INDIAN JOURNAL OF PRACTICAL PEDIATRICS

IJPP

- **A quarterly medical journal committed to practical pediatric problems and management update presented in a readable manner**
- **IJPP is a subscription Journal of the Indian Academy of Pediatrics**
- **Indexed in Excerpta Medica from January 2003**
- **Annual subscription:Rs. 300/- 10 years subscription:Rs.3000/-**

Vol.5 No.4	**OCT-DEC 2003**
Dr. A. Balachandran Editor-in-Chief	**Dr. D.Vijayasekaran** Executive Editor

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FROM THE EDITOR'S DESK

We have been publishing this journal since January 1993 and will be completing eleven years in December 2003. The journal has been indexed in Excerpta Medica and journal committee is striving to maintain the high standards.

We are thankful to all our reviewers for peer reviewing the articles, various experts in their respective fields for answering the queries raised by our readers and for the valuable suggessions and guidance offered by our senior faculty and colleagues.

This issue will highlight on HIV infection in children. Our guest editor for this issue is Dr. Nitin K. Shah, Programme Co-ordinator, IAP Project on "Child to Adolescent HIV/AIDS" and Honorary Pediatrician, LTMG Hospital, Mumbai. With his vast experience and knowledge he has carefully chosen the topics and authors suitably for both academicians and practitioners' point of view. In his editorial, he has given a brief outline on the current scenario on HIV infection in children.

Epidemiology of HIV in India written by Dr.Joshi et al is thought provoking and has projected the major challenge for India in the future on preventive programmes. Dr Chourjit et al has written about IV drug abuse and HIV in North Eastern India.

Clinicial manifestations of HIV infections in children is enumerated very well by Dr. Kabra et al. In his article on laboratory diagnosis of pediatric HIV, Dr.Shivanandha has outlined the various laboratory tests available to detect HIV infection. Dr.Mathur et al have given us an overview of the basic treatment principles of pediatric HIV infection.

As vividly narrated by Dr.Swati Y Bhave, in the fight against HIV/AIDS more than the drugs and other interventions, counselling is indispensible. Dr.Rinku Agarwal et al has highlighted that efforts should be made to identify the causative organisms so that early treatment can be instituted against opportunistic infections.

The review on antiretroviral therapy by Dr.Archana Kher will provide the primary care physician with practical information on drugs that are available for treatment. Dr. Nitin K. Shah et-al have discussed the various protocols available to prevent the mother to child transmission.

We are grateful to Dr.Nitin K.Shah for his wonderful work as Guest Editor for this important issue on HIV infection. His work for this issue as a Guest Editor and his untiring involvement in bringing out this issue will be remembered by every one in IJPP. We thank all the authors for their contribution in this issue

Published and owned by Dr. A. Balachandran, from Halls Towers, 56, Halls Road, Egmore, Chennai - 600 008 and printed by Mr. D. Ramanathan, at Alamu Printing Works, 9, Iyyah Mudali Street, Royapettah, Chennai - 600 014. Editor : Dr. A. Balachandran.

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- Manuscript is arranged as follows: Title page, text, acknowledgements, references, tables, figure legends, figures.
- All pages are numbered at the top of the right corner, beginning with the title page.
- The letter of submission has been signed by all authors.

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EDITORIAL

INDIAN PERSPECTIVE OF HIV INFECTION IN CHILDREN

As on today, approximately 40 million people live with HIV infection world over. This includes approximately 4-5 million children with HIV infection. More than 90% of these patients are living in developing countries that neither have adequate resources nor the required infrastructure to tackle this problem. With the result, HIV infection continues to spread unabated in these countries. Some of the sub - Saharan African countries have 25% seroprevalence of HIV infection in the general population. Such countries are already experiencing doubling of the infant mortality rates, pushing these countries down in their health statistics by more than 2 to 3 decades.

Today India has approximately 4 million people living with HIV infection. Six states namely Maharashtra, Tamil Nadu, Andhra Pradesh, Karnataka, Manipur and Nagaland are high prevalence states. They have more than 1% seroprevalence of HIV infection amongst pregnant women attending the antenatal clinics. These states are doing relatively well in their childhood health statistics at present. However HIV related mortality could upset all the gains achieved in the last couple of decades with efforts like breast-feeding promotion, ARI and diarrhoea control program, immunizations etc. Rest of the country has low or intermediate HIV prevalence. However some of these states are still lagging behind in their health statistics, and spread of HIV infection is likely to make the scene worse in these states.

Pediatric HIV infection occurs mainly through vertical route. Twenty eight million deliveries occur in India annually. The average HIV prevalence in these pregnant women is 0.5%. This means 1.4 lakh deliveries occur in HIV infected women. Without any intervention, 30% of these HIV infected women will transmit HIV infection to their babies. It means that approximately 40,000 babies are HIV infected vertically in India annually. This figure could be higher than this if the seroprevalence is actually more than estimated. With effective measures of prevention of mother to child transmission 50-60% of these babies could be prevented from getting HIV infection, which means 20000-40000 babies can be salvaged by effective prevention of mother to child transmission (PMTCT) program. PMTCT program is a formidable yet rewarding exercise. The phase I and II Indian feasibility studies of prevention of mother to child transmission have shown good results and the benefits should now percolate down to the masses.

Less than 10% of the HIV infected patients can afford the ideal treatment in India. It is futile to treat these patients with haphazard anti - retroviral drugs without proper counselling. The need of the hour is to prevent HIV infection through mass education, counsel those who are already infected about the importance of treating their opportunistic infections, complete childhood immunization as per the guidelines for the children, treat the associated sexually transmitted infections (STI), offer voluntary counselling and testing of pregnant women attending the antenatal clinics and offer the prevention of mother to child transmission measures to those who are found HIV infected. It is important that we train the physicians in these aspects of HIV infection so

that they could diagnose HIV infection early and guide the patients to the best possible treatment within the constraints. Indian Academy of Pediatrics has taken up the responsibility of spreading these messages to our members through the IAP HIV/AIDS project. In the last 3 years we have conducted more than 14 state level workshops and hope to continue it in the future. We have evolved the training manual for our members, which will help our members to offer correct treatment of HIV infection in children.

This special issue of IJPP has articles, which will discuss the various aspects of HIV infection in children written by experts in childhood HIV infection. I am sure that this special issue will serve the purpose as a ready reckoner for the readers.

Nitin K. Shah
Programme Co-ordinator,
IAP Project on Child to Adolescent HIV/AIDS
Honorary Pediatrician, U.H.C,
LTMG Hospital, Mumbai.

BOOK REVIEW

Title : Blood Gas Analysis – A Practical Approach

Author : Dr.T.Shyam Sunder

Review : This is the first book written by an Indian author on "Blood Gas Analysis." This is commendable work. The author is an anesthetist. The most appreciable aspect of this book is its simplicity. Even complicated aspects are discussed in a simple manner. In the initial five chapters, the author has taken sincere efforts to explain the basic principles including the terminology. The chapter on collection of sample is written stepwise. However inclusion of diagrams would have made it self-explanatory. All the four acid base disturbances (Metabolic acidosis and alkalosis, respiratory acidosis and alkalosis) are analyzed in depth. Author has used algorithms to identify the underlying cause. The best part of the book are the last four chapters. A seven-step approach has been given to solve the mystery of acid base disturbances followed by case scenarios, self-assessments and FAQs. The book is very handy as a pocket book for reference with a colourful cover, nice printing with highlights and is also economically priced. As all the case scenarios and underlying causes are adult oriented, inclusion of a few pediatric cases and common causes observed in children would have made the book complete. From his experience, he could have written about the choice of ABG machines and about its maintenance. This could have been more useful for pediatricians who handle ABG machines in their institutions. There is some minor lacunae in the last minute works in the press – title is incomplete in the cover without the word 'practical approach', title of chapter five is missing and there are a few spelling mistakes. However these do not undermine the fantastic work of the author. This book is strongly recommended for Pediatric Students, Neonatologists, Pediatricians working in intensive care units and also for critical care nurses.

Publisher : M/s Paras Medical Publisher,
5-1-473, Putilibowli, Jambagh Road,
P.O.Box Number 544,
Hyderabad – 500 095. A.P. India

Price : Rs.125/-

HIV INFECTION

EPIDEMIOLOGY OF HIV IN INDIA WITH SPECIAL REFERENCE TO CHILDREN

**** Joshi PL***
***** Tripti Pensi***
****** Rewari BB***

Abstract: *The AIDS epidemic has claimed more than 3 million lives in 2002, and an estimated 5 million new people acquired the human immuno-deficiency virus (HIV) the same year – bringing the number of people living with the virus globally, to 42 million.*

The window opportunity of bringing the HIV/AIDS epidemic under control is narrowing rapidly in Asia. There is a vital need to expand activities that focus on people most at risk of infection. But targeted interventions alone will not halt the epidemic. More extensive HIV/AIDS programmes that reach the general population are essential.

