaccine* PCV7 [#]
≥ 15 months	Varicella ^{\$}
≥ 18 months	Hepatitis A ^{**}
<hr/>	
*	Rotavirus vaccine [2/3 doses (depending on brand) at 4-8 weeks interval]
#	PCV 7 (three doses at 6, 10 and 14 weeks and 1 booster at 15-18 months)
\$	Varicella (< 13 years single dose, > 13 years two doses at 4-8 weeks interval)
**	Hepatitis A (2 doses at 6 months interval)

22.

Prophylaxis for Opportunistic Infections in Children with HIV

Remember: ART started at the right time is the best OI prophylaxis. If ART is initiated at age appropriate CD4 counts, most children might never require additional OI chemoprophylaxis.

Role of chemoprophylaxis: To prevent opportunistic infections in children with HIV, which otherwise are associated with increased morbidity and mortality.

Other measures such as general prevention advice for caregivers, e.g. hand washing, drinking clean water, washing of raw fruits and vegetables before consumption, nutritional counseling and ensuring good diet etc. are also important.

Specific chemoprophylaxis is equally crucial when the CD4 counts are below the recommended thresholds.

Primary OI prophylaxis

Prophylaxis to prevent primary infection and is provided for:

- PCP
- MAC
- TB (if there is definite possibility of exposure from a close contact)

1. PCP prophylaxis

Pneumocystis jiroveci pneumonia (PCP) remains the commonest OI and the most important cause of mortality in young children.

Drugs

TMP-SMX (Co-trimoxazole)(5/25 mg/kg/day of TMP-SMX) is the drug of choice.

Alternative regimen Dapsone (2 mg/kg once daily OR 4 mg/kg once weekly

TMP-SMX prophylaxis also prevents infection against:

- toxoplasmosis
- bacterial pneumonias
- bacterial and other diarrheas
- malaria

It is extremely cheap and definitely a cost effective intervention.

While prescribing the regimen, care providers should be explained that–

- It does not treat and cure HIV infection. It only protects from some serious life threatening infections more common to occur in immune compromised children.
- It does not replace the need for ART.
- Adherence is crucial.

- There is need for careful monitoring as some children may develop allergic reactions to TMP-SMX and sometimes bone marrow toxicities.

Indications for TMP-SMX prophylaxis

- A. All HIV-exposed children: Starting at 4-6 weeks after birth and maintained until exclusion of HIV infection.
- B. For children with confirmed HIV infection
 - Age < 1 year: all infants regardless of CD4 percent or clinical status.
 - Age 1-5 years:
 - WHO stages 2, 3 & 4 regardless of CD4%
 - Any WHO stage and CD4 <25%
 - Age ≥ 6 years:
 - Any WHO clinical stage and CD4 < 350 cells/mm³
 - WHO stage 3 or 4 regardless of CD4 count
 - All children being treated for pulmonary tuberculosis

When to discontinue prophylaxis?

- HIV exposed children: when HIV infection has been ruled out
- HIV infected infants and children < 5years: Continue until age 5 years irrespective of clinical and immune response
- HIV infected infants and children > 5years: Discontinue only when CD4 counts > 350 cells/mm³ on 2 occasions at least 3 months apart

2. Mycobacterium Tuberculosis

Indications

All HIV infected children below 6 yrs of age, exposed to active TB cases, particularly household contacts, regardless of CD4 counts (need to exclude clinical disease by physical examination and CXR)

Recommended Regimen

INH (5 mg/kg) (max 300 mg) daily for 6–9 months

3. *Mycobacterium avium* complex (MAC)

Indications

- CD4 count <50 cells/mm³ in >6-year-old
- CD4 count <75 cells/mm³ in 2–6-year-old
- CD4 count <500 cells/mm³ in 1–2-year-old
- CD4 count <750 cells/mm³ in <1-year-old

Stop when CD4 level is maintained above threshold level for more than 3 months

Recommended Regimen

- Clarithromycin 7.5 mg/kg/dose (max 500 mg) twice daily OR
- Azithromycin 20 mg/kg (max 1200 mg) once weekly OR
- Azithromycin 5 mg/kg (max 250 mg) once daily

Secondary OI prophylaxis

Guidelines for secondary prophylaxis to prevent recurrence of OIs in children

For children who have a history of OIs, secondary prophylaxis has been recommended **for life** to prevent recurrence in some conditions:

1. ***Pneumocystis jiroveci* Pneumonia** – Drug regimen same as primary prophylaxis
2. ***Mycobacterium Tuberculosis*** – Secondary prophylaxis is not recommended
3. ***Mycobacterium Avium Complex*** – Drug regimen:
 - a. Clarithromycin 7.5 mg/kg/dose (max. 500 mg) twice daily plus ethambutol 15 mg/kg/dose (max. 800 mg) daily OR
 - b. Azithromycin 5 mg/kg/dose (max. 250 mg) plus ethambutol 15 mg/kg/dose (max. 800 mg) daily

4. *Cryptococcus neoformans* AND *Coccidioides immitis*
Drug regimen:
 - a. Fluconazole 3-6 mg/kg/once daily OR
 - b. Itraconazole 2-5 mg/kg once daily
5. *Histoplasma capsulatum* AND *Penicillium marneffei*
Drug regimen:
 - a. Itraconazole 2-5 mg/kg once daily
6. *Toxoplasma gondii*
Drug regimen:
 - a. Sulfadiazine 85-120 mg/kg/day in divided doses 2-4 times/day **plus** pyrimethamine 1 mg/kg (max. 25 mg) once daily **plus** leucovorin 5 mg every 3 days
 - b. Clindamycin 20-30 mg/kg/day in 4 divided doses **plus** pyrimethamine and leucovorin as above OR
 - c. TMP-SMX as for PCP

Discontinuation of secondary prophylaxis:

The safety of discontinuing secondary prophylaxis among HIV-infected children has not been studied extensively. In adults, discontinuation of secondary prophylaxis is suggested if there is sufficient and persistent immune restoration. Many authorities do discontinue secondary prophylaxis even in children considering similar criteria.

23.

Overview of Anti-Retroviral Treatment (ART) in Children

ART is probably the best thing that has happened in the field of medicine in recent past. It has helped us to change a completely bleak picture of an invariably fatal disease merely a decade ago, to a chronic manageable medical disease. All children living with HIV, at some point of time, will need taking treatment to help control their HIV infection.

The goal of ART is to slow or stop HIV from replicating. This, in turn, helps to slow or stop the destruction of the immune system and the progression of HIV disease.

Antiretrovirals (ARVs) are used to treat HIV, however they do not cure HIV. As on today, ART once started has to be taken life long.

Goals of anti-retroviral treatment in children

1. Clinical Goals

- Extend life expectancy and quality of life in HIV infected individuals.
- Prevent disease progression
- Reduce risk of OIs
- Achieve optimum growth and development

2. Virological Goals

- Reduce viral load to the lowest level possible and maintain as such ['Undetectable plasma viral load' (< 25 or 400 HIV RNA copies/ml) depending upon the assay used]
- Limit development of ARV resistance.

3. Immunological Goal

Restore and preserve immunologic function by maintaining CD4 cell counts.

4. Epidemiological Goal

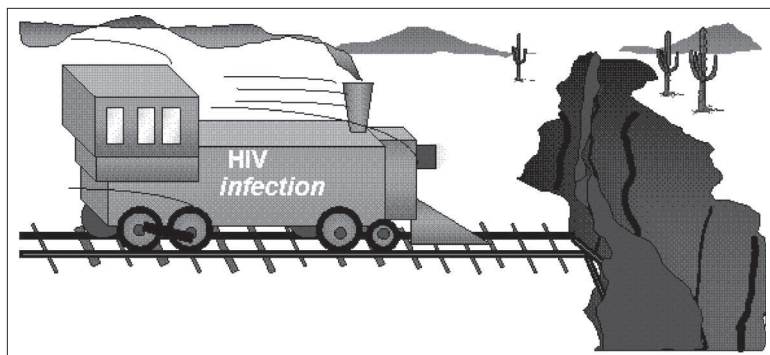
Reduce transmission of HIV to others.

Challenges in achieving these goals are

- Maximizing drug adherence
- Avoiding adverse drug reactions
- Avoiding drugs to which resistance has been demonstrated and also preserving future options for ART, in case drug resistance develops

To simplify the concept of action of ARVs, here is an illustrative cartoon.

Development of *AIDS* is like an impending train wreck. High speed (high viral load) and short distance from wreckage site (low CD4 count) increase the chance of impending accident. ART would reduce the speed of train (viral load), which would maintain the distance



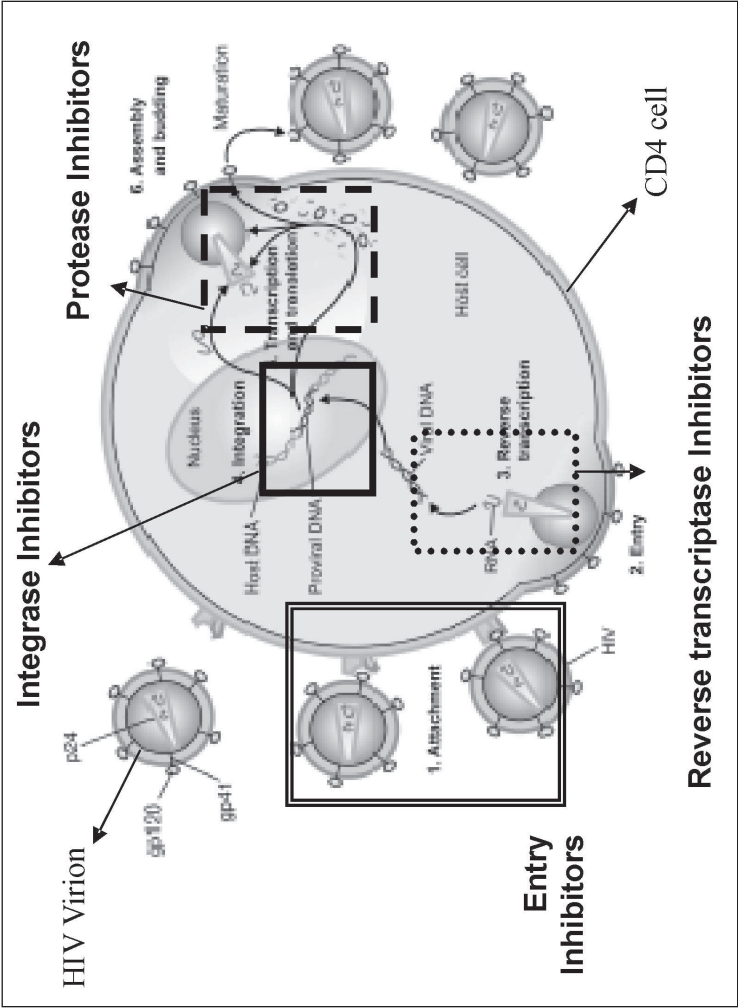
Viral Load = Speed of the train; CD4+ T lymphocyte Count = Distance from site of doom (J. Coffin, XI International Conf. on AIDS, Vancouver, 1996)

(CD4 count), thereby reducing the risk of accident (morbidity and mortality) significantly.

Revisiting our understanding of HIV life cycle here will help us to understand different anti-retroviral medicines.

ARV medicines act at different steps in the life cycle of HIV. The following figure illustrates various stages in the life cycle of HIV where different types of ARVs act.

HIV life cycle and different types of ARVs: (Please refer to the color atlas for structure of HIV)



Different classes of ARVs and available drugs

Nucleoside/Nucleotide Reverse transcriptase Inhibitors (NRTI/NtRTI)

- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zidovudine (AZT/ZDV)
- Zalcitabine (ddC)

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Nevirapine (NVP)
- Efavirenz (EFV)
- Etravir (ETR)
- Delavirdine (DLV)

Protease Inhibitors (PIs)

- Amprenavir (APV)
- Atazanavir (ATV)
- Darunavir (DRV)
- Fosamprenavir (F-APV)
- Indinavir (LDV)
- Lopinavir/Ritonavir (LPV/r)
- Nelfinavir (NFV)
- Ritonavir (RTV)
- Saquinavir (SQV)
- Tipranavir (TPV)

Fusion Inhibitors (FI)

- Enfuvirtide (T-20)

Chemokine Coreceptor

Antagonists (Entry Inhibitors)

- Maraviro (MVC)

Integrase Inhibitors

- Raltegravir (RGV)
-

Currently only some NRTIs, NNRTIs and PIs are available in India.

What is ART or highly active antiretroviral therapy (HAART)?

- Highly active antiretroviral therapy is a combination of 3 or more active ARV drugs from at least 2 different classes of ARVs
- 2 NRTIs are always used and are called the backbone of ART. HAART may be combination of
 - 2 NRTIs + NNRTI
 - 2 NRTIs + PI

As more and more molecules are being introduced and studies to understand their relative safety, efficiency and cost effectiveness are underway, the actual recommendations are always in flux. One must keep updating about the most recent guidelines as and when they are published. Guidelines are published by many organizations; e.g. DHHS, BHIVA, European association, WHO, NACO etc. One should be aware of the rationale behind these and adopt those appropriate.

24.

When to Start ART?

The decision 'when to start ART' in children depends not only on clinical and immunological criteria but also on multiple psychosocial issues. Care taker's as well as child's preparedness, availability of pediatric formulations, type of care taker (parents/other relatives/institution), access to treatment in terms of distance from health care facility, affordability etc. play an important role.

In general the focus of treatment has been **shifting towards immune preservation than immune restoration** and therefore towards starting ART earlier and before immune deficiency is advanced. Quite a few trials among adults have demonstrated advantage of initiating ART earlier than current recommendations (i.e. when CD4 cell counts are below 350 and not wait until they go below 250/cmm.) These have got reflected in most recent WHO guidelines for treatment of adults and adolescents (2009). The recommendations regarding these points in pediatric age group are still in flux. As pediatric HIV management is still evolving, the guidelines for the same keep being updated as newer evidence comes up. It is best to keep one updated about the current guidelines. We are providing current guidelines here. We will also discuss results of a few recent and important studies.

When to start?

It is essential that HIV status in the child is confirmed. The criteria of when to start ART are age dependent. Usually percent CD4 counts (CD4 %) are used to guide the decision as absolute lymphocyte counts vary greatly during early years and usually stabilize at adult levels by the age of 6 years.

It is necessary to

- Treat opportunistic infection if any, prior to initiation of ART
- Screen for TB before starting ART

Recent data from a South African clinical trial¹ demonstrated significant reduction in early mortality if treatment was started in the first year (as compared to delayed initiation of ART). Based on this study, **newer recommendations suggest initiation of therapy for all infants (age <12 months) regardless of clinical status, CD4 percentage or viral load.**

The revised recommendations by WHO (2008) are as follows:

- All infants under 12 months of age with confirmed HIV infection should be started on antiretroviral therapy, irrespective of clinical or immunological stage.
- For children age 12 months or older, clinical and immunological thresholds should be used to identify those who need to start antiretroviral therapy.
 - All children in clinical **stage 3 and 4** should be put on treatment irrespective of CD4 counts.
 - Children having TB, LIP, OHL and thrombocytopenia, to start the treatment based on CD4 counts.

1. Early antiretroviral therapy and mortality among HIV infected infants; Violari et.al; N. Engl J. Med. 2008, Nov. 20; 359 (21), 2233-34

Criteria to start ART (based on CD4 count and %)

Age	Infants <12 months	12 months through 35 months	36 months through 59 months	5 years or over
% CD4	All	< 20	< 20	< 15
Absolute CD4*	All	< 750mm ³	< 350mm ³	As in adults (<250)

* Absolute CD4 count is naturally less constant and more age dependent than %CD4; it is not therefore appropriate to define a single threshold.

But as there are only 25-30% rapid progressors, this also means over-treating large number of children who are not rapid progressors. The issue is complex, especially when we have very little experience about long-term metabolic side effects of ART in children. The decision could be based on viral loads, CD4 % and clinical assessment if resources permit.

Special consideration – HIV TB co-infection

- In HIV-infected children with TB, **initiation of TB treatment is the priority.**
- The potential for IRIS should be considered while starting ART, particularly in those with low CD4 values.
- Provide TMP-SMX prophylaxis to all HIV infected children with TB

For recommendations for the timing of ART following initiation of anti TB treatment (ATT), please refer chapter on TB in children with HIV.

Before Contemplating Anti-Retroviral Treatment (ART): Wait and think.

We have to keep it in mind that:

- As yet there is no 'cure' for HIV infection
- ART has to be taken life long
- Adherence to treatment is extremely important
- It requires regular monitoring by the health care provider

These factors demand in depth discussions with parents or caretakers of the child during pre-treatment-initiation counseling sessions in such a way that before starting ART they understand the issues. Around 2 to 3 counseling visits before starting ART are usually needed to confirm patients' preparedness for ART and ensure long-term adherence to the therapy. These issues are even more important in case of children than in adults, as for most children ART will be administered by a care taker. Prepare the care taker for the task. We usually say that the parents/guardians should be given time (at least 15 days) to think over these matters before starting ART. As children grow up, at appropriate time and in appropriate manner, they should be actively involved in counseling sessions to ensure adherence.

Issues regarding preparing the care takers and the child before starting ART are discussed in details in Chapter 30.

Remember starting ART is never an emergency. Give adequate space to the patient/care taker to cope with the decision.

Detailed history and examination including clinical staging are mandatory.

25.

What To Start? : Constructing an ARV Regimen

Factors to be considered while determining choice of first line regimen:

- age of the child
- availability of fixed dose combinations/pediatric formulations
- cost of therapy and storage requirements
- risk of short and long term adverse effects
- presence of co-morbidities
- possible drug interaction and pill burden etc.

Non-availability of pediatric formulations for many antiretroviral drugs limits the choice significantly.

Recommended first line regimen

The regimen should consist of at least 3 drugs from 2 different classes of medicines.

Recommended preferred first line regimen in our country is
2 NRTIs + 1 NNRTI

Constructing a first line regimen

2 nucleoside reverse transcriptase inhibitors (NRTIs) + 1 non-nucleoside reverse transcriptase inhibitor (NNRTI)

Step 1: Select NRTI to be used in combination with lamivudine (3TC) (which has proven efficacy and excellent safety profile).