Keywords : *Epidemiology, HIV, India, Children.*

One of the salient achievements of the twentieth century science is the triumph of medical fraternity over various infectious diseases, which have plagued mankind through the ages. Many deadly diseases like small pox and guinea worm have been eradicated, diseases like leprosy and polio are on the verge of elimination and many others are fairly controlled. Modern medicine has assured a reasonably good quality of life to mankind. But this happy scenario was rudely shattered in the early eighties when a new virus, later identified as Human Immunodeficiency Virus (HIV), struck the human race with consequences. Till date, all the ingenuity of man, money, effort and power has not found a way to counter the relentless onslaught of HIV which respects no territorial boundaries, makes no distinction between race, creed or colour and spares neither the rich nor the poor, neither the old nor the young.

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The problem

As the world enters the third decade of the AIDS epidemic, the evidence of its impact is undeniable. Wherever the epidemic has spread unchecked, it is robbing countries of the resources and capacities on which human security and development depend. In some regions, HIV/AIDS, in combination with other crises, is driving ever-larger parts of nations towards destitution.

In Eastern Europe and Central Asia, the number of people living with HIV in 2002 stood at 1.2 million. HIV/AIDS is expanding rapidly in the Baltic States, the Russian Federation and several Central Asian republics.

In Asia and the Pacific, 7.2 million people are now living with HIV. Almost 1 million people acquired HIV in 2002, a 10% increase since 2001. A further 490, 000 people are estimated to have died of AIDS in the past year. About 2.1 million young people (aged 15–24) are living with HIV.

The growth of the epidemic in this region is largely due to the growing epidemic in China, where a million people are now living with HIV and where official estimates foresee a manifold increase in that number over the coming decade. There remains considerable potential for growth in India, too, where almost 4 million people are living with HIV.

In several countries experiencing the early stages of the epidemic, significant economic and social changes are giving rise to conditions and trends that favour the rapid spread of HIV—for example, wide social disparities, limited access to basic services and increased migration.

Both China and India, are experiencing serious, localized epidemics that are affecting many millions of people.

India's national adult HIV prevalence rate of less than 1% offers little indication of the serious situation facing the country. An estimated 3.97 million people were living with HIV at the end of 2002—the second-highest figure in the world, after South Africa. HIV prevalence among women attending antenatal clinics was higher than 1% in Andhra Pradesh, Karnataka, Maharashtra, Manipur, Nagaland and Tamil Nadu.

Recent trends in India

Since the detection of HIV infection in commercial sex workers (CSWs) in Tamil Nadu in 1986, there has been a steady increase in the number of AIDS cases seeking treatment in various hospitals across the country. A cumulative total of 20,304 cases of AIDS had been reported to the National AIDS Control Organisation (NACO) till 31st March 2001. With an estimated number of 3.86 million HIV infections in the country, the number of AIDS cases is likely to continue to increase in the coming years.

The total number of estimated HIV infections among adult population based on nationwide sentinel surveillance data collected in the year 1998, 1999 and 2000 reveals that there is no dramatic upsurge in the spread of HIV infection in the country. It was 3.5 million infections in the year 1998, 3.71 million in the year 1999 and 3.86 million in the year 2000.

Based on HIV prevalence rates in adult population in States/Union Territories, estimated from National Sentinel Surveillance round conducted during the period August to October 2000,(Fig.1) States/Union Territories have been classified into three groups as follows:–

Group-I *(High prevalence states)* — The states like Maharashtra, Tamil Nadu, Karnataka, Andhra Pradesh, Manipur and Nagaland where the HIV infection has crossed 1% or more in antenatal women.

Group-II *(Moderate prevalence states)* — The states like Gujarat, Goa and Pondicherry where the HIV infection has reached 5% or more among high risk groups but the infection is below 1% in antenatal women.

Group-III *(Low prevalence states)* — The remaining states where the HIV infection in any of the high risk groups is still less than 5% and less than 1% among antenatal women. (Fig.1)

As on date 37,566 AIDS cases were reported to NACO. These figures are considered only a fraction of AIDS morbidity. The low numbers and geographic distribution of AIDS cases shows that these numbers do not reflect the true situation in the country and there may be gross under reporting. (Fig.2)

Epidemiological analysis of reported AIDS cases reveals that:

1. The disease is affecting mainly the people in the sexually active age group. The majority of the patients are in the age group of 15 - 44 years
2. Males account for 78.5% of AIDS cases and females 21.5%. the ratio being 3:1, but now more and more women are being infected.
3. The predominant mode of transmission of infection in the AIDS patients is through heterosexual contact (84.5%), followed by blood and blood product infusion (3.27%), injectable drug use (3.36%), perinatal route (2.14%) and others 6.7% (Fig 3).
4. The major opportunistic infection in the AIDS patients in our country is tuberculosis (65%) indicating a threat of dual epidemic of TB and HIV in the future.
5. The major presenting signs and symptoms in AIDS cases in India are weight loss (89%), fever (88%) and diarrhoea (86%). (Fig.4 and 5)
6. HIV is prevalent in all the parts of the country, though distribution is heterogeneous.

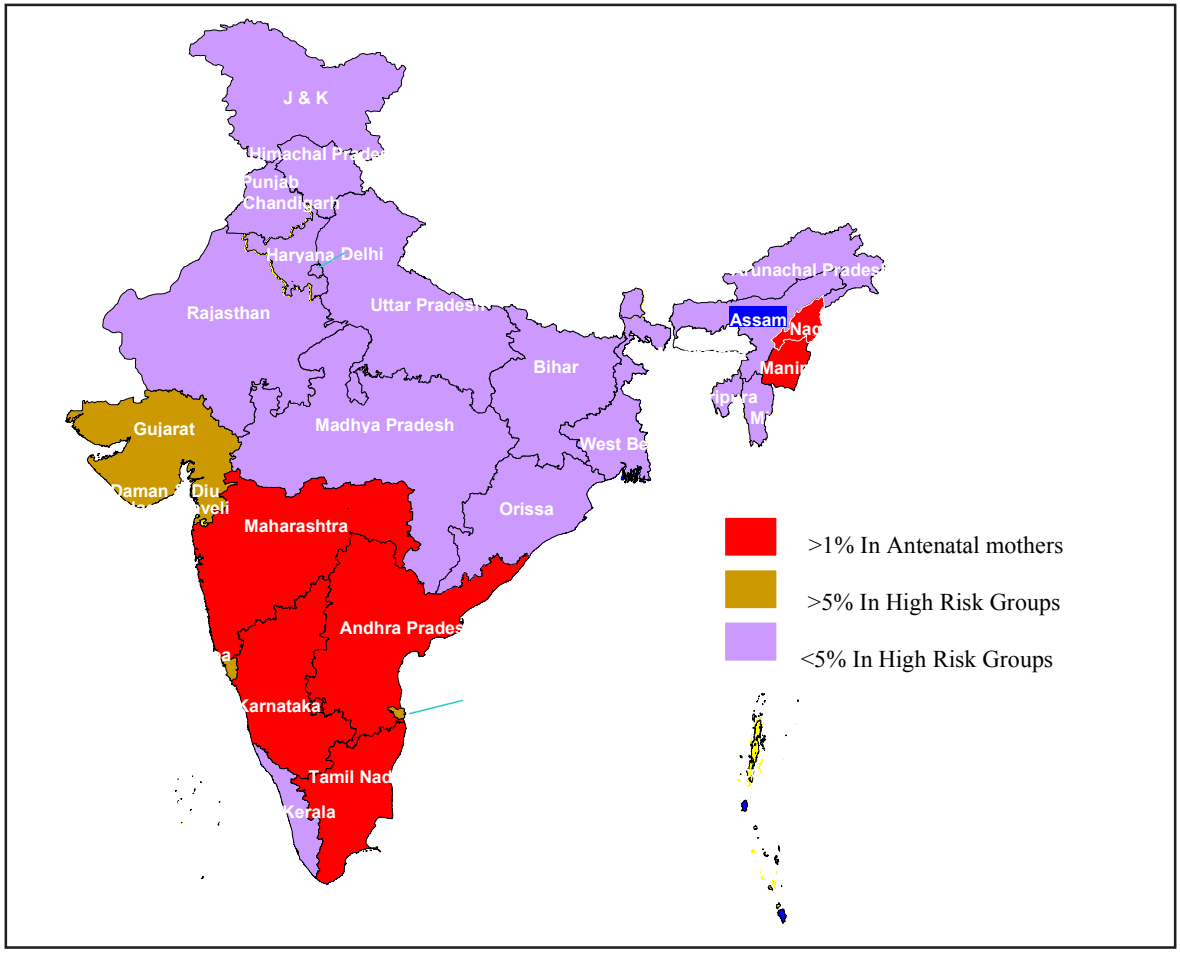

Fig. 1. Adult HIV prevalence in 2002 in India

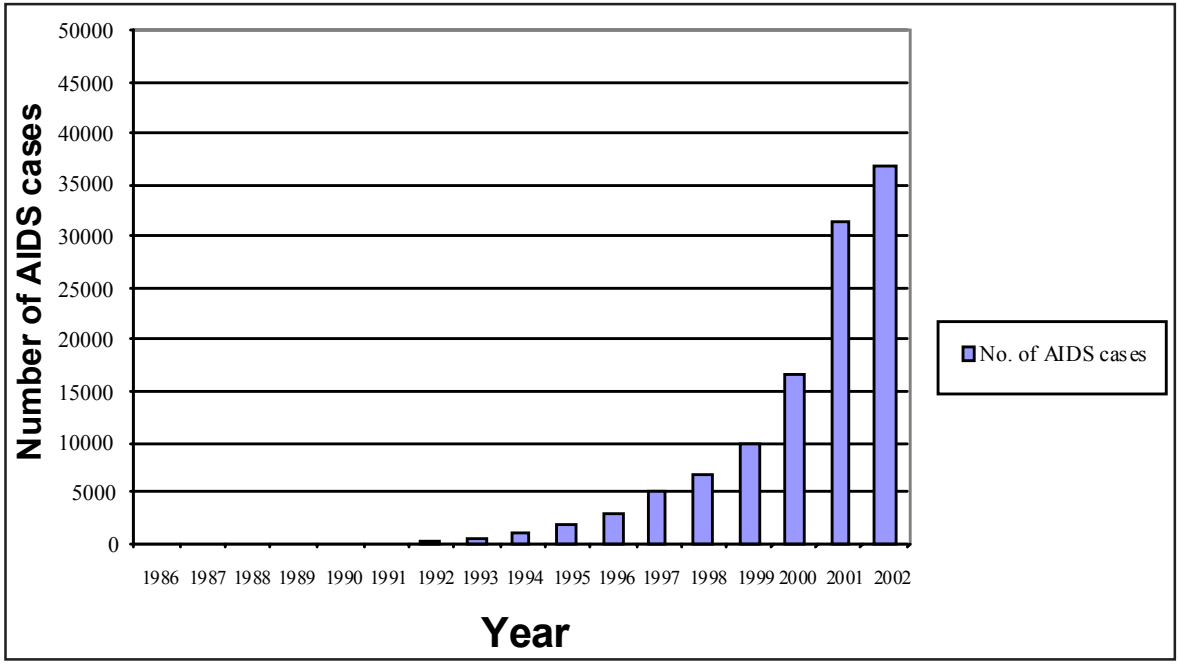

Fig.2. Cumulative number of AIDS cases in India - December 2002

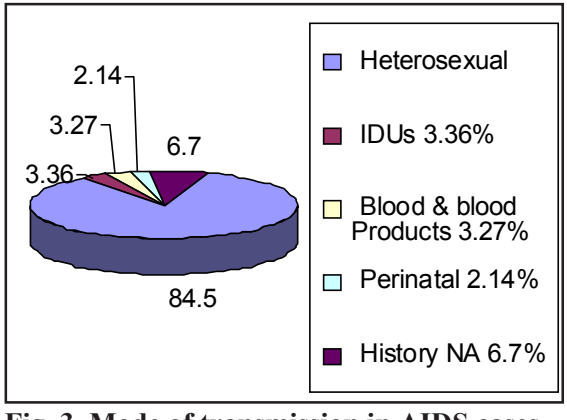

Fig. 3. Mode of transmission in AIDS cases in India : December 2002

7. HIV is now spreading from high risk behaviour groups to general population, as well.
8. HIV is spreading from urban to rural areas.
9. More and more women attending ante-natal clinics are testing positive, thus with the added risk of perinatal transmission, more children may be HIV infected

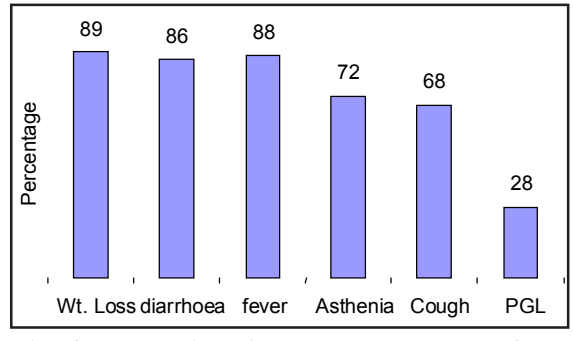

Fig. 4. Presenting signs and symptoms of AIDS cases in India, December 2002

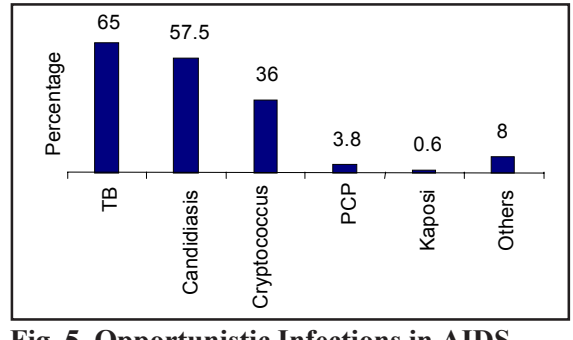

Fig. 5. Opportunistic Infections in AIDS cases in India : December 2002

10. Highest number of infection are reported to occur through the sexual contact.
11. About 89 percent of the reported cases are from the sexually active age group of 15 - 49 years.
12. Migration and mobility has increased the chance of the disease spreading to other areas/persons.
13. The social stigma attached to sexually transmitted infections also holds good for HIV/AIDS with more disastrous consequences.

Mode of HIV Transmission

Epidemiological studies throughout the world have shown three modes of HIV transmission. In adults 2/3 of the transmission occurs by hetro-sexual route, whereas in children, mother to child transmission is the predominant mode.

Mother - to- child transmission: HIV-infected woman can transmit HIV to her foetus or infant before, during, or after birth. A pregnant woman with HIV infection has an approximately 30% chance of passing the virus to her foetus or newborn baby. There is evidence that infection can occur as early as the first 12-15 weeks of gestation. 60% of perinatal infections are in utero or during the birth process. It is estimated that 40% of perinatal infections occur through breast-feeding.

Blood-borne infection: HIV-infected blood, blood products, transplanted organs or tissues and the use of improperly sterilized needles and syringes that have been in contact with infected blood can transmit HIV. This is the most efficient way of transmission of HIV. Even a small transfusion of infected blood results in virtually 100% seroconversion.

Sexual Route : Heterosexual or homosexual contact, is the major route of transmission. HIV can be transmitted through any individual act of unprotected sexual intercourse, that is, any penetrative sexual act in which a condom is not used where one partner is infected with HIV. Male-to-male sex occurs in all countries of the region and features significantly in the epidemic. Countries that have measured HIV prevalence among men who have sex with men have found it to be high

Throughout the region, injectable drug use drug use offers the epidemic huge scope for growth. About 50% of injecting drug users already have acquired the virus in parts of Malaysia, Myanmar, Nepal, Thailand and in Manipur in India, while HIV infections among Indonesia's growing population is increasing. Despite sweeping epidemics among injecting drug users, minimum services that can protect those drug users against HIV infection are not available in most of the region.

Issues in children

The epidemiological profile of HIV/AIDS in children in our country has not been clearly defined. As more and more women are being infected, the number of children born with HIV infection is increasing. It is estimated that 25 million pregnancies occur annually in India. With a prevalence of HIV around 1% in antenatal mothers.25, 000 children may be born every year with HIV infection. Children in households beset by illness and lack of food are severely affected. As parents fall ill and die, family burdens shift to the children. For many, neither money nor time is available for normal schooling to be continued. Opting out of school may help with cash needs over the short term but, in the long term, it entrenches the household's poverty and puts the children at greater risk of becoming infected with HIV. The result is a vicious circle linking poverty, food insecurity and HIV/AIDS. . It is estimated that about 1,20,000 children orphaned by AIDS epidemic are living in India. The responsibilities

of looking after younger brothers and sisters fall on the young shoulders of the eldest child in the family. There is a danger that orphaned children are ostracized or abused and their property rights trampled upon by their relatives. They face rejection, exclusion and discrimination. They tend to suffer from non- fulfilment of their nutritional, emotional and educational needs. These facts emphasize that Pediatric AIDS is not only a medical illness but also a psychological and social issue.

Conclusion

The future trajectory of the global HIV/ AIDS epidemic depends on whether the world can protect young people everywhere against the epidemic and its aftermath.

Just as certain sectors of society are at particular risk of HIV infection, certain conditions favour the epidemic's growth. As the current food emergencies in southern Africa show, the AIDS epidemic is increasingly entangled with wider humanitarian crises. The risk of HIV spread often increases when desperation takes hold and communities are wrenched apart. At the same time, the ability to stall the epidemic's growth also suffers, as does the capacity to provide adequate treatment, care and aupport.