It could be zidovudine (ZDV) or abacavir or stavudine (d4T)

Table showing comparison of ZDV and d4T

NRTI	Pros	Cons
Zidovudine (ZDV) (preferred NRTI if Hb ≥ 7.5 g/dl)	<ul style="list-style-type: none">– It causes less lipodystrophy and lactic acidosis than stavudine.– Liquid formulation does not need refrigeration.	<ul style="list-style-type: none">– Has more initial gastrointestinal (GI) side-effects.– A large volume of ZDV liquid formulation is often poorly tolerated.– Severe anemia and neutropenia can occur. CBC monitoring before and after treatment is recommended.– Liquid formulation comes in glass bottles and is sensitive to light.

Stavudine (d4T)	<ul style="list-style-type: none"> – Usually very well tolerated. – Causes less GI side-effects and anemia than ZDV. 	<ul style="list-style-type: none"> – Causes more lipodystrophy, lactic acidosis and peripheral neuropathy than ZDV. – Liquid formulation needs refrigeration.
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- **Lamivudine (3TC)** is a potent NRTI with an excellent record of efficacy, safety and tolerability in HIV-infected children and is a core component of the dual NRTI backbone of therapy. It is usually given twice daily in children and has been incorporated into a number of fixed dose combinations.
- **ZDV** is the drug of choice for first line regimen. However, for a child with Hb <7.5 g/dl, d4T should be considered.
- Because long-term use of **d4T** may cause lipodystrophy, consider switching from d4T to ZDV once anemia is treated. Current directive is to phase out stavudine gradually.
- **Abacavir** is not available as pediatric formulation, is costly and can cause fatal hypersensitivity in 3% children. However other toxicities such as lipodystrophy / hematological toxicity are less likely.
- **Tenofovir (TDF)** - Because of concerns about the limited data on safety and toxicity, (i.e. bone mineralization and potential renal toxicity) use of TDF in children is not encouraged until further data becomes available. (Recommended only in adolescents-Tanner stage IV)

Following NRTI drug combinations **should be avoided**

- Stavudine + Zidovudine - both drugs work through common metabolic pathways
- Stavudine + Didanosine - these drugs have overlapping toxicities

- Tenofovir + Lamivudine + Abacavir- Associated with a high incidence of early virological failure
- Tenofovir + Lamivudine + Didanosine - Associated with a high incidence of early virological failure
- Tenofovir + Didanosine + NNRTI- Associated with a high incidence of early virological failure

Step 2: Select 1 NNRTI from Nevirapine (NVP) or Efavirenz (EFV)

Table showing comparison of NVP and EFV

1 NNRTI	Pros	Cons
Nevirapine (NVP)	<ul style="list-style-type: none"> – Can be given to children at any age – Does not have a teratogenic effect – Is available in both pill and liquid formulation and does not require refrigeration – Is part of several three drug fixed dose combinations that can be used in older children 	<ul style="list-style-type: none"> – It causes rash more often than EFV – The rash may be severe and life-threatening – Is associated with the rare but potentially life-threatening risk of hepatotoxicity – For adolescent girls, the risk of NVP-associated hepatotoxicity or severe rash increases with a CD4 count >250 cells/mm³ – Rifampicin lowers the NVP level more than EFV

<p>Efavirenz (EFV)</p>	<ul style="list-style-type: none"> – Causes less rash and hepatotoxicity than NVP, the rash is generally mild. – EFV levels are less affected by rifampicin and can be considered the NNRTI of choice in children receiving rifampicin-based anti-TB treatment – For children unable to swallow pills, an EFV capsule can be opened and added to liquids or a small amount of food 	<ul style="list-style-type: none"> – Can only be used in children ≥ 3 years of age and >10kg wt. – Transient CNS disturbance can occur in 26–36% of children; therefore, EFV should be avoided in children with a history of severe psychiatric illness – Has a teratogenic effect and should be avoided in adolescent girls with the potential for pregnancy – Is not available in liquid formulation in most countries – Is more expensive than NVP
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- NNRTIs may lower the drug levels of estrogen-based contraceptives. A condom or diaphragm should always be used to prevent HIV transmission. Adolescent girls in the reproductive age group taking EFV should avoid pregnancy.

Special scenarios

A. What to start in a child co-infected with TB?

Consider following

- Rifampicin has drug interaction with NVP and almost all PIs. Rifampicin lowers drug level of NVP by 20-58% and EFV by 25%. In children, there is no information on appropriate dosing of NVP and EFV when used with rifampicin.
- Apart from rifampicin, other anti-TB drugs do not have drug interactions with ART.
- There is no drug interaction between NRTI and rifampicin.
- Both Anti-TB drugs and NNRTI (especially NVP) can cause hepatotoxicity;

(Refer Annexure 6 for various drug interactions of ARVs)

If ART is to be given along with ATT

1. Rifampicin *should be part of ATT* especially during the first 2 months of treatment. Consideration to change from rifampicin-based to non-rifampicin-based ATT during the maintenance phase is up to the discretion of the treating physician.
2. *If ART is to be started in a child on rifampicin containing ATT*
 - a. ART should be initiated between 2-8 weeks of ATT in children with clinical stage 3 or 4 disease.
 - b. Use efavirenz (2 NRTI + EFV) if the child > 3 yrs and/ > 10 kg. NVP should be avoided.
 - c. Following completion of anti TB treatment, we may change from EFV to NVP; 2 weeks after stopping ATT.
 - d. If efavirenz can not be used, consider using abacavir but remember it is not available in pediatric formulation, is costly and 3 NRTI are known to be less efficacious.
 - e. As an alternative regimen, NVP can be used with rifampicin in the usual dosages and closely monitored for hepatotoxicity.

3. *If the child is already on ART and needs to be put on rifampicin containing ATT*
- If the ART regimen contains EFV, continue the same.
 - If the ART regimen contains NVP, switch to EFV if child is > 3 yrs old and weigh is > 10 kg.

B. Child with Hepatitis B

Hepatitis B and HIV co-infection may often be seen in children who have transfusion transmitted infection and adolescents who may be injection drug users.

In these children and adolescents, exercise caution with the drugs that cause hepatotoxicity, especially zidovudine and didanosine amongst the NRTIs, nevirapine amongst NNRTIs and PIs in general (especially higher doses of ritonavir).

The desired choice of drugs would be lamivudine and tenofovir. However keep in mind limitations of TDF

C. ART in infants with prior ARV exposure through PMTCT interventions or breast feeding

For HIV infected infants with a history of exposure to single dose nevirapine or NNRTI containing maternal ART or preventive ARV regimens, a PI based triple ART regimen should be started. Where PIs are not available , affordable or feasible NVP based therapy should be used.

List of medicines currently available in pediatric formulations

Currently following drugs are available as pediatric formulations:

NRTIs:

Zidovudine - syrup: 10 mg/ml, capsules: 100 / 250 mg, tablet: 300mg

Lamivudine - oral solution: 10 mg/ml, tablet: 150 mg

Stavudine - oral solution: 1 mg/ml, capsules: 15 / 20 / 30

NNRTIs:

Nevirapine - oral suspension: 10 mg/ml, tablet: 200 mg
 Efavirenz - syrup: 30 mg/ml, capsules: 200 mg / 600 mg

PIs:

Lopinavir/ritonavir - Oral solution: 80 mg /ml lopinavir and 20 mg / ml ritonavir Oral solution contains 42% alcohol, Capsules: 133.3mg lopinavir and 33.3 mg ritonavir.

Fixed dose combinations available in pediatric dosages

SLN 6 – D4T (6 mg), 3TC (30 mg), NVP (50 mg)

SLN 12 - D4T (12 mg), 3TC (60 mg), NVP (100 mg)

SLN 5 - D4T (5 mg), 3TC (20 mg), NVP (35 mg)

SLN10 - D4T (10 mg), 3TC (40 mg), NVP (70 mg)

Common antiretroviral drugs for children, their doses and side effects:

ARV Drugs	Age /Weight bands	Dose	Adverse effects
Stavudine (d4T/STV)	< 30 kg 30 kg to 60 kg	1 mg / kg / dose BD 30 mg /dose BD	Lactic acidosis with hepatic steatosis, peripheral neuropathy, lipodystrophy
Zidovudine (ZDV/AZT)	< 4 weeks 4 week - 13 yrs > 13 yrs	4 mg / kg / dose BD 240 mg/ m ² /dose BD maximum dose 300mg/dose BD 300mg/dose BD	Anemia and neutropenia, GI intolerance, hepatitis, lactic acidosis

Lamivudine (LMV)	< 30 days > 30 days	2 mg/kg/dose BD 4 mg/kg/dose BD Maximum dose: 150 mg/dose BD	Pancreatitis (seen in children, rare in adults)
Nevirapine (NVP)	15 -30 days >30 days to 13 years > 13 years	5 mg/kg/dose OD x 2 weeks then 120 mg/m ² /dose BD x 2 weeks, then 200 mg/m ² /dose BD 120 mg/ m ² /dose OD x 2 weeks, then 120-200mg/m ² /dose BD 200 mg/dose OD x 2 weeks, then BD	Early hepatotoxicity, skin rash
Abacavir (ABC)	Only prescribed for > 3 months of age < 16 yrs or < 37.5 kg > 16 yrs or > 37.5 kg	8 mg/kg/dose BD 300 mg/dose BD	Hypersensitivity reaction, nausea, vomiting, rarely lactic acidosis

Efavirenz (EFV)	Only for children >3 yrs, weight > 10 kg 10 to 15 kg 15 to < 20 kg 20 to < 25 kg 25 to < 33 kg 33 to < 40 kg > 40 kg	200 mg/dose OD 250 mg/dose OD 300 mg/dose OD 350 mg/dose OD 400 mg/dose OD Maximum dose: 600 mg/dose OD	Skin rash, CNS side effects like dizziness, impaired concentration, somnolence, hallucinations and vivid dreams, rarely hepatotoxicity
Nelfinavir (NFV)	< 1 yr > 1 yr to 13 yrs > 13 yrs	50 mg/kg/dose TDS <i>or</i> 75 mg/kg/dose BD 55 to 65 mg/kg/dose BD Maximum dose : 1250 mg/dose BD	Diarrhea, lipodystrophy, abdominal pain, and rashes, rarely diabetes

Lopinavir/ ritonavir (LPV/r)	> 6 mths to 12 yrs	225 mg/ m ² LPV with 57.5 mg/ m ² of ritonavir/ dose, BD	Gastrointestinal upset and diarrhea, insulin resistance, fat accumulation, hyperlipidemia, increased levels of triglycerides and cholesterol, exacerbation or new onset of diabetes mellitus
	or Weight based dosing 7 to < 15 kg wt.	12 mg/kg LPV and 3 mg/kg ritonavir/dose, BD	
	15 to 40 kg wt.	10 mg/kg LPV and 5 mg/kg ritonavir/dose, BD	
	> 40 kg wt.	Maximum dose: 400 mg LPV/100 mg ritonavir BD	
Saquinavir/r (SQV/r)	Use only in weight > 25 kg	Approved dosage in adults: SQV 1000 mg/ RTV 100 mg BD There is no data in children. For children weighing >25 kg, the approved adult dose can be used	Diarrhea, abdominal pain, headache, nausea ,hepatic toxicity, fat accumulation, photosensitivity, rarely diabetes

Atazanavir (ATV)	Used only in > 6 years of age and weight >15 kg	15-20 kg:8.5mg/kg boosted with ritonavir 4mg/kg OD >20 kg: 7mg/kg boosted with ritonavir 4mg/kg OD	Jaundice, I st degree AV block, GI intolerance, lipodystrophy
Tinofovir (TDF)	Used only in adolescents	300 mg OD (adjust doses in renal impairment)	Nephrotoxicity, decreased bone mineral density

(Refer Annexure 7 and 8 for details of pediatric formulations and dosages of ARVs and drug storage)

SL combinations in the same proportion but without NVP are also available. They are used for initial phase or for use with EFV. Soon fixed dose pediatric formulations of ZLN are likely to be available.

The dosages are adjusted for the weight band. Individual physician may use other FDCs for convenience of pill burden.

- *Syrups and oral solutions* remain necessary for very young children but for older children it is preferred to give solid formulations.
- Because of unavailability or high cost of pediatric formulations some may use ***split / crushed adult FDC tablets***. This can result in the under dosing or overdosing of children, and may lead to an increased risk of resistance or toxicity. Moreover, the doses cannot easily be adjusted as the children grow. The use of tablet cutters is beneficial but it is preferable not to cut tablets to fractions below a half.

- Current adult three-drug formulations do not contain adequate doses of Nevirapine for children. So if these tablets are split for use, additional Nevirapine must be provided.

Calculation of dosages based on body surface area

Several of the antiretroviral drugs require calculation of the child's body surface area (BSA) prior to prescription of ART. This may be done by

- Using Mosteller's formula - $BSA \text{ (in M}^2\text{)} = \frac{\sqrt{\text{height in cm} \times \text{weight in kg}}}{3600}$
- Using nomogram (refer Annexure 9)
- Specially designed programs that can be stored on the desktops of the computers are also available. (*Grandir growing up program calcul-ART* <http://www.remed.org/calcul.art-fr-1.xls>)

Effective antiretroviral therapy leads to fairly rapid gains in weight and height, body surface area should be re-calculated at each subsequent follow-up visit to ensure that the child is receiving adequate doses of antiretroviral medication as it grows.

Protease inhibitors are better reserved for second line regimens.

For details please refer to Chapter 'When to consider change in ART?'

Recently NACO has revised its guidelines regarding use of FDCs in children and suggested that only SLN 6 should be used at ART centers

Drug	Strength in child tablet (mg)	3 - 5.9 kg	6 - 9.9 kg	10 - 11.9 kg	12 - 13.9 kg	14 - 14.9 kg	15 - 16.9 kg	17 - 19.9 kg	20 - 24.9 kg	Strength in adult tablet	25 - 29.9 kg	30 - 34.9 kg
d4T/3TC/ NVP	6/30/50	1	1.5	2	2	2.5	2.5	2.5	3	30 / 150 / 200	1	1
d4T/3TC	6/30	1	1.5	2	2	2.5	2.5	2.5	3	30/150	1	1

Weight Bands in Kilograms with Dosing of Various Formulations

Weight Band in kgs	Zidovudine Syrup (50 mg /5 ml) 12 mg/m sq twice daily	Lamivudine syrup (50 mg /5 ml) 4 mg/kg twice daily	Stavudine Syrup (1 mg /ml) 1 mg /kg twice daily	Nevirapine syrup (50 mg /5ml) <8 yrs 7 mg/kg	Nevirapine syrup (50mg/5ml) > 8 yrs 4 mg /kg	FDC- 10 d4T-10 3TC- 40 NVP- 70	FDC-6 d4T-6 3TC- 30 NVP- 50	FDC- 30 d4T-30 3TC- 150 NVP- 200	Strength	NVP Lead in-50 mg /ml
5 - 6.9	7 ml	2 ml	5 ml	4 ml	-	1	1	-		2 ml
7 - 9.9	9 ml	3 ml	8 ml	6 ml	-	1.5	1.5	-		3 ml
10 - 11.9	12 ml	4 ml	11 ml	8 ml	-	1.5	1.5		3 ml	4 ml
12 - 14.9	14 ml	5 ml	13.5 ml	9 ml		1.5	2	0.5	4 ml	5 ml
15 - 16.9	15 ml	6 ml	15.5 ml	10 ml	10 ml	2	2	0.5	5 ml	6 ml
17 - 19.9	17 ml	7 ml	18 ml		11 ml	2.5	2.5	1	5 ml	7 ml
20 - 24.9	20 ml	9 ml	22 ml		13 ml	2.5	2.5	1	8 ml	9 ml
25 - 30	25 ml	11 ml	25 ml		15 ml	3	3	1	10 ml	11 ml

26.

ARV Side Effects and Toxicities

As is the case with any other medicines, ARVs also have side effects and toxicities.

As the treatment is life long it is important to ensure that ARVs do not affect the quality of life while ensuring survival.

Adherence to treatment is *the* most important factor influencing success of ART and drug side effects/toxicities are one of the most important reason leading to non-adherence.

The events may vary in severity from mild to severe and may at times be life- threatening.

They may appear early or late.

Drug-related toxicity may be acute, sub-acute or chronic.

The toxicities may be mild, moderate or severe¹.

Some distinct adverse effects common with certain antiretroviral drugs or drug classes:

1. Refer Annexure 10 for severity and grading of different ARV toxicities.

Acute and subacute:

- *GI disturbances* - commonly associated with *zidovudine* and *PIs*
- *Headache* - *zidovudine*, *nevirapine*
- *Hematological events* associated with drug induced bone marrow suppression, most common with *zidovudine*
- *Allergic reactions* such as skin rashes and hypersensitivity reactions (occasionally even toxic epidermal necrolysis (TEN)), more common with the *nevirapine* and *abacavir*. Therefore nevirapine is always started with a lead in dose (once a day) for first 2 weeks.
- *CNS toxicity* in the form of hallucinations and psychosis associated with *efavirenz*
- *Hepatotoxicity* may be life threatening. (Especially if ALT is >5 times the normal upper limit)

Chronic

- *Mitochondrial dysfunction* including lactic acidosis, hepatic toxicity, pancreatitis, and peripheral neuropathy primarily seen with the *NRTIs* (more so with stavudine). Generally rare in children
- *Lipodystrophy and metabolic abnormalities* primarily seen with *stavudine* and *PIs*
- *Potential teratogenicity* seen with *efavirenz*. (The drug is therefore avoided in first trimester of pregnancy and post pubertal adolescent girls who are sexually active and not using adequate contraception. It is also avoided in young children less than 3 years old.)

Usual timings of appearance of adverse drug events

- Within first few weeks –
 - allergic reactions
 - GI toxicities (nausea, vomiting and diarrhea)
 - liver toxicities
 - efavirenz induced CNS toxicity
- Four weeks onwards –
 - hematologic toxicity (anemia/neutropenia)
- Six months onwards –

- hepatic toxicity
- pancreatitis
- peripheral neuropathy
- lipoatrophy
- myopathy
- lipodystrophy
- fat accumulation
- insulin resistance
- diabetes
- osteopenia.
- One year onwards –
 - nephrolithiasis (seen with indinavir)
 - renal tubular dysfunction (seen with tenofovir)

Lactic acidosis is not commonly seen in children but it is potentially life threatening. It can occur at any time but more commonly seen after few months of therapy.

Managing ARV drug toxicities

- Management differs as per the severity of the event.
- *Dose reduction is not always an option in the setting of antiretroviral toxicity.*
- In case of **mild to moderate transient toxicities** the drug may be continued however they may affect the adherence badly. Counseling support for adherence and **symptomatic treatment** is necessary in such cases.
- **Severe life threatening toxicities** require **immediate cessation** of therapy of all ARV drugs. A modified regimen is to be introduced only after managing the event. In case of severe toxicities **DO NOT** rechallenge with the same medicine.
- Some moderate toxicities (e.g. lipodystrophy or peripheral neuropathy) do require substitution.

(Refer Annexure 10 for severity and grading of different ARV toxicities)

Serious acute and chronic toxicities due to ARV drugs that may require therapy modification: clinical presentation, laboratory abnormalities and implications for ART Management

Possible clinical manifestations (Most common ARV drug(s) associated with the toxicity)	Possible laboratory abnormalities	Implications for antiretroviral drug treatment
Acute Serious Adverse Reactions		
Acute Symptomatic Hepatitis (NNRTI class, particularly NVP, more rarely EFV; NRTIs or PI class)		
<ul style="list-style-type: none"> • Jaundice • Liver enlargement • Gastrointestinal symptoms • Fatigue, anorexia • May have hypersensitivity component (rash, fever, systemic symptoms), usually occurs within 6-8 weeks • May have accompanying lactic acidosis if secondary to NRTI drug 	<ul style="list-style-type: none"> • Elevated transaminases • Elevated bilirubin 	<ul style="list-style-type: none"> • Discontinue all ARV until symptoms resolve • Monitor transaminases, bilirubin • If receiving NVP, it should NOT be readministered to the patient in future • Once symptoms resolve, either <ul style="list-style-type: none"> • restart ART with change to alternative ARV (if on NVP regimen, this is required); or • restart current ART regimen with close observation; if symptoms recur, substitute an alternative ARV

Acute Pancreatitis (NRTI class, particularly d4T, ddI; more rarely 3TC)		
<ul style="list-style-type: none"> • Severe nausea and vomiting • Severe abdominal pain • May have accompanying lactic acidosis (see below) 	<ul style="list-style-type: none"> • Elevated pancreatic amylase • Elevated lipase 	<ul style="list-style-type: none"> • Discontinue all ARVs until symptoms resolve • If possible, monitor serum amylase, lipase • Once symptoms resolve, restart ART with substitution of an alternative NRTI, preferably one without pancreatic toxicity
Hypersensitivity Reaction (ABC or NVP)		
<ul style="list-style-type: none"> • NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, with or without rash • ABC: Combination of acute onset of both respiratory and gastrointestinal symptoms including fever, fatigue, myalgia, nausea, vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnea; rash 	<ul style="list-style-type: none"> • Elevated transaminases • Elevated eosinophil count 	<ul style="list-style-type: none"> • Immediately discontinue all ARVs until symptoms resolve • NVP or ABC should NOT be readministered to the patient in future • Once symptoms resolve, restart ART with substitution of an alternative ARV for ABC or NVP

Lactic Acidosis (NRTI class, particularly d4T)

<ul style="list-style-type: none">• Generalized fatigue and weakness• Gastrointestinal features (nausea, vomiting, diarrhea, abdominal pain, hepatomegaly, anorexia, poor weight gain and/or sudden unexplained weight loss)• May have hepatitis or pancreatitis• Respiratory features (tachypnea and dyspnea)• Neurological symptoms (including motor weakness).	<ul style="list-style-type: none">• Increased anion gap• Raised lactic acid levels• elevated aminotransferase• Elevated CPK• Elevated LDH	<ul style="list-style-type: none">• Discontinue all ARVs until symptoms resolve• Symptoms associated with lactic acidosis may continue or worsen despite discontinuation of ART• Once symptoms resolve, restart ART with substitution of an alternative NRTI with lower mitochondrial toxicity risk (eg. ABC or AZT)
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Severe Rash/Stevens-Johnson Syndrome (NNRTI class, particularly NVP, less common EFV)

<ul style="list-style-type: none"> • Rash usually occurs during first 6-8 weeks of treatment • Mild to moderate rash: erythematous, maculopapular, confluent, most often on the body and arms, with no systemic symptoms • Severe rash: extensive rash with moist desquamation, angioedema, or serum sickness-like reaction; or a rash with constitutional findings such as fever, oral lesions, blistering, facial edema, conjunctivitis • Life-threatening Stevens Johnson Syndrome or toxic epidermal necrolysis 	<ul style="list-style-type: none"> • Elevated aminotransferases 	<ul style="list-style-type: none"> • If mild or moderate rash, can continue ART without interruption but close observation • For severe or life-threatening rash, discontinue all ARVs until symptoms resolve • NVP should NOT be re-administered • Once symptoms resolve, restart ART with substitution of an alternative ARV for NVP • Observe carefully if substituted with EFV
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Severe, Life-Threatening Anemia (ZDV)		
<ul style="list-style-type: none"> • Severe pallor, tachycardia • Significant fatigue • Congestive heart failure 	<ul style="list-style-type: none"> • Low haemoglobin 	<ul style="list-style-type: none"> • symptomatic treatment (e.g. transfusion), discontinue AZT only and substitute an alternative NRTI
Severe neutropaenia (ZDV)		
<ul style="list-style-type: none"> • Sepsis/infection 	<ul style="list-style-type: none"> • Low neutrophil count 	<ul style="list-style-type: none"> • discontinue AZT only and substitute an alternative NRTI
Chronic Late Serious Adverse Reactions		
Lipodystrophy/Metabolic Syndrome (d4T; PIs)		
<ul style="list-style-type: none"> • Fat loss and/or fat accumulation in distinct regions of the body: <ul style="list-style-type: none"> • Increased fat around the abdomen, buffalo hump, breast hypertrophy • Fat loss from limbs, buttocks, and face • Insulin resistance, including diabetes mellitus • Potential risk for later coronary artery disease 	<ul style="list-style-type: none"> • Hypertriglyceridaemia; • Hypercholesterolaemia; • Low HDL levels • Hyperglycaemia 	<ul style="list-style-type: none"> • Substitution of ABC or AZT for d4T • Substitution of an NNRTI for a PI may decrease serum lipid abnormalities

Severe Peripheral Neuropathy (d4T, ddI; more rarely 3TC)		
<ul style="list-style-type: none"> • Pain, tingling, numbness of hands or feet; refusal to walk • Distal sensory loss • Mild muscle weakness and areflexia can occur 	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • Stop suspect NRTI only and substitute a different NRTI that is not associated with neurotoxicity • Symptoms may take several weeks to resolve

Adapted from 'Management of HIV infection and ART in infants and children' a clinical manual by WHO, 2006.

27.

Immune Reconstitution Inflammatory Syndrome (IRIS)

Many children have paradoxical worsening in the initial period after commencing ART. This leads to considerable morbidity and mortality. This is associated with rapid recovery of the baseline severe immunodeficiency – and therefore is called Immune Reconstitution Inflammatory Syndrome (IRIS).

Definition

A collection of signs and symptoms resulting from regaining the ability to mount an effective immune response to antigens or organisms, resulting as a consequence of immune recovery after starting ART.

Frequency

IRIS is seen in approximately 10% of all patients initiating ART.

It is more common (up to 25%) among patients initiating ART with very low CD4 cell count or severe clinical disease (WHO clinical stage 3 or 4).

It occurs typically within 2-12 weeks of initiation of ART but may present later.

It is usually associated with rapid decline in plasma viral loads and increase in CD4 counts.

Signs and symptoms

- Unexpected deterioration of clinical status soon after commencing ART.
- Unmasking of sub-clinical infections such as TB, which presents as new active disease and development of abscess at BCG vaccination site.
- Worsening of co-existing infections such as flare of hepatitis B or C.

Common IRIS events seen with different infectious agents and their clinical expressions:

- *Mycobacterium tuberculosis* - fever, lymphadenopathy, pneumonitis, pleural effusion, lung abscess, expanding CNS lesion
- *Mycobacterium avium complex (MAC)* - lymphadenitis, pneumonitis, endobronchial lesions, osteomyelitis, septic arthritis, perispinal abscess, Addison's disease, peritonitis, skin lesions, ileitis, colitis, hepatosplenomegaly
- *Cryptococcus neoformans* - meningitis, necrotizing pneumonia with nodules and mediastinitis, skin abscess, spinal cord lesion
- *CMV* - retinitis
- *Herpes simplex (HSV)* - erosive lesions
- *Hepatitis B and C (HBV/HCV)* - hepatitis flare
- *Human papilloma virus (HPV)* - warts
- *Histoplasma capsulatum* - pulmonary lesion, adenitis, skin lesions
- *Molluscum contagiosum* - increased skin lesions
- *Pneumocystis jirovecii* - progressive pneumonia, ARDS
- *Toxoplasma gondii* - encephalitis - rare

Management

- Continue ART if the patient can tolerate it.
- Treat the OI.
- In most cases the symptoms of IRIS resolve after a few weeks, however some reactions can be severe or life-threatening and may require a short course of corticosteroid treatment to suppress exaggerated inflammatory responses.

Prednisone 0.5-1mg/kg/day for 5-10 days is suggested in moderate to severe cases of IRIS.

As these events occur after initiating ART, they must be differentiated from deterioration of disease and adverse drug reactions. Following table provides an idea about differential diagnosis.

Differential diagnosis of common clinical events developing during first 6 months of ART

Symptoms	Side effects of ARV or OI Prophylaxis	Immune reconstitution inflammatory syndrome (IRIS)
Nausea, vomiting	ART: <ul style="list-style-type: none">• ZDV, usually self-limiting after 2 weeks OI prophylaxis: <ul style="list-style-type: none">• Cotrimoxazole or INH	Hepatitis B and C Suspect if nausea, vomiting plus jaundice.
Abdominal or flank pain, and/or Jaundice	ART: <ul style="list-style-type: none">• d4T or ddI may cause pancreatitis.• NVP (and EFV less commonly) may cause liver dysfunctions which require stopping these drugs. OI prophylaxis: <ul style="list-style-type: none">• Cotrimoxazole or INH.	Hepatitis B and C Suspect if nausea, vomiting plus jaundice

Diarrhoea	ART: <ul style="list-style-type: none"> NFV commonly causes diarrhea 	MAC or CMV may cause diarrhea.
Headache	ART: <ul style="list-style-type: none"> ZDV or EFV usually self-limiting but can last 4-8 weeks. 	Assess for toxoplasmosis and cryptococcal meningitis
Fever	ART: <ul style="list-style-type: none"> ABC hypersensitive reaction or NVP adverse drug reaction 	MAC, TB, CMV, <i>Cryptococcus neoformans</i> , herpes zoster
Cough, difficulty in breathing	ART: <ul style="list-style-type: none"> NRTIs-associated lactic acidosis 	PCP, TB, fungal or bacterial pneumonia
Fatigue, pallor	ART: <ul style="list-style-type: none"> ZDV, which is usually developed during 4 to 6 weeks after initiation 	Suspect MAC if fever, fatigue and anaemia.
Skin rash, itch	ART: <ul style="list-style-type: none"> NVP or ABC Should assess carefully and consider stopping the drug in case of severe reaction. EFV rash is often self limiting. OI prophylaxis: <ul style="list-style-type: none"> Cotrimoxazole or INH 	Skin conditions can flare up due to IRIS in the first 3 months of ART - Herpes simplex and zoster - Papilloma virus (warts) - Fungal infections - Atopic dermatitis

28.

When to Consider Change in ART?

Treatment change may be required in case of

- Treatment failure
- Drug toxicities
- Possible drug-drug interactions

Treatment failure could be due to drug resistance; which can be primary (due to infection with resistant strain) or acquired.

Factors influencing emergence of drug resistance¹:

- Prior exposure to ARVs as a part of PMTCT programs (especially to single dose Nevirapine)
- Prior exposure to irrational ARV regimens
- Inappropriate dosing due to compromises made for non availability of pediatric formulations
- Inadequate dosing due to lack of adjustments for rapidly increasing weights and heights in children
- Food interactions due to different infant feeding practices
- Adherence related issues

1. Refer Annexure 11 for further understanding of drug resistance.

Evaluating ART response includes assessment of clinical, immunological and virological parameters at regular intervals.

Treatment failure should be suspected in case of children with no improvement or deterioration in these parameters in spite of good adherence and good nutritional support after ART.

Treatment failure can be defined as follows:

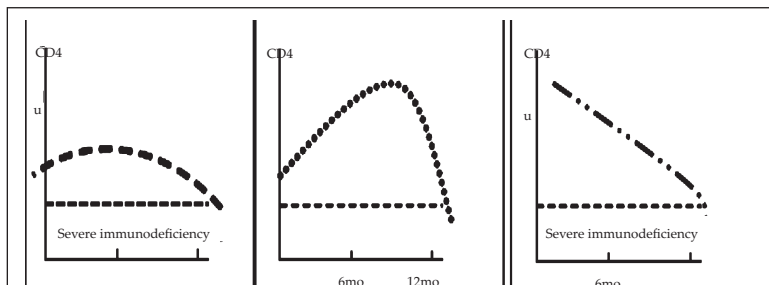
Virological failure

- Less than a minimally acceptable virologic response after 8-12 weeks of therapy. For children receiving HAART, such a response is defined as less than 10 fold decrease from baseline HIV RNA levels.
- HIV RNA not suppressed to undetectable levels after 4-6 months of ART.
- Repeated detection of HIV RNA in children who initially had undetectable levels in response to ART. Frequent evaluations needed in case of viral load <5000 copies/ml. Repeatedly detectable and increasing level indicate resistance.
- Substantial reproducible increase in plasma viremia from the nadir of suppression defined as
 - For children less than 2 years old, an increase more than 5 fold copies/ml
 - For children more than 2 years old, an increase of more than 3 fold copies/ml.

Immunological failure

- Return of CD4 cell count to pre-therapy baseline or below, after initial immune recovery, without any other concomitant infection to explain transient CD4 cell decrease
- A greater than 50% fall from on therapy CD4 cells peak level without any other concomitant infection to explain transient CD4 cell decrease.

Types of immunological failure



Type 1

Type 2

Type 3

Type 1 - Development of age-related severe immuno-deficiency after initial immune recovery

Type 2 - New progressive age-related severe immunodeficiency, confirmed with at least one subsequent CD4 measurement

Type 3 - Rapid rate of decline to below threshold of age-related severe immuno-deficiency

Clinical failure:

- Clinical disease progression with progressive neuro-developmental deterioration
- Growth failure despite adequate nutritional support
- Development of an opportunistic infection or malignancy, when the drugs have been given sufficient time (at least for six months) to induce a protective degree of immune restoration. This needs to be differentiated from immune reconstitution syndrome (IRIS)

Importance of early detection of treatment failure

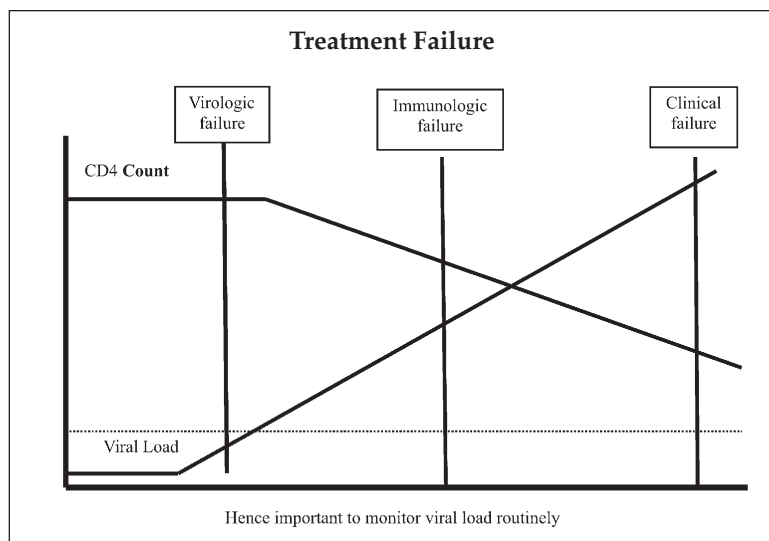
Most guidelines for resource poor settings consider that first line ART should be continued as long as possible because second line treatment

will not be feasible, accessible and affordable to all and also there will be no third line treatment to follow. However in the best interest of the patient it would be better to diagnose treatment failure as early as possible.

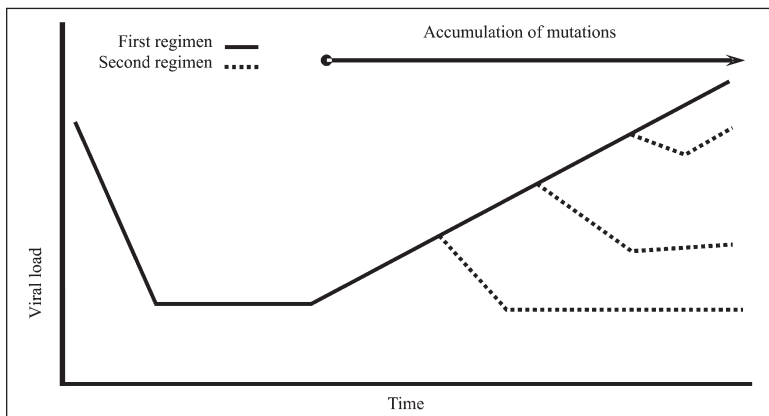
As discussed earlier, the virus develops resistance due to mutations and such mutations go on accumulating which in turn would jeopardize future options further.

As illustrated in the following graph, virological failure sets in first followed by immunological and clinical failure.