It is vital that HIV/AIDS-related activities become an integral part of wider-ranging efforts to prevent and overcome humanitarian crises. Given that many of the factors facilitating HIV transmission (including periodic economic upheaval and high rates of population mobility) are rife throughout this region, no country is immune to a rapidly spreading and wide-scale epidemic. Most countries, though, still have a window of opportunity for mounting and sustaining HIV/AIDS initiatives that could avert such an outcome. A major challenge for India now is that of rapidly expanding the awareness and preventive programmes to all vunerable groups including the illiterate population and the rural community especially the women and adolescents.

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CONTRIBUTORS TO CORPUS FUND OF IJPP

Rs. 1000/-

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HIV INFECTION

IV DRUG ABUSE AND HIV IN NORTH-EASTERN INDIA

**** Brajachand Singh Ng***
***** Chourjit Singh Ksh***

Abstract: *Heroin and intravenous drug users constitute a special health risk group in view of their predilection to develop HIV infection and AIDS through sharing of needles and unprotected sexual intercourse. The states mainly affected by this risk group are Manipur and Nagaland and to a lesser extent, Mizoram, Meghalaya and other States of North Eastern India.*

Keywords: *Intravenous drug abuse, HIV North-Eastern India*

Introduction

By the end of 2002, forty two million people had been infected with HIV and by the end of 1999, twenty one million people had died of AIDS. In India alone, 3.97 million people had been infected with the virus and the country has the largest number of people living with HIV, next to South Africa. According to the National AIDS Control Organization (NACO), 6.7% of the HIV infections in India are attributable to Injecting Drug Use (IDU) route of transmission. Sharing of infected needles for injecting drugs and unprotected sex makes Injecting Drug Users (IDUs) vulnerable to HIV and in turn, makes them core transmitters of the virus, transmitting the virus to the general population. In India, the epidemic of HIV among IDUs started in Manipur. There has been speculations on how the HIV/AIDS epidemic has spread so rapidly among the IDUs in Manipur compared to other North East states of India, i.e. Assam, Meghalaya, Mizoram and Nagaland.

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Manipur

Manipur is geographically very close to the notorious Golden Triangle (between Myanmar, Thailand and Laos) where more than 20% of world's heroin drug is reportedly produced. Due to proximity to the "Golden Triangle" with perforated borders, Manipur became an alternative route for illegal international drug trafficking in the late seventies and early eighties. Soon, Manipur became a "User State" by early eighties. Pure heroin which is the injectable form, locally known as "No 4" is easily available. The problem of "Heroin addiction" reached an explosive situation in 1984 when many gruesome murders connected with drug occurred in the state. [1]

The first positive case was, reported by the Government in February 1990. As of March 2003, a total of 15,043 HIV positive cases (2,253 females) and 1,998 AIDS cases (290 deaths) were reported out of 95, 256 blood samples screened, giving a seropositivity rate of 157.92 per 1000 blood samples screened.[2] Manipur, with hardly 0.2% of India's population is contributing to nearly 8% of India's total HIV positive cases.

In a study conducted by ICMR in Manipur in 1991, all the 450 drug users interviewed used injectable heroin. They were

predominantly (95%) male. The age range of the IDUs was found to be between 12 and 35 years. Peer pressure and curiosity were the most common reasons cited for initiating heroin use. It was reported that females comprised about 5 - 8% of injecting drug users, even though their numbers were increasing.[3] The occupational distribution of IDUs revealed that 53% of them were unemployed including 34% who were students. Most of the IDUs were staying with their families, who were trying to cope with social and economic pressures thus created within the home. The educational status of the IDU problem population was quite high. [4]

Nagaland

In 2001, the prevalence of HIV among the IDUs was 6.5% and among the STD clinic attendees, it was 7.4%. The prevalence of HIV in the antenatal population in 2001 was 1.25%. According to NACO's classification, Nagaland falls under the category of high HIV prevalent states. ICMR estimated the size of the IDU population in Nagaland as 1500 in 1992 - 93, nearly ten years back.[5] Different individuals and NGOs working with IDUs in the state as well as other parts of India have their own "guestimates", ranging from 5,000 to 20,000.

Meghalaya

Testing for HIV in Meghalaya began in the year 1990. The first seropositive case was detected in the year 1990. Upto the year 2002, 17,664 samples were screened, of which 62 tested positive for HIV; 10 cases of AIDS have been reported. Out of the 62 people tested positive for HIV upto March 1998, 13 were blood donors, 15 were IDUs, 3 were STD patients, 1 antenatal woman, 2 suspected AIDS cases and 28 others. The spouses of four of the seropositives were also found to be infected with HIV.[6] The estimated HIV prevalence among IDUs measured in the Sentinel Sites for IDUs was 1.41% in 2000[7].

Mizoram

According to the State AIDS Control Society, 29,870 blood samples were screened till March 1998 and 96 were found seropositive for HIV. In the study conducted by ICMR in 1991, HIV prevalence among IDUs in the state was found to be 8 - 10%. In a study at the Surveillance Center of Regional Medical College (presently Regional Institute of Medical Sciences), Imphal till the end of 1991,1.5% of the 1000 samples from Mizoram were positive for HIV and 80% of the HIV positives were IDUs[6]. In the 2000 round of the Sentinel Surveillance, the HIV prevalence among STD clinic attendees at Aizawl site was 2%. Among the women attending ANCs, the HIV prevalence was 0.37% during 2000[7].

Assam

Screening for HIV in Assam was started by Gauhati Medical College (GMC) and Indian Council of Medical Research in 1988 and 12 samples were found to be seropositive out of 11,352 samples tested for HIV. The first AIDS case in the state was detected in 1990[6]. 1n 2000, the prevalence of HlV among STD clinic attendees was 0.61 % and in 2001, it was 1.49%. The prevalence of HIV in the antenatal population in 2000 and 2001 was 0%. There is no surveillance of HIV among IDUs in Assam. According to NACO's classification, Assam falls under category of low prevalence states[7]. The study by the Regional Medical Research Centre found that the prevalence of HIV infection in Assam was at a lower level than the rest of the country and at a much lower level than the neighbouring states of Manipur and Nagaland. Between January 1990 and May 1993, the Regional Medical Research Centre, Dibrugarh undertook HIV screening in upper Assam. 1992 were tested from general population (501 tea garden labourers and 1491 oil industry employees) and none were found seropositive.

In another study among different high risk groups, 9350 samples were screened and nine of the samples were found seropositive. Of the ones who tested HIV positive, two were recipients of blood transfusion, two were IDUs from Nagaland, and five were from floating population, temporarily residing in Assam, with history of heterosexual promiscuity[6]. The NACO behavioral survey study conducted in Assam in 2002 has reported that 2.2% of the clients of sex workers in Assam have reported injecting in the past 12 months.[7]

Intervention for injecting drug users

The basic message for prevention of HIV infection among the injecting drug users are :

1. Total abstinence from drugs – Say No to Drugs and Yes to Life.
2. If you cannot do that, use orally and do not inject. You should use legal and less harmful drugs like Buprenorphine instead of more harmful and illegal drugs like heroin.
3. If you cannot give up injecting drugs, you should not share needles and syringes with others in all situations.
4. If you have to share needles and syringes under some compelling circumstances, then you should sterilize needles and syringes with 5% bleach with the standard sterilization procedure. The strategy is based on "Harm Reduction" or "Harm Minimization". In order to ensure effective implementation of the "Harm Reduction Programme" in Manipur, the programme is integrated with care component and it is called "Rapid Intervention and Care" (RIAC) Project. Manipur is the first state in India to have adopted Harm Reduction Programme.

Research needs:

1. To carry out community prevalence of Sexually Transmitted injection (STI) / HIV
2. To address cross border drug trafficking
3. To carry out behaviour survey among IDUs
4. To focus attention in youth and adolecents

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HIV INFECTION

CLINICAL MANIFESTATIONS OF HIV INFECTION IN CHILDREN

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Abstract : *Most of HIV-infection in children are vertically transmitted i.e. acquired from mothers. Blood and blood products, however, remain an important source and are responsible for infection in 10 – 30 % of total cases in the developing countries. Approximately 10 to 20% of infants experience rapid progression of disease and die of AIDS related complications by 4 years of age. The mean survival time for the remaining 80-90% infected children is approximately 9-10 years*

Clinical manifestations depend on the severity of immunosuppression. These in the initial stages may be nonspecific and consist of failure to thrive, recurrent fever, diarrhoea, and respiratory infections. Children may have hepatosplenomegaly, lymphadenopathy, neurological manifestation and recurrent bacterial infections.

Co-existent tuberculosis (TB) and HIV infections accelerate the progression of both the diseases. HIV infected children are more likely to have extra-pulmonary and disseminated tuberculosis; the course is also likely to be more rapid. The relative risk of active tuberculosis in children infected with HIV is at least 5 to 10 fold higher than that in children not infected with HIV.

Apart from infections, other manifestations include progressive encephalopathy (PE), cardiovascular problems including left ventricular dysfunction, lymphocytic interstitial pneumonitis (LIP), anemia, neutropenia, absolute or relative lymphopenia, thrombocytopenia, and eosinophilia, rheumatological manifestations such as biphasic Raynaud's syndrome, necrotising vasculitis, lip necrosis, livedo reticularis, knee arthalgia, vasculitis, and septic arthritis.

Clinical case definition of HIV infection given by WHO includes combination of symptoms and signs and has poor sensitivity but good specificity. One should suspect HIV infection in a child who presents with symptoms described in category C of CDC, has specific illness like LIP, has atypical manifestations of common illnesses, presents with combination of symptoms or born to HIV positive parents.

Key words: *Pediatric HIV, AIDS, Clinical manifestations.*

A syndrome of immune deficiency with opportunistic infections was first described in 1982 and the first publication of HIV/AIDS in children appeared in 1983. At the end of 2002, it is estimated a total of 42 million individuals were infected globally, of which 3.2 million (7.6%) were children below 15 years of age. Ninety five percent of the infected individuals are in the developing countries. Of the 3 million deaths due to HIV in 2001, 0.6 million (20%) occurred in children below 15 years. Disproportionately higher mortality in children suggests a more aggressive course in children. The estimated number of people living with HIV/AIDS in India

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by the end of 2001 were 3.97 million, of which 0.17 million (4.3%) were children below 15 years[1].

Modes of transmission

Most of the infections in children are vertically transmitted i.e. acquired from mothers. Blood and blood products, however, remain an important source and are responsible for infection in 10 – 30 % of total cases in the developing countries[2]. Some of the mothers also acquire HIV through blood transfusion and transmit the infection to their babies[3].

Natural history of vertically transmitted HIV infection.

The clinical course of vertical HIV-1 infection is highly variable, but before the widespread use of antiretroviral therapy, two general patterns of survival were described. Approximately 10% to 20% of infants experienced rapid progression of disease and died of AIDS related complication by 4 years of age. The mean survival time for the remaining 80-90% infected children was approximately 9-10 years[4]. In a cohort of infants followed from birth, by 12 months of age 83% had shown some sign of HIV disease, 74% had progressed to category A, 55% to category B, 21% to category C and 6% to death[5]. Hepatomegaly and lymphadenopathy were the most common category A signs during first 6 months of life. In another cohort study, category C events or deaths were estimated for 20% of perinatally infected infants in the first year of life, with approximately 5% succumbing per year thereafter[6].

Analysis of data from Pediatric Spectrum of Disease project in the USA showed that the mean time spent by perinatally infected children in each stage were: N, 10 months; A, 4 months; B, 65 months; and C, 34 months[4]. In this study, it was estimated that a child born with HIV infection had a 50% chance of severe signs or symptoms by 5 years of age, and a 75% chance of surviving to 5 years of age. The estimated mean time from birth to stage C was 6.6 years, and the estimated mean survival time was 9.4 years. This study highlighted that perinatally infected children progress to moderate symptoms in the second year of their life and then remain moderately symptomatic for more than half of their expected life span. This clearly underscores the need for their clinical care before the onset of AIDS.

In an African study, the estimated risk of death among perinatally infected children at 2 and 5 years of age was 45% and 62% respectively; the median survival time was 12.4 months[7]. This study observed that early infection, early onset of HIV-related conditions, failure to thrive, and generalized lymphadenopathy were associated with subsequent risk of death, whereas LIP was predictive of a milder illness. Thus the prognosis appears to be poorer in the African children. There are no Indian data to describe the natural history of HIV infection in Indian children.

The available pediatric data is in contrast with data from adults that link disease expression and survival with viral load or immunosuppression in each individual. In children the disease progression is much faster than in adults.

Clinical manifestations

Clinical manifestations depend on the severity of immunosuppression. These in the initial stages may be nonspecific and consist of failure to thrive, recurrent fever, diarrhoea, and respiratory infections. Children may have hepatosplenomegaly, lymphadenopathy, neurological manifestation and recurrent bacterial infections. In contrast to adults who present more frequently with distinct HIV-associated conditions, infected children in

Table 1. Clinical features in HIV infected children

	Tovo et al '92 [8]	Italian Register for HIV infection '94[10]	
	(n=285)	(n=22)	(n=22)
Failure to thrive	49.9%	49%	78%
Fever	43%	42%	71%
Diarrhea	30.9%	31%	50%
Hepatomegaly	86.8%	84%	83%
Lymphadenopathy	78%	91%	58%
Splenomegaly	75.3%	75%	76%
Neurological invl.	23.8%	11%	58%
LIP	13.9%	17%	20%
Recurrent serious bacterial infections	12.7%	15%	26%

Table 2. Clinical features in HIV infected African children (figures in %)[11]

	Rwanda (n=107)	Zaire (n=201)	Zimbabwe (n=190)	Uganda (n-755)	Nigeria (n=63)
Wt. Loss/FTT	89	97	54	80	50.8
Chr. diarrhea	83	62	25	66	38
LRTI	70	61	41	49	31
Chr. Fever	58	85	NA	71	50.8
Lymphadenopathy	91	24	65	31	58.7
Hepatomegaly	66	52	31	NA	19
Oral Thrush	40	NA	18	55	19
Neurological	NA	18	NA	3	9.5
Recurrent infection	NA	NA	41	17	NA

developing countries commonly present with a disease spectrum that is similar to uninfected children [3, 8-14] (Table 1-3).

The Centre for Disease Control and Prevention (CDC), USA has classified clinical features of Pediatric HIV infection into 4 clinical categories for children below 13 years of age[14]. Once classified, a child cannot be reclassified into a less severe category even if the child's clinical status improves such as in the case of immune reconstitution following institution of anti-retroviral therapy or resolution of clinical event.

1. Category N, describes asymptomatic children without signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.
2. Category A: Children classified as category A should have two or more mild symptoms

Table 3. Clinical features in HIV infected Indian children

Clinical features	Merchant et al [12] (n=285)	Lodha et al [3] (n=22)	Dhurat et al[13] (n=22)
Failure to thrive (FTT)	45.6	100	48.6
Recurrent/ Persistent pneumonia	8.4	86.3	24.3
Chronic/ recurrent diarrheoa	15.1	45.5	27.2
Lymphadenopathy	23.5	40.9	35.1
Hepatomegaly		81.8	51.9
Oral candidiasis	14.3	36.4	48.6
Splenomegaly		63.6	
Hepatosplenomegaly	28.8		67.5
Tuberculosis	29.5	59.1	
CNS involvement	4.6	13.6	
Bronchiectasis		9.1	
Asymptomatic	16.8		

Figures are in %.

of HIV – related conditions such as: lymphadenopathy, hepatomegaly, splenomegaly, dermatitis, parotitis, recurrent upper respiratory infections, sinusitis, otitis media. Children with category B or C clinical conditions do not remain in category A, even if they have multiple category A conditions.

3. Category B defines children who are moderately symptomatic with HIV– related conditions. These include anemia, neutropenia or thrombocytopenia persisting for more than 30 days; single episode of bacterial meningitis, pneumonia, or sepsis; CMV infection before 1 month of age; hepatitis; recurrent or chronic diarrheoa; lymphoid interstitial pneumonia (LIP); disseminated varicella – zoster virus infections. Inclusion in category B can occur only in the absence of category C conditions.

4. Category C conditions, with the exception of LIP, are AIDS defining conditions. These include recurrent severe bacterial infection (meningitis, pneumonia, septicemia, etc.), esophageal/pulmonary candidiasis, cryptosporidiosis, CMV disease at >1 month of age, disseminated/extra pulmonary mycobacterial tuberculosis, pneumocystis carinii pneumonia (PCP), HIV-encephalopathy.

This classification system provides a useful guideline for pediatricians to evaluate HIV progression in children. In addition, it serves as a standard for researchers world wide to measure the importance of clinical events and in drug trials.

Apart from clinical manifestation the severity of illness can be assessed by CD4 cell counts in blood [14]. Lymphocyte counts and their subgroups depend on age and the cut-off values are different from adults. Status of immunologic function based on CD-4 counts according to age is given in Table 4.

Table 4. Immunologic categories based on age specific CD-4 T Lymphocyte counts.

Immunologic categories	Age of Child					
	<12 mo		1-5 yrs		6-12yrs. %	
	Cells/mm^3	. %	Cells/mm^3	%	Cells/mm^3	%
1. No evidence of Suppression	> 1500	> 25	> 1000	> 25	> 500	> 25
2. Moderate Suppression	750-1499	15-24	500-999	15-24	200-499	15-24
3. Severe Suppression	>750	<15	<500	<15	<200	<15

Some of the conditions are described in detail in the following sections.