It would be disastrous if we keep on waiting till clinical failure sets in. Ideal would be to identify virological failure as early as possible. As we do not regularly monitor viral loads in most of the cases, it is



Timing of Treatment Switch



essential that immunological monitoring is done extremely regularly. At the first instance of probable failure CD4 counts should be repeated within 1-3 months for confirmation of failure. If confirmed further work up (viral load and drug resistance testing) could be done if there is possibility of switching to second line of treatment. If this is not possible it is preferable to continue the failing regimen.

Change in first line ART regimen is done for different reasons

1. Treatment substitution – When a medicine in the regimen is replaced by another one from the same class because of drug toxicity (e.g. ZDV is replaced by stavudine because of ZDV induced anemia).
2. Treatment switch – When first line regimen is changed because of treatment failure.
3. Treatment fortification – When a medicine is added to working regimen.

4. Rescue/Salvage therapy is difficult in children. This applies to patients with virological failure and exposed to all three classes of ARVs. Try to construct a regimen based on the drug resistance report, so that there are at least 3 partially active drugs.

Remember switching to second line is not an emergency

Plan before switching to second line regimen

- It needs to be ensured that adherence to therapy has been assessed and considered to be adequate prior to considering switching to second-line regimen.
- Differentiation of opportunistic infections from immune reconstitution syndrome is important.
- In considering changing treatment because of growth failure, it should be ensured that the child is not failing to grow due to lack of adequate nutrition and that any intercurrent infections have been treated and resolved.
- Pulmonary or lymph node TB, clinical stage 3 conditions, may not be an indication of treatment failure, and thus not require consideration of second-line therapy; response to tuberculosis therapy should be used to evaluate the need for switching of therapy.
- Adherence must be investigated and supportive mechanisms reinforced prior to any change in regimen. These cases should be managed by expert HIV pediatrician with full counseling and/or NGO support.
- A failing regimen usually retains some anti- HIV activity, therefore in general- a child should continue the failing regimen until he/ she is ready to switch to second-line.
- Ensure that the child is on appropriate OI prophylaxis.

We have said that ideally, treatment failure should be picked up as early as possible and not after there is clinical deterioration. However,

WHO guidelines as well as national guidelines are designed for public health program. Therefore the basis of switching to second line is switching late. The following staging system helps in timing this switch appropriately.

WHO Pediatric Clinical Staging System to guide decision-making regarding **switching to second-line therapy** for treatment failure:

Clinical stages in this table refer to the WHO clinical stage as per revised classification *while on ART* (a new or recurrent stage at the time of evaluating the infant or child on ART)

WHO clinical stage on ART	Management options
T1	<ul style="list-style-type: none"> • Do not switch to other regimen • Maintain scheduled follow up visits including CD4
T2	<ul style="list-style-type: none"> • Treat and manage staging event • Do not switch to new regimen • Assess and offer adherence support • Assess nutritional status and offer support • Schedule earlier visit for clinical review and consider CD4
T3	<ul style="list-style-type: none"> • Treat and manage staging event and monitor response • Check if on treatment 24 weeks or more • Assess and offer adherence support • Assess nutritional status and offer support • Check CD4 - where available • Consider switching regimen • Institute more frequent follow up

- T4
- Treat and manage staging event
 - Check if on treatment 24 weeks or more
 - Assess and offer adherence support
 - Assess nutritional status and offer support
 - Document CD4 - where available
 - Switch regimen
-

Factors influencing options for second line regimens:

- Delayed diagnosis of treatment failure and late switching leading to accumulation of more mutations, especially thymidine analogue mutations (TAMs)
- Fewer medicines approved for pediatric use
- Non-availability of newer options
- Lack of guidelines appropriate for use in Indian (middle income country) settings
- Costs
- Drug side effects

Problems with available guidelines:

- Drawn largely from WHO guidelines, but defining treatment failure and determining switch points is in flux
- Other guidelines rely heavily upon virologic as well as genotyping criteria
- Overdependence on virologic criteria may lead to 'over' switching
- Efficacy of second line regimens constructed empirically based on previous drug history is yet to be established
- There could be a disconnect between immunologic failure and virologic failure
- Limited data about genotyping patterns

Second line therapy after failure of NNRTI based regimens:

- 2 NRTI with boosted PI is most preferred regimen

- Difficult to choose optimal NRTI backbone as extended use may have already compromised their efficacy
- Tenofovir recommended only for Tanner stage IV and above, therefore problems with younger children
- Newer drugs: new classes, new drugs may become available in future
- Salvage therapy for multi-class resistance

Constructing second line regimen

After establishing treatment failure for first line we must select the correct second line treatment that would last long. Compromising at this stage may prove disastrous. Remember, as of now, there is no third line ART available for most of our patients.

Guiding principles while selecting second line regimen

- Ideally change all medicines currently being used. But if this is not possible due to limited options, change at least 2 ARV drugs. Change of one drug or addition of a single drug to a failing regimen is suboptimal.
- The new regimen should contain at least 3 medications.
- The potential for cross-resistance between antiretroviral drugs should be given due consideration.
- In children with neurodevelopmental signs of clinical failure, consider drugs with ability to penetrate CNS.
- Take into consideration all concomitant medications for possible drug interactions.
- Whenever possible the decision should be guided by reliable drug resistance data. Though the test is extremely costly, as the second line treatment is costly too (especially if it is to be paid for by the patient), this may prove cost effective. Remember that resistance testing should be requisitioned while the patient is still on the failing regimen.

- It would be worthwhile to ensure that there is adequate viral suppression at the end of 6 months after switching to second line therapy.

Constructing second line treatment:

- *If first-line regimen was 2 NRTIs + NNRTI*

change to

2 new NRTIs plus boosted PI

2 new NRTIs: ABC + ddI (if first-line was ZDV or d4T + 3TC + NVP/EFZ) or

ddI + ZDV (if first-line was ABC + 3TC + NVP/EFZ)

plus a (boosted) Protease Inhibitor (LPV/r or NFV)

(Tenofovir has been recommended in post pubertal or tanner stage 4 adolescents as a preferred NRTI for first line regimen so can be used in second line. It is not recommended in children, tanner stage 1 – 3 adolescents due to lack of pediatric dosing data and concern related to bone toxicity.)

- *If first-line regimen was 3 NRTIs (ZDV or d4T) + 3TC + ABC*

change to

1 new NRTI (ddI) + NNRTI (NVP/EFZ) + PI (LPV/r or NFV)

29.

HIV Counseling in Pediatric Age Group

Counseling children with HIV has a totally different context.

- Children almost never identify counseling as their need.
- HIV counseling for children is different from that for adults in form, content and nature.
- Everyone else from the family might know, but the child does not know about the HIV status.
- The schedule and order of counseling has to be adapted according to the age, mental status, clinical status and level of compliance.
- Counseling is meant for children but provided to parents as well.
- Care providers should never out-step parents or guardians as they are the ones in charge day in and day out.

Counseling young children especially in setting of HIV is a completely different kind of challenge for counselors and health professionals. An asymptomatic child is a 'normal' child but the issues regarding adherence to the treatment and disclosure are crucial and call for development of extremely good rapport. The responsibility to develop healthy and extremely un-stressful communication lies with

the medical care provider and the parents. Disclosure, adherence and age appropriate issues (e. g. adolescence) are required to be dealt during counseling.

Content of counseling

Issues such as risk assessment, pre-test messages, post-test counseling etc. are generally less relevant here as in most cases it is mother to child transmission and there is no need to disclose this. There is little chance that the child could comprehend the pre and post test messages.

The most crucial aspect remains adherence to investigations and treatment protocols. Many times it may confront us before complete disclosure. From the health angle, ART adherence is the most important factor determining long-term prognosis.

As the child grows other issues would also arise. The issues are discussed in following chapters.

Adherence related counseling to child should start when the child starts taking medicines if given in his/her hands. Before that only parents are counseled about adherence. Though older children should take responsibility of taking medication that is prescribed, parents should understand that adherence is best when the treatment is supervised. It has been observed that adherence to such prolonged treatment is always enhanced when there is another person responsible to oversee it. In a sense the treatment needs to be directly observed (DOT). Involving the child at an appropriate time actually reinforces adherence. The strict scheduling guidelines, side effects and the need to take multiple (at times unpalatable) medications are issues not easy to execute. The health care team, family and friends are vital components of the success in adhering to treatment.

Barriers to adherence in children:

1. Lack of access to refills,
2. Insufficient food along with which the pills are consumed.
3. Inability to get to the clinic for scheduled appointments because of various reasons such as
 - Preoccupation with pre-exam studies and examination scheduled on the dates
 - Lack of relative/friend to accompany
 - Fear of stigmatization from friends, relatives and acquaintances
 - Problems with transportation
 - Lack of a personal support system.
 - Illness of the child
 - Illness of parents

These issues should be discussed either with the parent and/or with the child in pre-ART visit and then are reiterated according to the situation at every follow up visit.

The interventions to ensure adherence are to be designed by health-care providers and family members with love and compassion for the child. While designing or implementing intervention tools-

- They should be seen not as an additional burden but something that adds fun to their lives.
- Something from the daily routine affable to the child could be linked to taking medicines.
- The plan for taking medicines regularly should be evaluated at every follow up visit.
- Patients should be educated to understand results of good adherence and identify problems of non-adherence as well as adverse events related to the medications.
- As children are almost always dependant on parents; the health, financial status and behavior of the parents affect adherence.

But the most important factor is the communication of parents with the child. If there is lack of communication the adherence is almost certain to get hampered.

As a health care provider, what can we do?

- Health care providers should help developing a schedule that has cues for remembering to take medications (e.g. brushing of teeth every morning could be used as a cue to take medicines every morning).
- Parents need to be educated to intervene appropriately if child refuses to take the medication. Coercion and/or enticement/bribery are not recommended. These promote short-term compliance but would never lead to long-term adherence. Parents should be explained that if child refuses to take the medications be firm and not panic. They should never cajole the child to take the medications. The child should simply not be allowed to do anything until the medicines are consumed. Children should be explained in very gentle way that taking medication is an inevitable part of their daily routine. Motivational tools such as booklets written in child friendly language and having attractive illustrations, can do wonders¹. Small film clips prepared for the very purpose and personal medication calendars are found to be useful.
- The children relate medicines with their experience of the health care providers whatever good or bad. Therefore a friendly relation of the entire health care team with the child matters a lot. Our experience shows that a compassionate doctor can increase child's readiness for the medicines manifold.

1. Prayas has prepared a small booklet in Marathi '*Doctorkakankade gelyawar*' (Visiting a doctor uncle) for this purpose.

30.

Preparation Before Starting ART

Preparing the caregiver

- The parents should have the essential knowledge regarding HIV infection and treatment; which could include knowing-
 - HIV is not transmitted through day to day household interactions.
 - Regular clinical as well as laboratory monitoring is essential for being vigilant to prevent opportunistic infections or treat if any.
 - There is no complete cure available for HIV as yet.
 - The available treatment i.e. ART, has to be taken extremely regularly.
 - ART reduces morbidity and mortality significantly.
 - ART has some side effects. Most of them get resolved after initial few months. But serious ones need to be reported immediately.
- The parents should be committed from within for doing whatever that is needed for the care of the child/ren. Care includes nutrition, parenting, education, clinical care including OI prevention, correctly mixing/measuring and administration of the selected

ART regimen, adherence with medication, disclosure and emotional comfort of the child.

- Parents should assume that to ensure compliance to medicines is their primary responsibility. Even if they are confident that their child will take medicines regularly, direct observation of drug intake is a good policy.

Preparation of the child

- Explain why they need to take ART by using culturally and age-appropriate explanations.
- Ready them and ensuring they agree to take ART (depending on their level of maturity but mostly in children >6 years). The acceptance to the treatment is an important issue that influences adherence.
- Assess the caregiver/child's understanding of the reason for taking ART.
- The child should understand dose, time and food requirements regarding the medicine.
- We need to tell the child regarding anticipated treatment response and probable side effects of ART.
- Assess the factors that may affect adherence and work with the caregiver and child in finding solutions for these anticipated problems.
- Assess the readiness for disclosure of HIV status. Disclosure is not a prerequisite for starting ART but is encouraged when the caregiver is ready and the child is felt to be mature enough and can keep secrets.
- Preparing for and performing disclosure is a process that takes time. (Issues regarding disclosure are described in the next chapter).

31.

Disclosure in Pediatric HIV

In case of children the issue of disclosure has three aspects

- 1. Disclosure of the serostatus to the child**
- 2. Disclosure of the parents' serostatus to the child**
- 3. Disclosure by the child about serostatus to others**

1. Disclosure of the serostatus to the child

The story of disclosure of a child's infection mostly starts with the disclosure of the child's status to the parent/s. Many parents could take their own infection in a stride but were afraid even to listen about their child's status. They keep postponing the testing of their children. This could invite unbearable implications.

It is our experience that many parents try to elude the disclosure of the infection to their HIV infected children as long as possible. Many times parents who avoid disclosure until their children are in their teens often experience many negative consequences. Teenagers in such situations are likely to have more risky behaviors and turbulent relationships especially with the parents.

Every person is entitled to know his/her disease or infection and also has some control over dissemination of the information to others. But when it comes to children, all other family members and even some of the neighbors may know about it except the child. The situation *per se* is inevitable when the child is young. The commonest implication is that the child faces stigma and discrimination without understanding and knowing why. Sometimes the child listens something from others and then questions parents. This is certainly an embarrassing situation for the parents. Parents then try to avoid the answers and get nervous. After sensing the odd responses, children may either shut down or some even try exploiting the situation.

To understand regarding one's infection and to have control over disclosure to others is the basic right of any individual. The violation of this right in any manner, for any reason or intention is detrimental in the long run. Parents must gather whatever courage they need and disclose so as to prepare the child for coming to terms with the facts of his/her life at some point of time.

The reason behind writing this is basically to assure parents and health care providers that our experience shows that disclosure, if done rightly and courageously has almost always had extremely positive impact. It is also to assure them that, most importantly, if counseled well all parents, even from different backgrounds, can do it.

While treating this chronic but now medically manageable disease of the child and the parent/s, health care providers may overlook the process of preparation of the parents for disclosure. The preparation of parents in some cases may need long hours of counseling and demand patience. At the same time as a counselor or as a health care provider we should always keep in mind not to overstep the rights of parents. Ultimately they are the ones who are going to face the implications. We should never consider that the decision regarding

disclosing to the child could be done without a nod from the parents. We could tell, suggest, counsel, discuss but should never insist or order parents for disclosure. Disclosure if done hastily and halfheartedly could be detrimental rather than beneficial.

Concerns faced by parents when they decide to disclose to children:

1. Would the child be able to bear the burden of the family secret? Would s/he break open and disclose to the society? Or will s/he experience anxiety and fear about his/her own health and contagion?
2. Almost every infected adult at some point of time has passed through the wave of suicidal thoughts. Would the child too lose desire to live life?
3. Would people around discriminate the child? Children always like to have people around and if they face stigmatization, would they retaliate and hate parents?
4. Parents feel that they are the source of the infection to their children and thus feel the guilt too. But would the child blame them for the same?

Parents go through four stages regarding disclosure.

- **No disclosure phase** - the parents decide from within that they do not want to and would never disclose to the children. Counselors have experienced that majority of parents at some point of time are at this stage.
- **Tentative phase** - Parents understand the problems of nondisclosure, though are ignorant or inattentive about the advantages of the gentle, intentional disclosure. They start thinking if they are or would be ready to disclose.
- **Decision phase** - Parents understand the importance of the disclosure, but since the fear and hesitance exists, they do not start moving towards it. They try to understand the 'when, how and what' of disclosure. They ask questions to counselors and

medical care providers. They almost always want to explore whether the counselors are offering to take the responsibility of the disclosure. Counseling for disclosure is an ongoing process and the health care provider needs to work along with parents at every visit. Ideally parents should be the ones to disclose information to the child.

- ***Disclosure phase*** - Here the actual disclosure occurs.

Disclosure in children is a long process and will require time. Disclosure to children should be done in following steps

- Encouraging them to ask questions,
- Providing truthful answers and
- Making the child understand that they can come back with more questions at any time.

If the process is started at younger age then the child and the parent, both get more space to cope with it. One cannot do the disclose when the child is very young. It is extremely difficult if started in adolescence. There could be partial age specific disclosure in the beginning and as

Partial disclosure aims at describing what's happening to the body and what treatment will help to resolve this, rather than naming the virus or illness. Appropriate techniques such as puppets could be used. This can facilitate the expression of the child and increase the quality of disclosure. Even when the actual disclosure process is not started, the child should be made aware about the medical/surgical procedures the child is going to undergo.

Complete disclosure involves open discussion about the virus, infection and all other issues relating to HIV infection. This could be done together with the child and parent/caregiver.

the child grows and his/her understanding increases and matures, the process could move further towards complete disclosure.

Ideally disclosure should start around age of five years keeping in mind the child's intellectual and emotional maturity. The disclosure can avail enough time for the elaborate course. Many times it is experienced (especially in a country like ours) that parents rarely treat their children age appropriately. They consider their son/daughter to be always a child and always too young to understand the facts. Health care professional's responsibility in such situation is to prepare them for disclosing to the child before it is too late. For the convenience of the parents and the health care workers a list of issues according to the age of the children is given at the end of this chapter. The parents should do the complete disclosure before the child reaches adolescence. Regarding adolescent's own HIV status, the American Academy of Pediatrics states that adolescents should know their diagnosis in all cases. That way teen are fully informed of their health status and can make informed decisions.

2. Disclosure of the parent's serostatus to the child

Is it essential at all? There are multiple answers to this question and all are right in their own way. If the parents do not want to disclose for any reason, irrespective of the child's status, then it is their call and we should support their decision. But it is our experience that only those parents who are dependant on their children financially or emotionally, decide to disclose to those children who are not infected. But when the child is infected and the parents disclose regarding the child's infection they should talk about their infection too. This stands true even for uninfected sibling of infected child, especially if the age difference is less than 10 years. This gives the child a kind of support, as s/he or his/her sibling is not alone to bear the brunt.

Many health care providers believe that parents must disclose to their children irrespective of the serostatus of the children. They believe that it should be made obligatory for the parents as the child is going to face the implications one way or the other. This had some sense before the era of ART. But now, when parents can remain fit for many years and they can lead a normal symptom-free life with almost normal life expectancy and so the children are not going to face any disastrous implications then there seems no need why they should disclose to children. The only caution is to remain prepared for any eventuality if the child finds it out at some point of time.

3. Disclosure by the child about serostatus to others

This problem has two aspects- inadvertent, unknowing disclosure to others by a child or conscious disclosure. Young children living with HIV (YLH) have to face the decision about whom else to tell about their serostatus. Telling somebody is often experienced as an apparently independent motive. Studies show that majorities of youth have disclosed to their family members and many have disclosed to close friends, some even disclose it to short acquaintance such as person sitting next in a bus. Disclosing to others is mostly associated with positive outcomes especially when the decision is made consciously. However, stigma surrounding HIV/AIDS makes people more cautious about disclosure. As a form of stigma management, YLH often are selective about when and whom they tell. They thus protect themselves against negative reactions and social isolation. It is seen that teens those are able to find a good circle of support, including people who are aware and accepting of their diagnosis, have greater self-esteem and more positive outcomes.

Once HIV-infected youth begin sexual activity, they enter a realm where they have responsibilities towards their sexual partners. Whether it should be mandatory for HIV-positive people to disclose their status to sexual partners is widely debated. No matter what

the law requires, partners need to have the confidence and trust to disclose their status. The youth should feel a moral obligation to disclose their HIV status so their partners are aware of the risk of transmission. YLH should be supported through these decisions and provided with alternatives to direct disclosure. This may take time; **however it is absolutely essential that they practice safe sex in the interim period.**

Disclosing sero-status can be very stressful, especially if the HIV-positive adolescents have deep feelings for their partner and are fearful of rejection. Strong support is needed at this time and should be offered before, during and after disclosure. This support should be offered to the partner as well.

Age appropriate issues regarding disclosure

3–6 years

- Stimulate questions by asking the child what s/he understands about having to go to the clinic, taking medicine, being often sick, and what s/he fears.
- Use simple language. Listen carefully and answer truthfully and naturally, giving little information at a time, as the child seems ready to take it in.
- Provide ongoing loving re-assurance and support. Tell the child that s/he can play with, hug and hold hands with other children, without giving them the germ and that if some adults seem afraid it is because they don't know enough about this.

Information can be given in simple language as:

"A virus (or germ) inside you that can make you sick", "Medicine will make the body stronger to fight against the virus", "the same virus your mother has and she also has to take medicines regularly." "To check what the virus has done or is planning to do in the body we can just check your blood. It is not that painful too."

6–9 years

- Start disclosure process as soon as possible, paying attention to non-verbal expressions of anxiety and denial.
- If the screening is done after six years of age, then along with the consent of parents assent from the child is also suggested.
- Encourage and stimulate questions by the child. If the child does not ask questions, ask him about his fears.
- Talk about the illness openly and simply, giving information a little at a time, as the child seems ready to take it in.
- Provide information to ascertain a link between illness and medicines, such as “We all fall ill sometimes and take medicines.”
- Reassure the child that s/he must lead a life like all children and can go to school, play games, hold hands and hug other children without transmitting the infection.

Information to be given:

Name of the illness, causes and how it could have entered the body. Explain that medicine will fight against the infection and make him/her feel better, and it needs to be taken very regularly.

10 to 13 years

- The early adolescents are mature enough to understand how people behave and verbal as well as nonverbal communications.
- If diagnosis is done and the child is brought to health care system catering to HIV infected people, then even if the child is not saying so s/he most likely knows regarding the infection.
- They at the least develop some kind of suspicion regarding the illness, so they could try to find it out by exploring their own ways.
- When they understand and are well helped till accepting the infection, they take the medicines regularly, even remind parents for it.

Additional issues should be discussed are:

- What is immunity?
- The virus affects immunity.
- What could happen if immunity is decreased?
- So we take medicines that could obstruct the work of the virus.
- If the medicines are not taken regularly then the virus could be able to affect the immunity.
- To check if the medicines work as desired, certain blood tests are required.
- The number of a kind of immunity cells- CD4 and CD8 cells are checked.
- If the number of immunity cells is increasing it means virus is losing the battle and immunity is increasing.
- Reading ones own reports is a better way to understand the situation at any point of time. One could learn how to read in no time if wants to.

13 to 17 years

- The children from this age group have understanding capability comparable to adults. If anybody, for example, the parents are saying that the child does not know anything it is just not possible.
- Almost always s/he knows but may be in bits and pieces and some links could be missing.
- They have the ability to ask very difficult questions and can comprehend the parents psyche too.
- If parents have not started the process earlier then it is extremely hard and volatile arena for the parents to start disclosure at this level. One could seek help from others for example counselors. If parents have already begun the process they could complete it till this level.

>17 years

- The process of disclosure is beginning at this level then some hard hits as a consequence are expected.
- Preferably parents should not try doing it now and a professionally skilled and experienced counselor should intervene and do the complete disclosure.

32.

Adolescents and HIV

Adolescents are children with 'special' needs.

In India adolescents (especially 12-14 years) contract the infection from mother to child transmission and thus survive with HIV till they reach adolescence. If they are diagnosed when already reached adolescence then more likely are immune-deficient.

There are possibilities of new HIV infections also in the next stage (15-19 years) group due to increased opportunities of sexual exposure, early marriages especially for girls from rural background, and a little percentage could be from sexual assaults. HIV infected adolescents who are not aware regarding their infection, and if not counseled about safe sex practices do carry a risk of transmission to others. Therefore counseling about safe sex is essential for HIV infected as well as uninfected adolescents, both for prevention of acquisition as well as transmission of the infection.

The late adolescents (17-19 years) are more vulnerable to HIV infection. This is evidenced from the fact that most women detected

to be HIV infected during routine ANC check up are from this age group. It is a fact that many girls in India are already married before this age. There is sizable number of women getting detected as infected who are recently married and pregnant for the first time. The most important risk factor for them could be the risk taking behavior of their husbands, who have also recently passed the adolescence but have contracted the infection for some time.

Special needs

Issues about social orientation, peer pressures, self image and psychosexual development need attention of counselor and care providers anyway, even if the virus is absent. Issues related to migration due to unemployment are also independently important. Sexuality is always an important topic for adolescents, who are at the age when sexual exploration begins. Issues of safe sex practice has to be addressed but in an extremely careful approach.

Some adolescents who contracted infection from mother and are diagnosed during early childhood are likely to have experienced ARV treatments; In most of the circumstances their parents are aware of the HIV status. With respect to these adolescents, challenges relate mainly to:

- The disclosure of the HIV status to them if this has not already been done by their parents, health care professionals earlier.
- Developmental delays
- The transition from pediatric to adult care, including the choice of appropriate ARV regimens; and
- Adherence to ART

Adherence to long-term therapy is particularly difficult among adolescents. In addition to providing routine adherence assessment and support, health care providers may want to consider issues that

are particularly relevant to adolescents and may impair optimal adherence to ART. Such issues will possibly include -

- Adolescents' perception of being immortal
- Desire for independence
- Lack of disclosure of HIV status and stigma.

The parents of adolescents may find it hard to share the diagnosis of HIV with their children because of fear of blame as well as guilt from their own children. However, without this disclosure it is impossible for adolescents to progress through the transition. Adolescents who have been on ART for a long time are likely to suffer from long term side effects such as lipodystrophy, gynecomastia, metabolic complications, etc. In a delicate period when external appearance means a lot to the person. Disfigurement may lead to non-adherence. It would be ideal to switch therapy at the earliest sign of disfigurement. .

It is important to establish a mutually trusting relationship between the child/adolescent and the counselor/physician.

Tanner Staging (Sexual Maturity Rating)

Stage	Female					Male			
	Age range (yrs.)	Breast growth	Pubic hair growth	Other changes	Age range (yrs)	Testes growth	Penis growth	Pubic hair growth	Other changes
I	0-15	Pre-adolescent	None	Pre-adolescent	0-15	Pre-adolescent testes (<2.5 cm)	Pre-adolescent	None	Pre-adolescent
II	8-15	Breast Budding (the-larche); areolar hyperplasia with small amount of breast tissue	Long downy pubic hair near the labia, often appearing with breast budding or several weeks or months later	Peak Growth velocity often occurs soon after stage II	10-15	Enlargement of testes; pigmentation of scrotal sac	Minimal or no enlargement	Long downy hair, often appearing several months after testicular growth; variable pattern noted with pubarche	Not applicable

III	10-15	Further enlargement of breast tissue and areola, with no separation of their contours	Increase in amount and pigmentation of hair	Menarche occurs in 2% of girls late in stage III	10.5-16.5	Further enlargement	Significant enlargement, especially in diameter	Increase in amount; curling	Not applicable
IV	10-17	Separation of contours; areola and nipple form secondary mound above breast tissue	Adult in type but not in distribution	Menarche occurs in most girls in stage IV, 1-3 years after thelarche	Variable: 12-17	Further enlargement	Further enlargement, especially in diameter	Adult in type but not in distribution	Development of axillary hair and some facial hair

V	12.5-18	Large breast with single contour	Adult in distribution	Menarche occurs in 10% of girls in stage V.	13-18	Adult in size	Adult in size	Adult in distribution (medial aspects of thighs; linea alba)	Body hair continues to grow and muscles continue to increase in size for several months to years; 20% of boys reach peak growth velocity during this period
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Source: Adapted from Arpadi SM, Cuff PA, Kotler DP, Wang J, Bamji M, Lange M, et al. Growth velocity, fat-free mass and energy intake are inversely related to viral load in HIV-infected children. *J Nutr.* 2000 Oct;130(10):2498-502

WHO PMTCT Guidelines: Rapid Advice (Dec. 2009)

Option A: Maternal AZT	B : Maternal triple ARV prophylaxis
Mother	Mother
<ul style="list-style-type: none"> • Antepartum AZT (from as early as 14 weeks gestation)+ • sd-NVP at onset of labor*+ • AZT + 3TC during labor and delivery*+ • AZT + 3TC for 7 days postpartum* 	Triple ARV from 14 weeks until one week after all exposure to breast milk has ended <ul style="list-style-type: none"> • AZT + 3TC + LPV/r or • AZT + 3TC + ABC or • AZT + 3TC + EFV or • TDF + XTC + EFV
Infant	Infant
<ul style="list-style-type: none"> • Breastfeeding infant: Daily NVP from birth until one week after all exposure to breast milk has ended • Non-breastfeeding infant AZT or NVP for 6 weeks 	<ul style="list-style-type: none"> • Breastfeeding infant Daily NVP from birth to 6 weeks • Non-breastfeeding infant AZT or NVP for 6 weeks

(AZT – zidovudine, 3TC – lamivudine, LPV/r – lopinavir + ritonavir, ABC – abacavir, EFV – efavirenz, NVP – nevirapine TDF – tenofovir, XTC – emtricitabine)

* sd-NVP and AZT+3TC can be omitted if mother receives >4 weeks of AZT antepartum

Annexure 2

Presumptive and Definitive Criteria for Recognizing HIV/AIDS-related Clinical Events in Infants and Children with Confirmed HIV Infection:

	Presumptive	Definitive
Primary HIV infection		
Asymptomatic infection: Acute retroviral syndrome	Acute febrile illness 2–4 weeks post-exposure, often with lymphadenopathy, pharyngitis and skin rashes	In children 18 months or over sero-conversion from HIV antibody negative to antibody-positive. A positive virological test for HIV virus or its components (RNA or DNA or ICD HIV p 24 antigen) confirmed by a second virological test obtained from a separate determination. Profound temporary lymphopaenia and other transient blood abnormalities may occur.
Clinical Stage 1		
Asymptomatic	No HIV related symptoms reported and no signs on examination.	Not required.

Persistent generalized lymphadenopathy (PGL)	Swollen or enlarged lymph nodes >1 cm at two or more non-contiguous sites, without known cause.	Not required.
Clinical Stage 2		
Unexplained persistent hepatosplenomegaly	Enlarged liver and spleen without obvious cause.	Not required.
Papular pruritic eruptions	Papular pruritic vesicular lesions. Also common in uninfected children; scabies and insect-bites should be excluded	Not required.
Fungal nail infections	Fungal paronychia (painful, red and swollen nail bed) or onycholysis (painless separation of the nail from the nail bed). Proximal white subungual onychomycosis is uncommon without immunodeficiency.	Not required.

Angular cheilitis	Splits or cracks on lips at the angle of the mouth with depigmentation, usually responding to antifungal treatment but may recur.	Not required.
Linear Gingival Erythema (LGE)	Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding.	Not required.
Extensive wart virus infection	Characteristic warty skin lesions; small fleshy grainy bumps, often rough, flat on sole of feet (plantar warts); facial, more than 5% of body area or disfiguring.	Not required.

Extensive molluscum contagiosum infection	Characteristic skin lesions: small flesh coloured, pearly or pink, dome-shaped or umbilicated growths may be inflamed or red; facial, more than 5% of body area or disfiguring.	Not required.
Recurrent oral ulcerations (two or more in six months)	Apthous ulceration, typically with a halo of inflammation & yellow-grey pseudo-membrane.	Not required.
Unexplained parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause, usually painless.	Not required.
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, can be hemorrhagic on erythematous background, and can become large and confluent. Does not cross the midlines.	Not required.

Recurrent upper respiratory tract infection (URTI)	Current event with at least one episode in past 6 months. Symptom complex; fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup like cough (LTB). Persistent or recurrent ear discharge.	Not required.
Clinical stage 3		
Unexplained moderate Malnutrition	Weight loss: low weight-for-age, up to 2 standard deviations (SDs), not explained by poor or inadequate feeding and or other infections, and not adequately responding to standard management.	Confirmed by documented loss of body weight of 2SD, failure to gain weight on standard management and no other cause identified during investigation.

Unexplained persistent diarrhoea	Unexplained persistent (14 days or more) diarrhoea (loose or watery stool, three or more times daily), not responding to standard treatment.	Confirmed by stools observed and documented as unformed. Culture and microscopy reveal no pathogens.
Unexplained persistent fever (intermittent or constant, for longer than one month)	Reports of fever or night sweat for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or anti-malarials. No other obvious foci of disease reported or found on examination. Malaria must be excluded in endemic areas.	Confirmed by documented fever of $>37.5^{\circ}\text{C}$ with negative blood culture, negative malaria slide and normal or unchanged CXR, and no other obvious foci of disease.

Oral candidiasis (outside first 6–8 weeks of life)	Persistent or recurring creamy white to yellow soft small plaques which can be scraped off (pseudo membranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form).	Confirmed by microscopy or culture.
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off.	None
Lymph node TB	Non acute, painless “cold” enlargement of lymph nodes, usually matted, localized to one region. May have draining sinuses. Response to standard anti -TB treatment in one month.	Confirmed by histology or fine needle aspirate for Ziehl Neelsen stain. Culture.

Pulmonary TB	Nonspecific symptoms, e.g. chronic cough, fever, night sweats, anorexia and weight loss. In the older child; also productive cough and haemoptysis. Abnormal CXR. Response to standard anti-TB treatment in one month.	Confirmed by positive sputum smear or culture.
Severe recurrent presumed bacterial pneumonia	Cough with fast breathing, chest indrawing, nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous 6 months.	Confirmed by isolation of bacteria from appropriate clinical specimens (induced sputum, BAL, lung aspirate).

Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odor, and rapid loss of bone and/or soft tissue.	None
Symptomatic LIP	No presumptive diagnosis.	Diagnosed by CXR: Bilateral reticulonodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently <90%. May present with cor pulmonale and may have increased exercise induced fatigue. Characteristic histology.

Chronic HIV-associated lung disease (including bronchiactesis)	History of cough productive of copious amounts of purulent sputum (bronchiactesis only), with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation;	Confirmed by CXR: May show honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, with fibrosis and loss of volume.
Unexplained anaemia (<8g/dl), or neutropenia (<1000/mm ³) or chronic thrombocytopenia (<50 000/ mm ³)	No presumptive diagnosis.	Diagnosed on laboratory testing, not explained by other non-HIV conditions, or not responding to standard therapy with haematinics, antimalarials or anthelmintic as outlined in IMCI.

Clinical stage 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	<p>Persistent weight loss not explained by poor or inadequate feeding, other infections and not adequately responding in two weeks to standard therapy.</p> <p>Characterized by: visible severe wasting of muscles, with or without oedema of both feet, and/or weight-for-height of -3 SDs, as defined by WHO IMCI guidelines.</p>	Confirmed by documented weight loss of > 3 SD \pm oedema

Pneumocystis pneumonia (PCP)	Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in IMCI). Usually of rapid onset especially in infants under six months of age. Response to high-dose co-trimoxazole +/- prednisolone.	Confirmed by CXR: Typical bilateral perihilar diffuse infiltrates; microscopy of induced sputum or BAL or NPA, or histology of lung tissue.
Recurrent severe presumed bacterial infection, e.g. empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous 6 months.	Confirmed by culture of appropriate clinical specimen.

Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by HSV infection present for more than one month.	Confirmed by culture and/or histology
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)	Chest pain and dysphagia (difficulty in swallowing), odynophagia (pain on swallowing food and fluids), or retrosternal pain worse on swallowing (food and fluids) responds to specific treatment. In young children, suspect particularly if oral candida observed and food refusal occurs and/or difficulties/ crying when feeding.	Confirmed by macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology.