Recurrent bacterial infections [15,16]

There is failure of both cell mediated and humoral immunity. Despite hypergamma globulinemia, these children are at risk for severe and recurrent bacterial infections. There is delay in clearing of infections caused by the usual pathogens. Serious bacterial infections include bacteremia, meningitis, pneumonia, osteomyelitis, septic arthritis, and abscesses at various sites. Bacteremia is the most common laboratory-documented serious bacterial infection. Acute pneumonia is the most common clinically diagnosed severe bacterial infection. In various Indian studies, up to 90% of HIV-infected children had history of recurrent pneumonias. Initial episodes of pneumonia often occur before the development of significant immuno-supression. As the immunosupression increases the frequency increases. The common pathogens for community-acquired pneumonia in these children are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*. However in children with severe immunosupression and in hospital-acquired infections, gram negative organisms, such as, *Pseudomonas aeruginosa* gain importance.The clinical features of pneumonia in HIV-infected children are similar to those in uninfected children. However, in severely immuno-compromised children, the signs may be subtle. Often, the response to therapy is slow and the relapse rates are high. Bacteremia may be more common, seen in up to 50%. Sinusitis is the second most common clinically diagnosed bacterial infection in HIV-infected children. The clinical presentation is similar to those of immunocompetent children. A history of nasal discharge and persistent cough for more than two weeks should prompt suspicion of sinusitis in HIV-infected children. The prevalence of meningitis, osteomyelitis, septic arthritis, pericarditis and cellulitis does not appear to be unusually high. The pathogens for these infections are the same as those isolated from immunocompetent children; the clinical features are also similar. In addition, these children are prone to develop various minor bacterial infections; the clinical features are similar to immunocompetent children.

Tuberculosis [17,18]

With the spread of the HIV infection, there has been resurgence in tuberculosis. The two

diseases have significantly detrimental interactions. Co-existent TB and HIV infections accelerate the progression of both the diseases. HIV infected children are more likely to have extra-pulmonary and disseminated tuberculosis; the course is also likely to be more rapid. An HIV infected child with tubercular infection is more likely to develop the disease than a seronegative child. The overall relative risk of active TB in children infected with HIV is at least 5 to 10 fold higher than that in children not infected with HIV. In the absence of significant immunosupression, the clinical manifestations are not much different from that in seronegative children. In patients with low CD4 counts, the pulmonary lesions are more extensive. Mediastinal adenopathy is also more frequently seen. Pleural effusions are uncommon. Diagnosis of TB in infected children poses greater challenges than in other children. Even with the use of a lower cut-off of 5 mm, the tuberculin test is often negative, particularly in children with severe immunosupression. In extensive disease, the bacteriological confirmation rates are likely to be greater. All attempts should be made to isolate Mycobacterium tuberculosis. Other than providing definitive diagnosis, it offers the opportunity to do sensitivity analysis. The incidence of multi-drug resistant tuberculosis is higher in HIV infected patients.

Infection with Mycobacterium avium-intracellulare (MAI) [19]

Pulmonary disease with MAI is uncommon in children with HIV infection, despite immunosuppression. The common symptoms and signs include: persistent fever, failure to thrive, night sweats, lymphadenopathy, organomegaly, and refractory anemia. The pulmonary lesions are usually limited to lymphadenopathy and localized parenchymal lesions. The diagnosis of disseminated disease primarily depends on isolation of the organism from blood. Current therapy for disseminated MAI infection includes the use of a combination of clarithromycin or azithromycin with ethambutol.

Pneumocystis carinii pneumonia [19,20]

PCP is the most common opportunistic infection in HIV-infected children. However, there is lack of data from India to define the magnitude of the problem. The data from Africa show a low incidence of PCP. Children with PCP are more sick than the adults with this infection. The case fatality rates are also higher. In 1992, the estimated median survival after diagnosis of PCP, was 19 months. The onset may be acute in infants. Older children are more likely to have a more indolent and protracted course. The clinical manifestations include tachypnea, dyspnea and fever. The examination of the chest is unremarkable except for tachypnea and retractions. Asymmetric breath sounds, crepitations and rhonchi are uncommon. The chest radiograph commonly reveals diffuse interstitial lung disease without hilar adenopathy. Other patterns include localized infiltrates, hyperinflation, and non-cardiogenic pulmonary edema. The radiograph may be normal in less than 5% children. Hypoxemia is the hallmark of PCP. A markedly elevated (A-a)DO_2 and a high serum LDH level are often seen.

The diagnosis of PCP begins with the suspicion. The diagnosis requires demonstration of cysts or organisms in lung secretions or tissue. Induced sputum, nasopharyngeal swab and BAL are feasible techniques to detect Pneumocystis carinii. Various stains can be used for detection: 1) Stains for the organism such as Giemsa stain, 2) Cyst wall stains such as Gomori's methenamine-silver nitrate, toluidine blue Ostain, and 3) immunospecific stain which stains both the trophozoites and cysts. The latter technique may provide a far more accurate and specific diagnosis of PCP. However, it is time

consuming. PCR has also been used for detecting the organism in respiratory secretions.

Viral infections[19]

In children with AIDS, disseminated CMV is a known opportunistic infection, but pneumonia is rare. Prospective data showed that when HIV-infected children develop respiratory syncytial virus disease, they are less likely to wheeze and more likely to have pneumonia and prolonged shedding of the virus. Infections with influenza, herpes simplex and varicella viruses have been reported but are uncommon.

Fungal infections [19]

Fungal infections especially invasive infections are also seen more frequently. These include candidiasis, cryptococcosis, histoplasmosis and aspergillosis. Mucosal and cutaneous fungal infections are more commonly seen than systemic infections. Most HIV-infected children develop oral candidiasis at least once. These children are also at an increased risk of esophageal candidiasis. Pulmonary fungal infections usually present as a part of disseminated disease in immuno-compromised children. Primary pulmonary fungal infections are uncommon. Pulmonary candidiasis should be suspected in any sick HIV-infected child with lower respiratory tract infection that does not respond to the common therapeutic modalities. A positive blood culture supports the diagnosis of invasive candidiasis. Aspergillosis is an uncommon infection in HIV-infected children. Invasive disease is common in these children. It usually presents as persistent pneumonia associated with atelectatic or large apical cavitatory lesions. Pneumothorax is common. Diagnosis of invasive bronchopulmonary aspergillosis must be considered in a child with compatible clinico-radiologic picture and recovery of organism in pure culture from BAL, if other causes are excluded. In children with advanced HIV infection, the disease runs an aggressive course. Cryptococcosis commonly presents as a subacute meningitis or meningoencephalitis; many children may present with nonspecific, subtle symptoms, including fever and headache. Pulmonary involvement may be seen in half of these children. However, isolated pulmonary cryptococcosis is not commonly seen. Other uncommonly reported fungal infections include histoplasmosis and coccidioidomycosis.

Lymphoid interstitial pneumonitis (LIP)[21]

LIP has been recognized as a distinctive marker for pediatric HIV infection and is included as a Class B condition in the revised CDC criteria for AIDS in children. While the prevalence in HIV infected children in the west has been reported to be around 20%, figures from Africa suggest that it is not common. The etiology and pathogenesis of LIP are not well understood. Suggested etiologies include: an exaggerated immunologic response to inhaled or circulating antigens, and/ or primary infection of the lung with HIV, Ebstein-Barr Virus, or both. There is evidence to suggest that EBV plays significant pathogenetic role in LIP. LIP is considered to reflect the local response to persistent antigenic stimulus. This stimulus could be EBV, which is a potent, polyclonal stimulator for B cells. Primary infection with HIV may be directly responsible for LIP. LIP is more common in children with perinatally acquired HIV infection than in children who acquire the infection by other route. This may be due to direct intrauterine or intrapartum exposure of lung tissue to HIV. It is likely that LIP represents primary infection of the lungs. Subsequent histopathologic and clinical expression of the disease may be driven by postnatally acquired primary EBV infection. LIP is characterized by nodule formation and diffuse infiltration of the alveolar septae by lymphocytes, plasmacytoid lymphocytes, plasma cells and

immunoblasts. There is no involvement of the blood vessels or destruction of the lung tissue. Children with LIP have a relatively good prognosis compared to other children who meet the CDC surveillance definition of AIDS. LIP is usually diagnosed in children with perinatally acquired HIV infection when they are older than 1 year of age. In contrast, PCP is diagnosed typically in the first year of life. Most children with LIP are asymptomatic. Tachypnea, cough, wheezing and hypoxemia are usual signs of fully expressed disease; crepitations are uncommon. Clubbing is often present in advanced disease. These patients can progress to chronic respiratory failure. Long standing LIP may be associated with chronic bronchiectasis. The presence of a reticulonodular pattern, with or without hilar lymphadenopathy, that persists on chest radiograph for 2 months or greater and that is unresponsive to antimicrobial therapy is considered presumptive evidence of LIP. Care should be taken to exclude other possible etiologies. A definitive diagnosis of LIP can only be made by histopathology.

Diarrhoea [22, 23]

Diarrhoea – acute, recurrent and persistent – is a common disorder in HIV infected children. In a HIV child, infection with any enteropathogen can result in prolonged diarrhea and malabsorption with subsequent malnutrition. The etiologic agents for diarrhea in HIV infected children include the common enteropathogens, C. jejuni, Helicobacter cinaedi, Shigella and cryptosporidium. Cryptosporidium is associated with voluminous profuse watery diarrhea, anorexia, weight loss and even death in HIV–infected individuals. Stool contains mucus but no blood or leukocytes. Diarrhea may also be due to systemic infection with atypical mycobacteria, CMV, HIV enteropathy, drugs or bacterial overgrowth. The risk of persistant diarrhea is increased especially with cryptosporidium.

HIV encephalopathy [21,24]

Human immunodeficiency virus type-1 (HIV-1)-associated neurologic disease, known as "HIV-1-associated progressive encephalopathy" (PE), is a common concomitant in the progression towards AIDS. PE, characterized by a triad of symptoms including impaired brain growth, progressive motor dysfunction, and loss or plateau of developmental milestones, is believed to result from both direct and indirect effects of HIV-1 infection on the central nervous system (CNS). Consequent to the hallmark systemic immune deficiency of HIV infection, the CNS becomes susceptible to opportunistic infections, which add further morbidity and mortality, and may contribute either directly or indirectly to neurologic symptoms which can often mimic PE. Static encephalopathies (SE) represent fixed, nonprogressive neurologic or neurodevelopmental deficits in HIV-infected children. SE may or may not be caused by HIV infection but are often associated with such identifiable insults as prematurity, in utero exposure to toxins or infectious agents, or head trauma. Additional neurological manifestations of HIV infection are seizures, cerebrovascular complications (i.e., stroke), myelopathies, neuromuscular syndromes, and CNS complications of opportunistic infections. Neurobehavioral aberrations have also been observed in pediatric HIV infection.

Cardiomyopathy[25]

Cardiovascular problems associated with HIV infection including left ventricular dysfunction and increased left ventricular mass are common and clinically important indicators of survival for children infected with HIV. A prospective multicenter cohort study has evaluated 205 vertically HIV-infected children enrolled at a median age of 1.9 years, 600 HIV-exposed children enrolled prenatally or as

neonates, of whom 93 were ultimately HIV-infected. The main outcome measures were echocardiographic indices of left ventricular dysfunction. Left ventricular dilatation, heart failure, and/or the use of cardiac medications were more common in infected compared with uninfected children. The mortality rate 1 year after the diagnosis of heart failure was 52.5% [95% CI, 30.5-74.5]. Authors concluded that cardiac dysfunction occurred in 18% to 39% of HIV-infected children and was associated with an increased risk of death. They have recommended that HIV-infected children should undergo routine echocardiographic surveillance for cardiac abnormalities. Zidovudine-induced cardiomyopathy has also been reported[21].

Hematological manifestations [21]

Hematological manifestations in pediatric HIV infection include anemia, neutropenia, absolute or relative lymphopenia, thrombocytopenia, and eosinophilia. Severe thrombocytopenia and anemia are correlated with poor prognosis. These abnormalities may occur because of peripheral destruction of blood elements, HIV replication, poor nutritional status, and adverse effects of medications.

Rheumatological manifestations

Rheumatological manifestations are uncommon in HIV-infected children. In one study, these were identified in 5 (19.2%) of 26 children [26]. These included biphasic Raynaud's syndrome, necrotising vasculitis, lip necrosis, livedo reticularis, knee arthalgia, vasculitis, and septic arthritis of the ankle. All of the rheumatologic manifestations were seen in advanced stages of HIV disease. These rheumatologic changes were similar to those reported for HIV-positive adults.

Oral manifestations

Oral manifestations are directly related to the degree of immunosuppression and such lesions can be considered as indicators of the progression of the HIV infection in children. In one study[27] involving 80 HIV-infected children (average age 6.30+ 3.32 years), 30 (38%) had some type of oral lesions; the CD4 counts were lower than that found in lesion-free children. Common lesions included candidiasis (22.5%), gingivitis (17.5%), enlargement of parotids (8.8%), herpes simplex (1.3%) and hairy leukoplakia (1.3%).

Other manifestations [19,21]

HIV-infected children also suffer from various infectious and non-infectious conditions of the skin. Non infectious conditions include seborrheic dermatitis, atopic dermatitis, eczema, drug eruptions and skin lesions associated with nutritional deficiencies. Up to 10% of HIV-infected children may have nephropathy. This may manifest with hematuria, proteinuria, renal tubular acidosis, and acute renal failure. These manifestations are more common in children with advanced disease. Majority of HIV-infected children suffer from nutritional and growth abnormalities. Growth retardation in HIV infected infants is evident as early as 4- 6 months of age. HIV infection or associated opportunistic infections first affect linear growth. Overall effect on height for age is more than weight for age. Early growth delay has been correlated with high viral load. In addition, recurrent infections, decreased oral intake because of oral and esophageal lesions, and various organ dysfunctions also contribute to failure to thrive. Hepatomegaly is a common clinical manifestation of pediatric HIV disease. Histopathological findings in liver include: fatty infiltration of hepatocytes, portal inflammation, CMV inclusion bodies and giant cell transformation, and chronic active hepatitis characterized by lymphocytic infiltration in portal spaces and lobules. Lymphadenopathy is seen in infants and children infected with HIV.

Generalized lymphadenopathy may be because of HIV infection, other viral infections (Ebstein Barr virus or CMV), opportunistic and mycobaterial infections and malignancies (lymphoma/ leukemia). The prevalence of malignancies in HIV infected children is believed to be significantly higher than in the normal population. The common malignancies reported in HIV infected children include: non Hodgkin's lymphoma, leiomyosarcoma or leiomyoma, leukemia, Kaposi's sarcoma, Hodgkin's lymphoma, vaginal carcinoma in situ and tracheal neuroendocrine carcinoma.

Clinical case definition of HIV infection

Since majority of HIV infection are acquired vertically, the best method for identification of HIV infection would be to screen all mothers and suspect HIV in babies born to HIV positive mothers. Since screening of mothers for HIV is not done universally and some patients get HIV infection through transfusion of blood and blood products, we may see children with clinical manifestations of HIV in majority.

Because of the limited availability of HIV diagnostic testing, attempts have been made to formulate clinical AIDS definitions for adult and children in developing countries. Use of the Center for Disease Control and Prevention (CDC) guidelines for clinical classification of HIV infection in children is problematic because they were designed to measure HIV disease progression, not for the identification of children infected with HIV. In addition, many category C (or AIDS) diagnoses are beyond the diagnostic capabilities of most of the developing world.

Table 5. Clinical Case Definitions of Pediatric AIDS

World Health Organization (WHO) Clinical Case Definition for AIDS in Children

Major signs:	Minor signs:
Weight loss or failure to thrive	Generalized lymphadenopathy
Chronic diarrhea (>1 mo)	Oro-pharyngeal candidiasis
Prolonged fever (> 1 mo)	Repeated common infection (otitis, pharyngitis, etc.)
	Persistent cough (> 1 mo)
	Generalized dermatitis
	Confirmed maternal HIV infection

Pediatric AIDS is suspected in an infant or child presenting with at least two major signs associated with at least two minor signs in the absence of known causes of immunosuppression.

Modified WHO clinical Case Definition for Pediatric AIDS

Major criteria:	Minor criteria:
Weight loss or failure to thrive	Generalized lymphadenopathy
Chronic diarrhea (>1 mo)	Oro-pharyngeal candidiasis
Prolonged fever (> 1 mo)	Repeated common infection
Severe or repeated pneumonia	
Generalized dermatitis	
Confirmed maternal HIV infection	

Pediatric AIDS is suspected in an infant or child presenting with at least two major signs associated with at least two minor signs in the absence of known causes of immunosuppression.

Several simple clinical case definitions pertinent to the developing world have been devised and tested, including the WHO clinical case definition[28] (Table 5). These definitions detect the presence of symptomatic AIDS and not HIV infection itself and are confounded by prevalent conditions such as malnutrition, diarrhoeal disease and tuberculosis. There are no published studies in literature to test the sensitivity and specificity of WHO's modified criteria in Indian patients. The reported[12,13] sensitivity of individual factors including weight loss or failure to thrive is 45-100%, Chronic diarrhea (>1 mo) 15-45%, and severe or repeated pneumonia 8-86%. For minor criteria such as generalized lymphadenopathy is 23-41% and for oro-pharyngeal candidiasis 14-48%. The wide variation in sensitivity is due to different clinical settings. The published studies do not mention about the sensitivity of two major signs associated with at least two minor signs.

One should suspect HIV infection in a child who presents with symptoms described in category C of CDC, has specific illness like LIP, has atypical manifestations of common illnesses, presents with combination of symptoms or born to HIV positive parents.

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HIV INFECTION

LABORATORY DIAGNOSIS OF PEDIATRIC HIV

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Two distinct human immunodeficiency viruses, HIV-1 and HIV-2 are the etiologic agents of AIDS. HIV-1 subtype C is the commonest variant in India. The prevalence of HIV-2 in India is believed to be between 6-11%. Initially the HIV infection alone does not cause significant clinical manifestations. Thus, laboratory diagnosis is the only method of determining the status of HIV infection in an individual during the long asymptomatic period.

The purpose of this article is to outline various laboratory tests available to detect HIV infection.