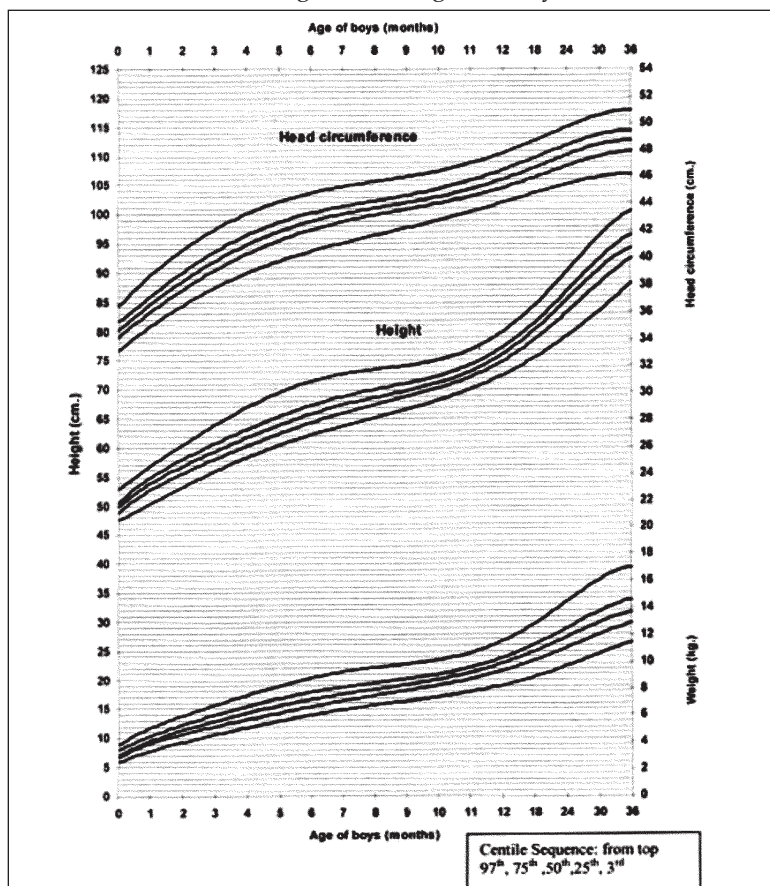
Extrapulmonary/ disseminated TB	Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features of organs involved, e.g. sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis. Responds to standard anti-TB therapy.	Confirmed by positive microscopy showing AFB or culture of <i>Mycobacterium tuberculosis</i> from blood or other relevant specimen except sputum or BAL, biopsy and histology.
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Source: Adapted from Annex 3 of Guidelines for HIV Care and Treatment in Infants and Children published by NACO, November 2006.

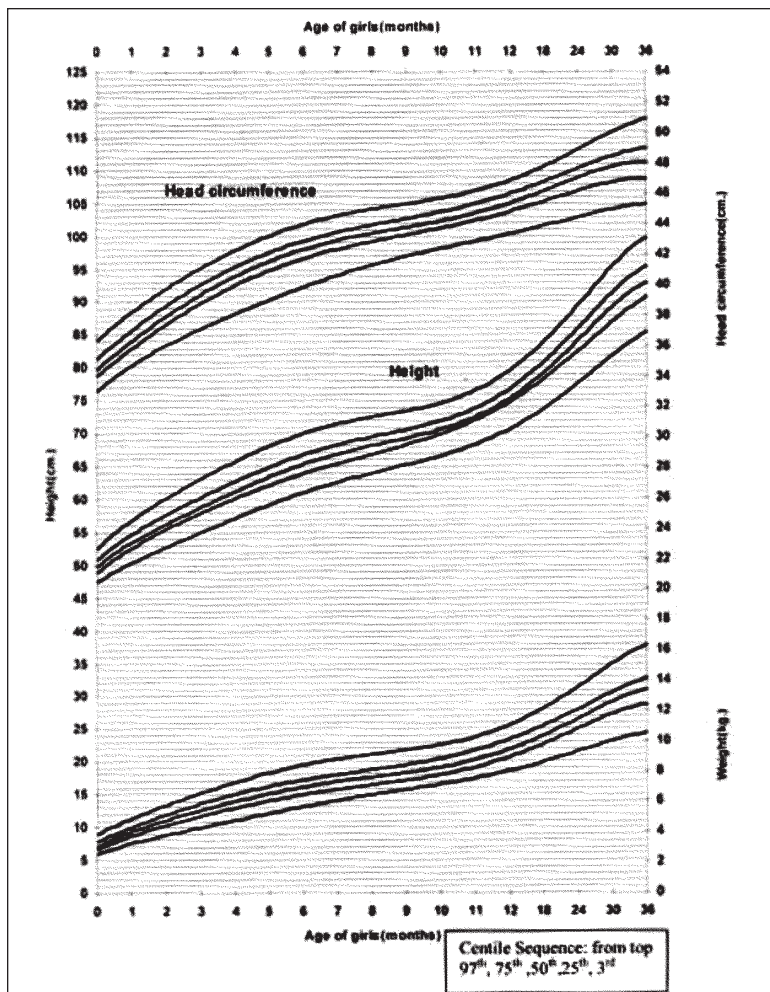
Annexure 3

Growth Monitoring Charts

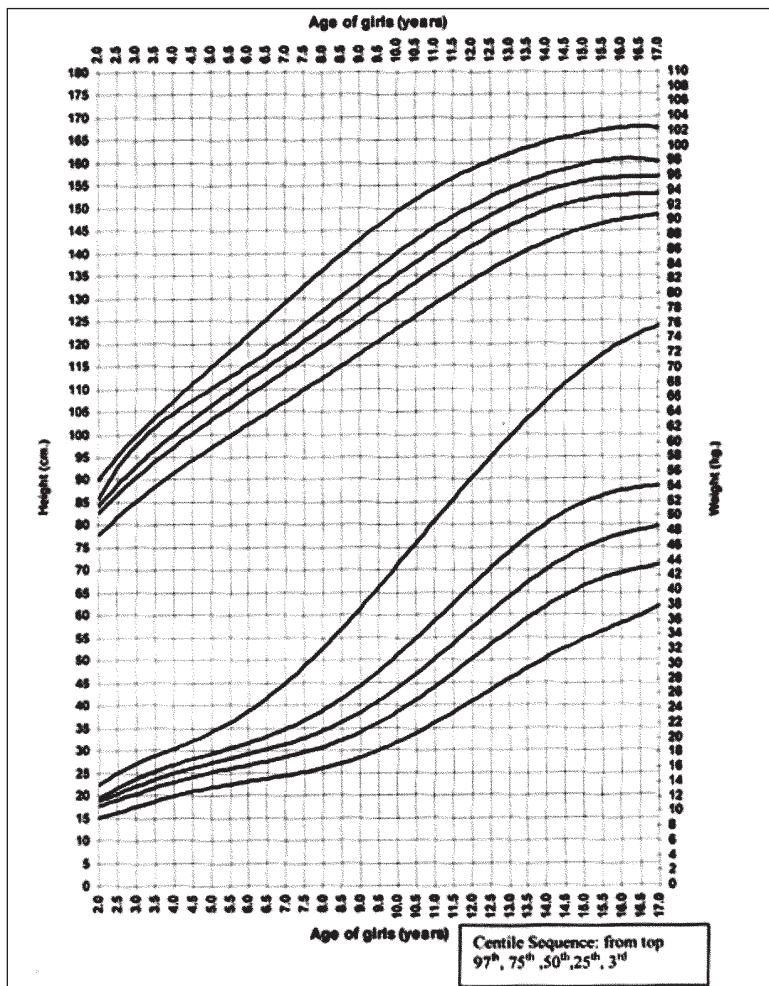
Head Circumference, Height and Weight for boys from 0-36 months



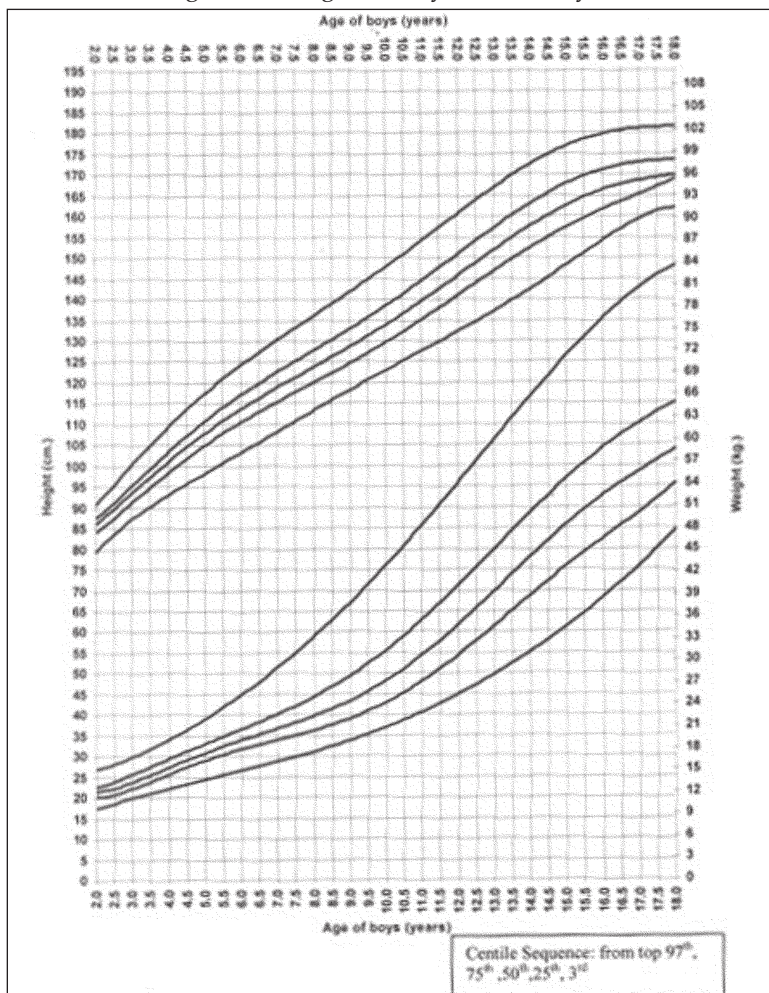
Head Circumference, Height and Weight for girls from 0-36 months



Height and Weight for girls from 2-17 years



Height and Weight for boys from 2-18 years



Annexure 4

Specific Criteria for Classification of HIV Related CNS Disease in Children (Used at the HIV and AIDS Malignancy Branch of the National Cancer Institute)

I] HIV-related encephalopathy (One or more of the following criteria must be met):

- loss of previously acquired skills;
- significant drop in cognitive tests scores, generally to the borderline/delayed range with functional deficits (deficits in day-to-day functioning);
- cognitive tests scores are in the border line to delayed range with functional deficits (and no history of significant drop or previous testing available);
- significantly abnormal neurologic examination with functional deficits (i.e. significant tone, reflex, cerebellar, gait or movement abnormalities);
- significant improvement in cognitive tests scores over approximately a 6-months period associated with a new treatment when baseline scores are in the borderline to delayed range (no history of previous testing) with or without significant brain imaging or neurologic abnormalities (retrospective classification).

Subtypes of HIV encephalopathy:

- ***Progressive:***
 - Subacute – children exhibit a loss of previously acquired skills, resulting in a significant decline in raw and standard score on psychometric tests and development of new neurological abnormalities.
 - Plateau – children either do not gain further skills or exhibit a slowed rate of development compared to their previous rate

of development; resulting in a significant drop in standard scores on psychometric tests.

- **Static:**
children exhibit consistent but lower than normal development in the delayed range or their neuropsychological functioning remains stable for at least 1 year after a significant decline (IQ scores remain below average and without significant decline for at least 1 year).

III] HIV – related CNS compromise: (One or more of the following criteria must be met):

- significant drop in cognitive test scores, but generally still above the delayed range, with or without mild brain imaging abnormalities, with no loss of previously acquired skills and no apparent functional deficits (adaptive behavior and school performance stable); or
- cognitive test scores in the borderline range, with no significant functional deficits (and no history of significant drop or previous testing);
- cognitive test scores within normal limits (low average range or above) with no significant functional deficits and moderate to severe brain imaging abnormalities consistent with HIV-related changes;
- abnormal neurologic findings but not significantly affecting function;
- significant improvement in cognitive test scores over approximately a 6-months period associated with a new treatment when baseline scores are in the low average to average range (no history of previous testing) and no neurologic or brain imaging abnormalities (retrospective classification).

Non-HIV-related CNS condition

- overall cognitive scores or selective areas of deficits below the low average range, but careful review of medical and family history suggests factors other than HIV disease most likely explain the low scores.

Considerations for classification of HIV encephalopathy or CNS compromise

- no other factors can reasonably explain the drop in cognitive test scores, compromised/delayed cognitive functioning, and/or abnormal neurologic exam (such as myopathy, neuropathy, cord lesions, CNS opportunistic infections, neoplasms, or vascular diseases, non-HIV-related developmental or learning disabilities, behavioral problems, or psychosocial/environmental circumstances), and the impairments are considered most likely due to HIV, classify as either HIV-related encephalopathy or CNS compromise (depending on the criteria met).
- if other factors (i.e. behavioral, acute illness, other infection, etc.) may possibly explain the drop in scores or low cognitive functioning, do not classify as HIV-related CNS compromise or encephalopathy and re-evaluate at a later time.

Source: Adapted from 'Handbook of Pediatric HIV Care' by Steven L. Zeichner, Jennifer S. Read

This pediatric HIV CNS classification system was developed by Wolters, Brouwers and Civitello.

Annexure 5

Anti Tuberculosis Drugs - Dosages, side effects and drug interactions

Drug	Daily dose and	Three times weekly dose and range(mg/kg body weight)	Adverse reactions	Drug interactions
Isoniazid (INH)	5(4-6)	10 (8–12)	Rash, hepatic enzyme elevation, peripheral neuropathy	Increases levels of phenytoin and disulfiram
Rifampicin	8(10-12)	10 (8–12)	Rash, hepatitis, fever, orange-colored body fluids	Major effects on PIs and NNRTIs.
Pyrazinamide	25(20-30)	35 (30–40)	Gastrointestinal upset, hepatitis, rash, arthralgia, hyperuricemia	Might make glucose control more difficult in patients with diabetes

Etham- butol	Children 20 (15–25) Adults 15 (15–20)	30 (25–35)	Optic neuritis, decreased red-green color vision, rash	No known important interactions
Strepto- mycin	15 (12–18)	15 (12–18)	Ototoxicity, nephro- toxicity	

Source: Drug dosages adapted from table 13, chapter 21 of Management of HIV Infection and Antiretroviral Therapy in Infants and Children, a clinical manual of World Health Organization, 2006.

Drugs that may Interact with ART

ARV	NVP	EFV	LPV/r	NFV	SQV
Antimycobacterials					
Rifampicin	<p>↓ NVP level by 20-58%. Virological consequences are uncertain; the potential of additive hepatotoxicity exists. Co-administration is not recommended and should only be done with careful monitoring</p>	<p>↓ EFV level by 25%</p>	<p>↓ LPV AUC by 75% Should not be co-administered</p>	<p>↓ NFV level by 82% Should not be co-administered</p>	<p>↓ SQV level by 84% Severe liver impairment reported with co-administration, hence should not be co-administered</p>

ARV	NVP	EFV	LPV/r	NFV	SQV
Clarithromycin	None	↓ Clarithro- mycin by 39% Monitor for efficacy or use alternative drugs	↑ Clarithro- mycin AUC by 75%, adjust clarithromycin dose if renal impairment	No data	Without RTV, ↑ clarithro- mycin level by 45%, ↑ SQV level by 177% RTV can ↑ clarithro- mycin level by 75% No clarithro- mycin dose adjustment needed for unboosted SQV. For boosted SQV if renal impairment — no data

ARV	NVP	EFV	LPV/r	NFV	SQV
Antifungals					
Ketoconazole	↑ Ketoconazole level by 63% ↑ NVP level by 15-30% Co-administration not recommended	No significant changes in ketoconazole or EFV levels	↑ LPV AUC ↑ Ketoconazole level 3-fold Do not exceed a dose of 200 mg/day of ketoconazole	No dose adjustment necessary	↑ SQV level by 3-fold No dose adjustment necessary if given unboosted For RTV-boosted SQV - no data (RTV treatment dose can increase ketoconazole level 3-fold) No data
Fluconazole	↑ NVP C_{max} , AUC, C_{min} by 100% No change in fluconazole level Possible increase in hepatotoxicity with co-administration requiring monitoring of NVP toxicity	No data	No data	No data	No data

ARV	NVP	EFV	LPV/r	NFV	SQV
Itraconazole	No data	No data	↑ Itraconazole level Do not exceed a dose of 200 mg/day of itraconazole	No data but potential for bidirectional inhibition, monitor toxicities	Bidirectional interaction has been observed. May need to decrease itraconazole dose. Consider monitoring SQV level (especially if given unboosted with RTV)
Oral contraceptives	↓ Ethinyl estradiol by 20% Use alternative or additional methods	↑ Ethinyl estradiol by 37% Use alternative or additional methods	↓ Ethinyl estradiol level by 42% Use alternative or additional methods	↓ levels of norethin-drone by 18% and ethinyl estradiol by 47%	No data for unboosted SQV RTV treatment dose can ↓ level of ethinyl estradiol by 41%

ARV	NVP	EFV	LPV/r	NFV	SQV
Lipid- lowering agents					
Simvastatin, lovastatin	No data	↓ Simvastatin level by 58% EFV level unchanged Adjust Simvastatin dose according to lipid response, not to exceed the maximum recommended dose	Potential large ↑ in statin level Avoid concomitant use	↑ Simvastatin AUC by 505% Potential large ↑ in lovastatin AUC Avoid concomitant use	Potential large ↑ in statin level Avoid concomitant use
Atorvastatin	No data	↓ Atorvastatin AUC by 43% EFV level unchanged Adjust atorvastatin dose according to lipid response, not to exceed maximum recommended dose	↑ Atorvastatin AUC 5.88-fold Use lowest possible starting dose with careful monitoring	↑ Atorvastatin AUC by 74%, Use lowest possible starting dose with careful monitoring	↑ Atorvastatin level by 450% when used as SQV/RTV Use lowest possible starting dose with careful monitoring

Pravastatin	No data	No data	↑ Pravastatin AUC by 33% No dose adjustment Needed	No data	↓ Pravastatin level by 50% No dose adjustment needed
Anticonvulsants					
Carbamazepine, phenobarbital, phenytoin.	Unknown. Use with Caution. Monitor anticonvulsant levels	Use with caution. One case report showed low EFV levels with phenytoin Monitor anticonvulsant and EFV levels	↑ Carbamazepine from RTV Both phenytoin and LPV/r levels ↓ For all, avoid concomitant use or monitor LPV/anti-convulsant levels	Unknown but may decrease NFV level substantially Monitor NFV/anti-convulsant levels	Unknown for unboosted SQV but may markedly ↓ SQV level Monitor SQV/anticonvulsant levels

AUC - area under the curve C_{max} - maximum concentration C_{min} - minimum concentration

Note: Concomitant use of fluticasone with RTV results in markedly reduced serum cortisol concentrations. Co-administration of fluticasone with RTV or any RTV-boosted PI regimen is not recommended unless the potential benefit outweighs the risk of systemic corticosteroid side-effects.

Source: Adapted from the *Guidelines for the use of antiretroviral agents in pediatric HIV infection*, Nov 3, 2005, www.aidsinfo.nih.gov.

Summary of Formulations and Dosages of Antiretroviral Drugs for Children

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dosage frequency	Other comments
Nucleoside analogue reverse transcriptase inhibitors				
Zidovudine (AZT)	Syrup: 10 mg/ml Capsules: 100 mg; 250 mg Tablet: 300 mg	All ages	<6 weeks: 4 mg/kg/ dose twice daily 6 weeks to 13 years: 180-240 mg/m ² /dose twice daily Maximum dose: >13 years: 300 mg/ dose twice daily	Large volume of syrup is not well tolerated in older children. Syrup needs to be stored in glass jars and is light-sensitive Can be given with food Doses of 600 mg/m ² /dose per day are required for HIV encephalopathy Capsule can be opened and contents dispersed or tablet crushed and contents mixed with a small amount of water or food and taken immediately (solution is stable at room temperature) Do not use with d4T (antagonistic ARV effect)

Lamivudine (3TC)	Oral solution: 10 mg/ml Tablet: 150 mg	All ages	<p><30 days: 2 mg/kg/ dose twice daily</p> <p>>30 days or <60 kg: 4 mg/kg/dose twice daily</p> <p>Maximum dose: >60kg: 150 mg/ dose twice daily</p>	<p>Well tolerated</p> <p>Can be given with food</p> <p>Store solution at room temperature (use within one month of opening)</p> <p>Tablet can be crushed and contents mixed with a small amount of water or food and taken immediately</p>
FDC of AZT + 3TC	No liquid preparation available Tablet: 300 mg AZT + 150mg3TC	Adolescents and adults	<p>Maximum dose: >13 years or >60 kg: 1 tablet/dose twice daily (should not be given if weight <30 kg)</p>	<p>Ideally, the tablet should not be split</p> <p>Tablet can be crushed and contents mixed with a small amount of water or food and taken immediately</p> <p>At weight <30 kg, the correct dose of AZT and 3TC cannot be given in tablet form</p>

Stavudine (d4T)	<p>Oral solution: 1 mg/ml</p> <p>Capsules: 15 mg, 20 mg, 30 mg</p>	All ages	<p><30 kg: 1 mg/kg/ dose twice daily</p> <p>>30 kg: 30 mg/ dose twice daily</p>	<p>Large volume of solution</p> <p>Keep solution refrigerated; stable for 30 days; must shake well. Needs to be stored in glass bottles</p> <p>Capsules can be opened and mixed with a small amount of food or water (stable in solution for 24 hours if kept refrigerated)</p> <p>Do not use with AZT (antagonistic ARV effect)</p>
Fixed dose com- bination of d4T + 3TC	<p>No liquid preparation available</p> <p>Tablet: d4T 30 mg + 3TC 150mg</p>	Adolescents and adults	Maximum dose: one 30 mg d4T-based tablet twice daily	Ideally the tablet should not be split

Didanosine (ddl, dideoxyinosine)	Oral suspension paediatric powder/ water: 10 mg/ml. In many countries needs to be made up with additional antacid Chewable tablets: 25mg; 50mg; 100mg; 150mg; 200mg Enteric-coated beadlets in capsules: 125 mg; 200 mg; 250 mg; 400 mg	All ages	<3 months: 50 mg/m ² /dose twice daily 3 months to <13 years: 90-120 mg/m ² /dose twice daily or 240 mg/m ² /dose once daily Maximum dose: >13 years or > 60 kg: 200 mg/dose twice daily or 400 mg once daily	Keep suspension refrigerated; stable for 30 days; must be shaken well Administer on empty stomach, at least 30 minutes before or 2 hours after eating If tablets are dispersed in water, at least 2 tablets of appropriate strength should be dissolved for adequate buffering Enteric-coated beadlets in capsules can be opened and sprinkled on a small amount of food
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Abacavir (ABC)	Oral solution: 20mg/ml Tablet: 300 mg	>3 months	<16 years or <37.5 kg: 8 mg/ kg/dose twice daily Maximum dose: >16 years or >37.5 kg: 300 mg/dose twice daily	Can be given with food Tablet can be crushed and contents mixed with a small amount of water or food and ingested immediately MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION ABC should be stopped permanently if hypersensitivity reaction occurs
FDC of AZT + 3TC + ABC	No liquid preparation available Tablet: AZT 300 mg + 3TC 150mg+ ABC 300 mg	Adolescents and adults	Maximum dose: >40 kg: 1 tablet/dose twice daily	Ideally, the tablet should not be split At weight <30 kg, AZT/3TC/ABC the correct dose cannot be given in tablet form MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION AZT/3TC/ABC should be stopped permanently if hypersensitivity reaction occurs

Non-nucleoside reverse transcriptase inhibitors			
Nevirapine (NVP)	<p>Oral suspension: 10 mg/ml</p> <p>Tablet: 200 mg</p>	All ages	<p>Avoid using if rifampicin is being co-administered</p> <p>Store suspension at room temperature</p> <p>Must shake well</p> <p>Can be given with food</p> <p>Tablets are scored and can be divided into two equal halves to give a 100 mg dose; can be crushed and combined with a small amount of water or food and administered immediately</p> <p>MUST WARN PARENTS ABOUT RASH</p> <p>Do not increase the dose if rash occurs (if mild/moderate rash, hold drug; when rash clears, restart dosage from beginning of dose escalation; if severe rash, discontinue drug)</p>
			<p>15-30 days: 5mg/kg/dose once daily for 2 weeks, then 120 mg/m²/dose twice daily for 2 weeks, then 200 mg/m²/dose twice daily</p> <p>>30 days to 13 years: 120 mg/m²/dose once daily for 2 weeks, then 120-200 mg/m²/dose twice daily</p> <p>Maximum dose: >13 years: 200 mg/dose once daily for first 2 weeks, then 200 mg/dose twice daily</p>

Efavirenz (EFV)	<p>Syrup: 30 mg/ml (note: syrup requires a higher dosage than capsules, see dosage chart)</p> <p>Capsules: 50 mg, 100 mg, 200 mg</p>	Only for children over 3 years of age or weight > 10kg	<p>Capsule (liquid) dose:</p> <p>10-15 kg: 200 mg (270 mg = 9 ml) once daily</p> <p>15 to <20 kg: 250 mg (300 mg = 10 ml) once daily</p> <p>20 to <25 kg: 300 mg (360 mg = 12 ml) once daily</p> <p>25 to <33 kg: 350 mg (450 mg = 15 ml) once daily</p> <p>33 to <40 kg: 400 mg (510 mg = 17 ml) once daily</p> <p>Maximum dose: >40 kg: 600 mg once daily</p>	<p>Capsules may be opened and added to food but have a very peppery taste; however, can mix with sweet foods or jam to disguise taste</p> <p>Can be given with food (but avoid after high fat meals which increase absorption by 50%)</p> <p>Best given at bedtime, especially in the first 2 weeks, to reduce central nervous system side-effects</p>
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FDC of d4T + 3TC + NVP	No liquid preparation available Tablet: 30 mgd4T /150 mg.3TC / 200 mg NVP	Adolescents and adults	Maximum dose: >30 kg: one 30 mg d4T- based tablet twice daily	<p>Ideally, the tablet should not be split</p> <p>At weight <30 kg, d4T/3TC/NVP the correct dose cannot be given in tablet form; if tablets are split, NVP dose requirements will be inadequate for very young children and additional NVP is needed to give a total of at least 150 mg/m²/dose twice daily. Optimum NVP dosage is 200 mg/ m²/dose twice daily</p> <p>Since the FDC contains NVP, dose escalation is required (<i>SEE NVP DOSING RECOMMENDATIONS</i>)</p>
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Protease inhibitors				
Nelfinavir (NFV)	<p>Powder for oral suspension (mix with liquid):</p> <p>200 mg per level teaspoon (50 mg per 1.25 ml scoop): 5 ml</p> <p>Tablet: 250 mg (tablets can be halved; can be crushed and added to food or dissolved in water)</p>	<p>All ages</p> <p>However, extensive pharmacokinetic variability in infants, with requirement for very high doses in infants <1 year</p>	<p><1 year: 50 mg/kg/dose three times daily or 75 mg/kg/dose twice daily</p> <p>>1 year to <13 years: 55–65 mg/kg/dose twice daily</p> <p>Maximum dose: >13 years: 1250 mg/dose twice daily</p>	<p>Powder is sweet, faintly bitter, but gritty and hard to dissolve; must be reconstituted immediately prior to administration in water, milk, formula, pudding, etc. Do not use acidic food or juice (increases bitter taste); solution stable for 6 hours</p> <p>Because of difficulties with use of powder, use of crushed tablets preferred (even for infants) if appropriate dose can be given</p> <p>Powder and tablets can be stored at room temperature</p> <p>Can be taken with food</p> <p>Drug interactions (less than ritonavir-containing PIs)</p>

Lopinavir/ ritonavir (LPV/r)	<p>Oral solution: 80 mg/ ml lopinavir plus 20 mg/ml ritonavir</p> <p>Note: oral solution contains 42% alcohol</p> <p>Capsules: 133.3 mg lopinavir plus 33.3 mg ritonavir</p>	6 months of age or older	<p>>6 months to 13 years: 225mg/ m²LPV/57.5mg/ m² ritonavir twice daily or weight-based dosages</p> <p>7-15 kg: 12 mg/ kg LPV/3 mg/ kg ritonavir/dose twice daily</p> <p>15-40kg: 10mg/kg lopinavir/5mg/ kg ritonavir twice daily</p> <p>Maximum dose: >40 kg: 400 mg LPV/100 mg ritonavir (3 capsules or 5 ml)</p>	<p>Oral solution and capsules should preferably be refriger- ated; however, can store at room temperature up to 25°C (77°F) for 2 months; at temperature >25°C (>77°F), drug degrades more rapidly</p> <p>Liquid formulation has a small volume but bitter taste</p> <p>Capsules large</p> <p>Capsules should <i>not</i> be crushed or opened, but must be swal- lowed whole</p> <p>Should be taken with food</p>
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Saquinavir /r	Soft-gel capsule: 200 mg. Hard-gel capsule: 200 mg and 500 mg	>25Kg	Approved dosage in adults: SQV 1000 mg/ RTV 100 mg twice daily There are no data in children. For children weighing >25 kg, the approved adult dose can be used	Capsules large Capsules should <i>not</i> be crushed or opened, but must be swallowed whole Should be taken with food
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Source: Adapted from Annex F of *Management of HIV Infection and Antiretroviral Therapy in Infants and Children*, a clinical manual of World Health Organization, 2006.

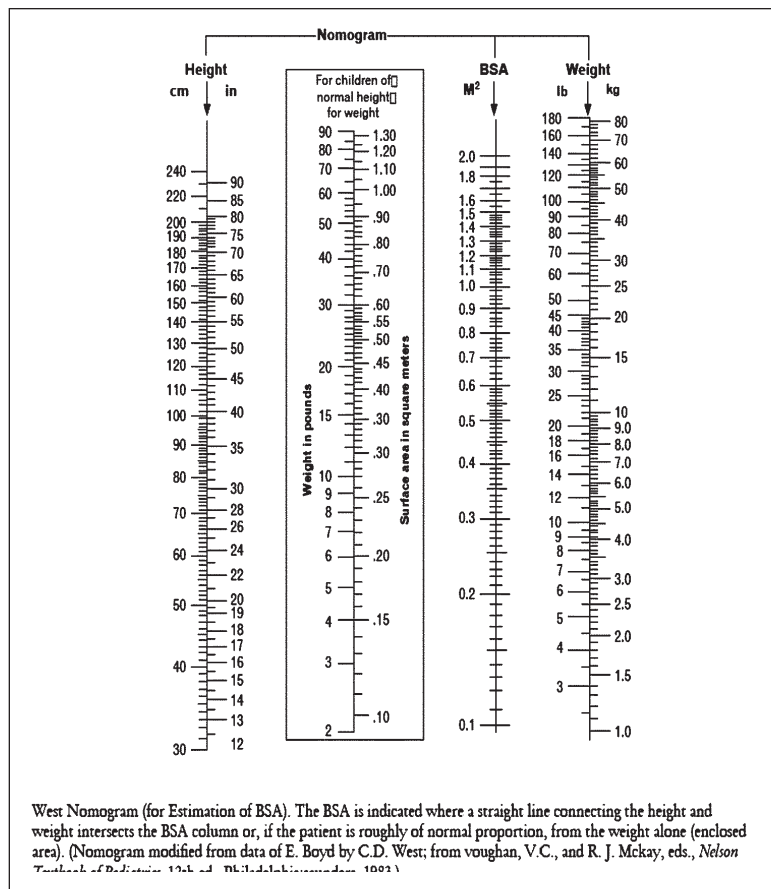
Storage of ARV Drugs

Generic name	Storage requirements
Nucleoside RTIs	
Abacavir (ABC)	Room temperature
Zidovudine (AZT)	Room temperature
Didanosine (ddI)	Room temperature for tablets and capsules. Reconstituted buffered powder should be refrigerated; oral solution for children is stable after reconstitution for 30 days if refrigerated.
Emtricitabine (FTC)	Room temperature
Lamivudine (3TC)	Room temperature
Stavudine (d4T)	Room temperature. After reconstitution, oral solution should be refrigerated; if so, it is stable for 30 days.
Non-nucleoside RTIs	
Efavirenz (EFV)	Room temperature
Nevirapine (NVP)	Room temperature
Protease inhibitors	
Atazanavir (ATV)	Room temperature
Indinavir (IDV)	Room temperature
Fos-amprenavir (Fos-APV)	Room temperature
Lopinavir/ritonavir (LPV/r) capsules	Refrigerate for long term storage At room temperature: stable for 30 days

Generic name	Storage requirements
Lopinavir/ritonavir (LPV/r) heat-stable tablets	Room temperature
Nelfinavir (NFV)	Room temperature
Ritonavir (RTV)	Refrigerate capsules until dispensed Stable at room temperature for 30 days Room temperature for oral solution (do not refrigerate)
Saquinavir - hard gel caps. (SQV _{hgc})	Room temperature
Drug Combinations	
Stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP)	Room temperature
Zidovudine (AZT) + lamivudine (3TC) + Abacavir (ABC)	Room temperature
Zidovudine (AZT) + lamivudine (3TC) + nevirapine (NVP)	Room temperature

Source: Adapted from Annex H of Management of HIV Infection and Antiretroviral Therapy in Infants and Children, a clinical manual of World Health Organization, 2006.

Nomogram for Estimation of Body Surface Area



To use the BSA nomogram, join the point corresponding to the child's weight in kilograms (marked on the line at the right of the figure) with the point corresponding to the child's height in centimeters (marked on the line at the left) with a straight object such as a ruler. Note the point where the ruler (or the line made by the joining of these points) crosses the line marked SA (m^2) (the second line from the right); the number at this point will give you the child's body surface area in meters squared.

Annexure 10

Severity Grading of Selected Clinical and Laboratory Toxicities most commonly seen with Recommended ARV Drugs

Parameter	Mild	Moderate	Severe	Severe, potentially life-threatening
General guidance to estimating grade of severity ^a				
Characterization of symptoms and general guidance on management	Symptoms causing no or minimal interference with usual social and functional activities: ^b No therapy needed, monitor	Symptoms causing greater than minimal interference with usual social and functional activities: ^b May require minimal intervention and monitoring	Symptoms causing inability to perform usual social and functional activities: ^b Requires medical care and possible hospitalization	Symptoms causing inability to perform basic self-care functions: ^c Requires medical or operative intervention to prevent permanent impairment, persistent disability or death
HAEMATOLOGY (Standard International Units are listed in <i>italics</i>)				

Parameter	Mild	Moderate	Severe	Severe, potentially life-threatening
Absolute neutrophil count	750-<1000/mm ³	500-749/ mm ³	250-500/mm ³ 0.25x10 ⁹ - 0.5x10 ⁹ /L	<250/mm ³
Haemoglobin (child >60 days of age)	8.5-10.0 g/dl	7.5- < 8.5 g/dl	6.5- <7.5 g/dl	<6.5 g/dl <1.01 mmol/L or severe clinical symptoms due to anaemia (e.g. cardiac failure) refractory to supportive therapy
Platelets	100,000- <125,000/mm ³	50,000- <100,000/ mm ³	25,000- <50,000/mm ³ 25x10 ⁹ - <50x 10 ⁹ /L	<25,000/mm ³ <25x10 ⁹ /L or bleeding
GASTROINTESTINAL				
Laboratory ^a				
ALT (SGPT)	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10.0 x ULN	> 10.0 x ULN

Parameter	Mild	Moderate	Severe	Severe, otentially life-threatening
AST (SGOT)	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10.0 x ULN	>10.0 x ULN
Bilirubin (>2 weeks of age)	1.1-1.5 x ULN	1.6-2.5 x ULN	2.6-5.0 x ULN	>5.0 x ULN
Lipase	1.1-1.5 x ULN	1.6-3.0 x ULN	3.1-5.0 x ULN	>5.0 x ULN
Pancreatic amylase	1.1-1.5 x ULN	1.6-2.0 x ULN	2.1 -5.0 x ULN	>5.0 x ULN
Clinical				
Diarrhoea >1 year of age	Transient or intermittent episodes of unformed stools or increase of ≤ 3 stools over baseline per day	Persistent episodes of unformed to watery stools or increase of 4-6 stools over baseline per day	Grossly bloody diarrhoea or increase of ≥ 7 stools per day or i.v. fluid replacement indicated	Life- threatening consequences (e.g. hypotensive shock)
<1 year of age	Liquid stools (more unformed than usual) but usual number per day	Liquid stools with increased number of stools per day or mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated or hypotensive shock

Parameter	Mild	Moderate	Severe	Severe, potentially life-threatening
Nausea	Transient (<24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24-48 hours	Persistent nausea resulting in minimal oral intake for >48 hours or aggressive rehydration indicated (e.g. i.v. fluids)	Persistent nausea with no or minimal oral intake resulting in dehydration and aggressive rehydration indicated
Pancreatitis	NA	Symptomatic and hospitalization not indicated (other than emergency treatment)	Symptomatic and hospitalization not indicated (other than emergency treatment)	Life-threatening consequences (e.g. circulatory failure, haemorrhage, sepsis)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension or aggressive rehydration indicated (e.g. i.v. fluids)	Life-threatening consequences (e.g. hypotensive shock)

Parameter	Mild	Moderate	Severe	Severe, otentially life-threatening
ALLERGIC/DERMATOLOGICAL				
Acute systemic allergic reaction	Localized urticaria (wheals) lasting for a few hours	Localized urticaria with indication for medical intervention or mild angioedema	Generalized urticaria or angioedema with indication for medical intervention or symptomatic mild bronchospasm	Acute anaphylaxis or life-threatening bronchospasm or laryngeal oedema
Cutaneous reaction - rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash or target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions or Stevens-Johnson syndrome or ulceration of mucous membrane involving two or more distinct mucosal sites or toxic epidermal necrolysis (TEN)

Parameter	Mild	Moderate	Severe	Severe, otentially life-threatening
NEUROLOGICAL				
Alteration in personality, behavior or in mood ^b	Alteration causing no or minimal interference with usual social and functional activities ^b	Alteration causing greater than minimal interference with usual social and functional activities ^b	Alteration causing inability to perform usual social and functional activities ^b and intervention indicated	Behavior potentially harmful to self or others or life-threatening consequences
Altered mental status	Changes causing no or minimal interference with usual social and functional activities ^b	Mild lethargy or somnolence causing greater than minimal interference with usual social and functional activities ^b	Onset of confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social and functional activities ^b	Onset of delirium, obtundation or coma

Parameter	Mild	Moderate	Severe	Severe, potentially life-threatening
Neuromuscular weakness (including myopathy and neuropathy)	Asymptomatic with decreased strength on examination or mild muscle weakness causing no or minimal interference with usual social and functional activities ^b	Muscle weakness causing greater than minimal interference with usual social and functional activities ^b	Muscle weakness causing inability to perform usual social and functional activities ^b	Disabling muscle weakness causing inability to perform basic self-care functions or respiratory muscle weakness impairing ventilation
Neurosensory alteration (including painful neuropathy)	Asymptomatic with sensory alteration on examination or minimal paraesthesia causing no or minimal interference with usual social and functional activities	Sensory alteration or paraesthesia causing greater than minimal interference with usual social and functional activities	Sensory alteration or paraesthesia causing inability to perform usual social and functional activities	Disabling sensory alteration or paraesthesia causing inability to perform basic self-care functions ^c

Parameter	Mild	Moderate	Severe	Severe, potentially life-threatening
OTHER LABORATORY PARAMETERS (Standard International Units are listed in italics)				
Cholesterol (fasting, pediatric < 18 years old)	170- <200 mg/dl	200-300 mg/dl	>300 mg/dl	NA
Glucose, serum, high: non fasting	116-<161 mg/dl	161-<251 mg/dl	251-500 mg/dl	>500 mg/dl
Glucose, serum, high: fasting	110-< 126 mg/dl	126- <251 mg/dl	251-500 mg/dl	>500 mg/dl
Lactate	<2.0 X ULN without acidosis	> 2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences (e.g. neurological findings, coma) or related condition present	Increased lactate with pH <7.3 with life-threatening consequences (e.g. neurological findings, coma) or related condition present
Triglycerides (fasting)	NA	500- <751 mg/dl	751-1200 mg/dl	> 1200 mg/dl

Notes

^a Values are provided for children in general except where age groups are specifically noted.

^b Usual social and functional activities in young children include those that are culturally- and age-appropriate (e.g. social interactions, play activities, learning tasks, etc.).

^c Activities that are culturally- and age-appropriate (e.g. feeding self with culturally appropriate eating implement, walking or using hands)

Source: Adapted from Division of AIDS, National Institute of Allergy and Infectious Diseases, Table for grading the severity of adult and pediatric adverse events, Bethesda, Maryland, USA; December 2004.

Understanding Drug Resistance

We have seen that ARVs act on specific stages of viral replication.

Drug resistance means that the concentration needed to suppress the viral replication is increased by 50%. This results from selection of mutations in the viral genome. This leads to the possibility of residual viral replication and gradual selection of the mutated virus over the susceptible virus. Development of resistance is thus a function of viral replication. Viral replication occurs at a very high and reasonably constant level. The reverse transcriptase (*RT*) enzyme plays a role in this process by converting the RNA genome of HIV to double-stranded DNA ready for insertion into the host genome..

Characteristics of HIV and reverse transcriptase (*RT*)

- HIV has a rapid replication cycle: billions of copies are produced every day.
- *RT* makes spontaneous errors: approximately 1 error per 10,000-30,000 nucleotide incorporations.
- The HIV-1 genome is $\approx 10,000$ base pairs long.

Implications

- One mutation may occur per new genome generated.
- Every possible mutation occurs at least once daily.
- A patient carries a large pool of genetically related isolates, also known as quasispecies.
- Drug pressure (treatment) selects for ARV-resistant viruses, meaning susceptible virus would remain suppressed while resistant strains would be in circulation.

Nucleotide mutations in HIV genes can result in various changes in HIV proteins and are not always detrimental.

Mutations can:

- **Improve the fitness** of the virus, making it better able to replicate, infect cells or resist therapies.
- **Decrease the fitness** of the virus.
- Result in **silent mutations** that have **no impact** on viral fitness because they do not substantially change the structure or function of the protein that they encode.

Mutations that confer an advantage to the virus become part of the HIV population of **quasispecies** and are passed on to progeny viruses.

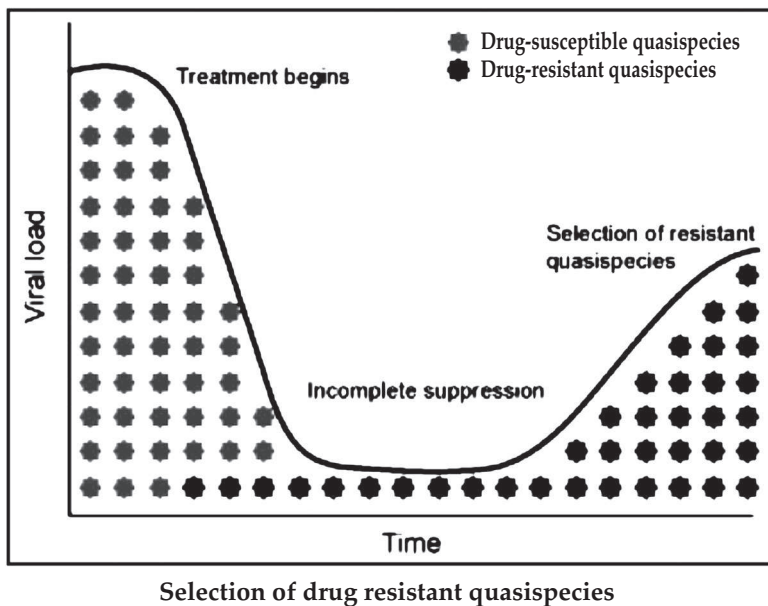
Current ARV regimens do not completely eradicate HIV. Viral replication continues even in the presence of ARV agents at certain sites, even when the plasma viral loads are below detectable levels.

Selection of ARV-resistant Virus

If incomplete suppression of viral replication occurs during ARV therapy, there is an opportunity for the virus population to evolve under a specific **selective pressure** and eventually develop resistance. Incomplete suppression of virus replication may occur for the following reasons:

- Characteristics of the ARV medication (e.g., insufficient potency or inability to reach certain productively infected cell-types including **reservoirs**)
- Drug-drug interactions
- Patients not adequately adhering to therapy
- Patients being infected with virus exhibiting pre-existing resistance to the current regimen

ARV therapy selects for quasispecies carrying mutations that confer viral resistance because these have a survival advantage over wild-type (WT) virus that remains sensitive to the regimen.



Concepts in Viral Resistance

The ability of ARV therapy to suppress viral replication depends on having virus that is susceptible to ARV agents in the ART regimen. Factors related to viral resistance that can influence the success of ARV therapy include:

- The rate at which mutations accumulate
- The **genetic barrier** of ARV agents

- **Cross-resistance** between agents and classes
- Archiving of mutations

The Rate at which Mutations Accumulate

When ARV regimens incompletely suppress viral replication, resistance usually develops. Mutations in the HIV genome continue to accumulate while ARV agents select for resistant or fit viruses. Importantly, resistant mutations do not occur all at once. Some types of resistance mutations are selected rapidly; others take longer to emerge.

The Genetic Barrier of ARV Agents

ARV agents differ in their genetic barrier to resistance. For example, resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) requires development of only one resistance mutation. In contrast, several resistance mutations must occur before an HIV isolate becomes resistant to most protease inhibitors (PIs). Thus, current NNRTIs generally have a lower genetic barrier to resistance than PIs.

Cross-Resistance between Agents and Classes

Different ARV agents select for different types of resistance mutations. However, mutations selected by one ARV agent can confer resistance to other ARV agents. Cross-resistance means that patients who develop resistance to one ARV agent may be resistant to ARV agents to which they have never been exposed. For example, patients who develop resistance to efavirenz will also be resistant to nevirapine.

Archiving of Mutations

Once they develop, resistance mutations usually persist and do not disappear. These mutations are archived in long-lived cells. If the quantity of virus containing these resistance mutations falls below a particular threshold, the resistant quasispecies may not be detected

by resistance testing assays, especially in plasma. The quasispecies remain present at a low level, available to reemerge in greater numbers if the right selective pressure is applied.

Transmission of Drug Resistant Viruses

HIV strains harboring resistance mutations can be transmitted from one person to another.

Terminology of Resistance Mutations

Resistance mutations lead to changes in the amino acid sequence, structure and function of the proteins involved. Most are substitu-

Abbreviation	Amino Acid
A	Alanine
C	Cysteine
D	Aspartic acid
E	Glutamic acid
F	Phenylalanine
G	Glycine
H	Histidine
I	Isoleucine
K	Lysine
L	Leucine
M	Methionine
N	Asparagine
P	Proline
Q	Glutamine
R	Arginine
S	Serine
T	Threonine
V	Valine
W	Tryptophan
Y	Tyrosine
Z	Glutamine

tions of one amino acid for another. These are named according to the location of the amino acid sequence and the change that occurs. Following table shows the amino acid abbreviations used conventionally.

In HIV resistance mutation nomenclature, these abbreviations are used to identify the amino acid normally present in wild-type (WT) HIV and the amino acid that replaces it in a resistant strain. E.g. **M184V** refers to a mutation in which the methionine normally at amino acid 184 of *RT* is substituted by valine. Sometimes the WT amino acid (the first letter) is not mentioned. Thus, the same mutation may also be called “184V.” In addition, a patient may harbor a mixture of viruses carrying different types of mutations in a particular amino acid position. For example, M184I/V denotes that a patient carries strains with either an isoleucine or valine substitution at amino acid 184 of the *RT*.

Other types of resistance mutations are characterized by an insertion of one or more amino acids into the sequence. Compared to substitution mutations, insertion mutations are quite rare

Types of Resistance Mutations

Resistance mutations may also be categorized according to type.

There are broad categories of resistance mutations:

- **Primary resistance mutations** are selected first and can cause significant loss in susceptibility to the ARV agent as a standalone mutation.
- **Secondary resistance mutations** usually appear after primary mutations are already selected and do not reduce susceptibility by themselves. Instead, these mutations significantly increase resistance to a drug in conjunction with primary mutations.

- **Multidrug resistance (MDR) mutations** occur as a single mutation or as a group of mutations and cause crossresistance within an ARV drug class.

NRTI resistance: It is mainly due to accumulation of Thiamidine analogue mutations (TAMS) or **Nucleoside analog mutations (NAMs):** Group of mutations that confer resistance to NRTIs via the process of nucleotide excision. Another mechanism is NRTI blockade which prevents NRTI from being incorporated into the DNA in the first place, which allows DNA synthesis to proceed. Both the M184V and Q151M mutations act in this manner.

NNRTI Resistance: Resistance to **NNRTIs** develops when amino acid substitutions change the position or three-dimensional structure of *RT* so that it cannot bind NNRTIs. Single NNRTI (e.g. K103N mutations can result in very strong resistance. Furthermore, since NNRTIs target the same structural feature of *RT*, there is substantial cross-resistance between all currently approved NNRTIs.

Resistance to PIs

PIs act later than NRTIs and NNRTIs in the HIV lifecycle. Most primary PI resistance mutations appear to alter the structure of the substrate binding cavity of protease by decreasing the inhibitor's binding capacity but still allowing the natural substrate to be processed. PI resistance may also involve mutations in its substrates. These types of mutations are called **compensatory mutations** because they compensate for the loss of cleavage capability of protease in the presence of PIs. Unlike the case with NNRTIs, individual mutations do not generally produce high-level resistance to PIs. Rather, several mutations are usually required. PIs select for mutations that tend to cause cross-resistance within the class.

Viral Fitness

Viral fitness describes the ability of a virus to replicate in a particular environment (e.g., *in vivo* in the presence of ARV agents and with immune pressure). In the presence of ARV medications for example, resistant viruses are more fit than WT viruses. The fitness of a resistant virus usually decreases in the absence of positive selective pressure. In the absence of ARV medications, resistant viruses are less fit than WT viruses. This is because the mutations that confer resistance to ARVs also often impact the functioning of the virus in other ways.

Implications in Clinical Practice

Although suppressed by ARV therapy, WT virus still exists in the body, poised to reemerge when ARV therapy is stopped. In patients failing therapy who stop treatment, WT virus reemerges because they are usually more fit. In some instances, the emergence of WT virus correlates with increased viral load and decreased CD4 cell counts. Therefore, in the absence of any alternative suppressive regimen, maintaining a failing regimen to keep the mutated virus with lower RC around may prove to be beneficial. Also **if we are going to order resistance testing it should be done while the patient is on failing regimen and not when patient is off treatment.**

Resistance testing

Currently, there are two types of resistance testing technologies available. These include those that identify:

- **Phenotypic resistance**, which describes the level of susceptibility of a virus to ARV medications
- **Genotypic resistance**, which reveals the presence of mutations in the genome that are linked to drug resistance

There is a third type called **virtual phenotyping**, in which genotyping data are interpreted to suggest possible phenotype.

Summary Points

- Resistance mutations do not arise all at once.
- Resistance mutations alter the structure or function of HIV proteins and render ARV agents ineffective.
- ARV agents differ in their genetic barriers.
- Cross-resistance reduces the sensitivity of an HIV strain to an agent to which it has not yet been exposed.
- Once they develop, resistance mutations persist and are archived in long-lived cells.
- Genetic barrier describes the number of resistance mutations required to confer resistance to a particular ARV agent.
- Cross-resistance occurs when a virus has acquired resistance to one drug through direct exposure and also has resistance to one or more other drugs to which it has not been exposed.
- Single NNRTI mutations can result in very strong resistance; there is substantial NNRTI cross-resistance.
- Even if they are not detected by resistance testing, resistant substrains of HIV are present at a low level, available to emerge in greater numbers if conditions allow.
- In HIV resistance mutation nomenclature, the normal amino acid abbreviation is followed by its numerical position and the mutant amino acid abbreviation substitution. In some cases, an insertion occurs, which is denoted by its numerical position in the protein chain.

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Other Publications of Prayas Health Group:

- 'HIV – AIDS' (Marathi) A booklet about frequently asked questions for doctors
- 'Aushadh Suru Karatana' (Marathi) (At the time of starting medicines) A booklet for HIV infected individuals who need to start ART
- 'Nigrani' (Marathi) (Nurture with Love) A booklet for parents or care providers in institutions looking after HIV infected children
- 'Anavaran' (Marathi) (Disclosure) A booklet for counselors that explores the issue of disclosure of HIV
- 'Dhusar' (Marathi film with English subtitles) (Blur – Improvising Disclosure) A film on issue of disclosure to HIV infected children
- 'Am I at Risk?' in English and 'Rugnaseva Detana Me Surakshit Ahe Ka?' in Marathi: A film about 'Universal Precautions'. Hindi and Telugu versions are being prepared.
- 'Doctor kakankade gelyawar''' (Marathi) (Visiting doctor uncle) - A booklet for children requiring prolonged medication
- 'Tari Suddha Aai Hotana' (Marathi) (Becoming a mother, In spite of) - A booklet for HIV positive pregnant women
- 'Aai Hotana''' (Marathi) - A booklet for pregnant women about care during pregnancy. This booklet is also available in Hindi as 'Maa Banane se Pahale'''', in English as 'Becoming a Mother' and also in Kannada.
- 'HIV Disease in Pregnant Women and Neonates' - A Manual for PMTCT Programs
- 'Surakshit Garodarpan ani Sukharoop Balantapan' (Marathi) - A booklet on antenatal care (in association with Lokvidnyan Sanghtana)
- 'Prashna Aapala Uttar Aapalech' (Marathi)- A booklet for HIV infected individuals
- 'HIV/AIDS Diagnosis and Management''' Editor: Dr. Vinay Kulkarni (Out of print, Second edition in process)
- 'HIV/AIDS Mhanaje Ahe Tari Kay?''' (Marathi)- Awareness booklet for media personnel
- 'Madhyamanshi Maitree' (Marathi) - Handbook for working with the media
- 'Pudhe Kay?' (Marathi) (What Next?) (1999) -A booklet for HIV infected individuals and their family members
- 'HIV/AIDS Vishayee He Apalyala Mahiti Have!' (Marathi) ("I must know this about HIV/AIDS) (First edition 1995, second edition 1999, third edition 2003). This is a general information booklet about HIV / AIDS, which deals with the issue intimately and sensitively. (So far more than 30,000 copies of the original and about 1,25,000 copies of an abridged version have been distributed).
- 'Children and AIDS' (English) (1996) (Out of Print). A compilation of articles dealing with different aspects of HIV in the pediatric age-group

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A Physician's Handbook



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या विषयांतील विशेष प्रयत्न

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