Kinetics of antibody response in a HIV infected person

An understanding of the sequence of events that follow the entry of the virus into the body will help to understand the optimal usage of various HIV tests during different stages of HIV disease.

- Viral entry into the body leads to a transient period of high plasma viremia and p24 antigenemia. Their levels come down within 1-2 months with concomitant immune response.
- Antibodies against structural envelope proteins (gag:p15,p17,p24,p55; env:gp41, gp120, gp160 and pol:p31,p51 and p66), regulatory proteins (nef, rev, tat) and accessory proteins (vif and vpu) are produced. Structural proteins are strongly immunogenic and almost all tests are based on the antibody detection against them.
- Antibodies against gag proteins (p24 and p55) are the first to appear and first to decline. However, antibodies to the 'env' proteins persist throughout.
- IgG response is consistent and better understood. IgM is valuable in the early identification of seroconversion. Anti HIV IgA assay in newborn is diagnostic of congenital infection as the IgA antibodies do not cross the placenta. However, IgA and IgM responses are inconsistent.

The adverse economic, social and psychological cost of false positive and false negative assays for HIV infection has pushed the investigators and manufacturers to develop diagnostic kits with high sensitivity and specificity.

Objectives of HIV testing

1] To monitor the trends of HIV infection in a population or a subgroup for facilitation of intervention.

2] To test donated blood and prior to organ donation for ensuring safety of the recipients.

3] To identify individuals with HIV infection [for diagnosis and for voluntary testing]

4] Research.

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HIV testing strategy

Depending upon the objectives different procedures and strategies are adopted.

Unlinked anonymous testing: This screening is not directed towards the individual, the blood collected for other purpose is used for testing. It is an epidemiological method for measuring the prevalence of infection.

Voluntary confidential testing: Testing for diagnosis. Maintaining confidentiality is important.

Mandatory testing: Such testing is recommended for screening of donors[semen, organs, tissues].

Strategies of HIV testing in India

Various categories of tests are used in combinations

1] ELISA/Simple/Rapid/, Elisa/Rapid/Simple used in strategy I, II

2] Supplemental tests like Western Blot, Line immunoassay are used in problem cases or when results are indeterminate.

Strategy I: Serum is subjected to one E/R/S for HIV. If negative it is to be considered free of HIV and if positive the sample is taken as positive. This method is used for ensuring donation safety.

Strategy II: A serum is considered negative if the first ELISA is negative. If reactive it is subjected to a second ELISA which utilizes a different system from the first one. It is reported reactive only if the second test confirms the results of the first. This strategy is used for surveillance and diagnosis only if some indicator of the disease is present

Strategy III: It is similar to the above strategy II with the addition of a third reactive ELISA being required for a sample to be considered as positive. The test for the first ELISA should have high sensitivity and for the second and third ELISA high specificity. It is used to diagnose infection in asymptomatic individuals.

Testing for HIV infection involves aspects of pretest counselling, explicit consent and confidentiality. Laboratory safety must be strictly followed according to good laboratory practice (GLP) guidelines and universal precautions must be observed.

Four types of tests are available:

1. Anti HIV antibody tests
2. Virus based tests
3. Immunological tests
4. Surrogate markers

Specimens used to test for HIV infection

1. Antibody detection: Blood, serum/plasma
2. Antigen detection: Serum/plasma, CSF, cell culture supernatant
3. Virus isolation and detection of viral nucleic acids: Plasma, semen, vaginal/cervical specimens, CSF.

Less successful- Saliva, urine, breast milk, amniotic fluid and tears.

Anti HIV antibody tests

There are two categories:

I. Screening tests

II. Supplemental tests

I. Screening tests

a. Conventional micro well ELISA tests

b. Rapid tests

Screening tests employed should test antibodies to both HIV-1 and HIV-2 and their subtypes including O and N.

a. ELISA (Enzyme Linked Immunosorbent Assay)

This is the most commonly performed test to detect HIV antibodies.

Types of ELISA based on the principle:

1. Indirect ELISA
2. Direct ELISA
3. Competitive ELISA
4. Antigen sandwich
5. Antigen antibody capture assay

Types of ELISA based on antigen utilized:

Generation	Antigen utilized
First	Infected cell lysate
Second	Glycoproteins (recombinant)
Third	Synthetic peptidase

ELISA can take up to 3 hours to yield results.

b. Rapid Tests:

They give results within minutes (3-30minutes). Various rapid tests available are-

1. Dot blot assays
2. Particle agglutination (gelatin, RBC, latex, micro beads)
3. HIV spot and coomb's tests
4. Fluorometric microparticle technologies

II. Supplemental Tests

These tests are used if the results of the screening tests are discordant and for research purposes. Otherwise according to the WHO guidelines, an individual reactive to three different systems of ELISA or rapid tests can be labelled to be having HIV infection.

These tests also identify and differentiate infections by HIV-1 and HIV-2.

These tests include –

Western Blot (WB)

Line Immunoassay (LIA)

Recombinant Immunoblotting Assay (RIBA)

Western Blot analysis is done by electrophoresis of plasma on a pre-impregnated strip containing various antigens of HIV. WB is interpreted as positive if at least 2 of 3 bands (p24, gp41, gp120/160) are positive.

Direct detection of HIV

Direct detection of virus would be needed in the following settings –

For diagnosis:

1. HIV infection in the newborn
2. Indeterminate WB/LIA/RIBA results
3. Monitor viral load during antiretroviral therapy
4. HIV infection status during the window period
5. Detection of site specific infection

For Research:

1. Sub typing of HIV
2. Cloning genes for diagnostic kits/vaccines
3. Generating chimeric viruses

Techniques used:

1. Detection of p24 antigen
2. Culture isolates of HIV
3. Detection of HIV specific DNA or RNA Polymerase Chain Reaction (PCR)

HIV p24 core antigen

HIV p24 antigen is detected and quantified using EIA. Sensitivity and specificity reported are 79% and 99% respectively. It correlates well with the disease progression. p24 is undetectable in most asymptomatic patients and infants. It also shows poor intrasample reproducibility. All these factors limit the utility of p24 assay.

Immune Complex Dissociated (ICD) p24 antigen

P24 antigen dissociated from the immune complexes improves the sensitivity of the assay. However, the sensitivity level is sub optimal for early diagnosis of HIV infection.

HIV isolation by viral culture

This requires at least P2+ containment facility and high degree of expertise. Autologous or heterologous peripheral blood mononuclear cells (PBMCs) activated with mitogen are co cultured with infectious material at 37°C in 5% CO_2 for about 28 days. The presence of the virus is detected by presence of p24 antigen or reverse transcriptase enzyme in the culture supernatant. This method has the sensitivity and specificity of PCR, however it is costly, labor intensive and takes 2 to 4 weeks.

Polymerase Chain Reaction (PCR) for HIV

HIV DNA PCR (Qualitative): This detects the proviral DNA that is integrated with the host cell. This is best done using Reverse Transcriptase (RT) PCR. Because of the high sensitivity of the test, care is taken to avoid cross contamination of samples or carry over of amplified products.

HIV RNA PCR (Quantitative): This is done using RT PCR or nucleic acid sequence based amplification (NASBA) and branched chain DNA (bDNA) techniques. Comparative analyses have shown that quantitative PCR studies are more sensitive measures of viral load than p24 assays and culture techniques at all stages of HIV infection, enabling detection of virus in plasma even when other assays are negative.

Prognostic surrogate markers of HIV/AIDS in children

These measures help the clinician identify stage of disease progression and to decide when to start antiretroviral therapy and also to monitor the response to treatment.

Four markers can be used:

1. CD4/CD8 lymphocyte count
2. HIV p24 core antigen
3. β-2 micro globulin
4. Neopterin

CD4 count is the most important marker. Based on this, the patient's immune status is classified.CD4 % are more consistent with age than their absolute values. Abnormal CD4 counts are always confirmed by a repeat test after one week. The counts vary with infections and time of the day, they are higher in the evening.

P24 antigen is useful if used with CD4 counts. β-2 globulin (increased levels due to lymphocyte activation and destruction) and Neopterin (produced by macrophages activated by interferon) are not reliable as independent markers.

Laboratory diagnosis of HIV infection in the newborn (congenital infection)

The risk of mother to child transmission of HIV is 25-45%. Maternal IgG to HIV crosses the placenta and persists for 6-18 months. It is essential to diagnose infections in newborns as early as possible. It relieves the parents' anxiety and is helpful to consider antiretroviral therapy

in infected babies. PCP prophylaxis can be stopped if the baby is not infected. Early diagnosis also helps timely decisions regarding breast feeding, immunization etc. Distinction between maternal and neonatal IgG is difficult. The following tests can be used for early detection of congenital HIV infection:

1. Detection of IgA and or IgM anti HIV antibodies: IgA antibodies appear at 3-4 months of age and IgM by six months of age. IgA after 3 months of age has a sensitivity of 97.6% and specificity of 99.7%. IgM production is erratic and elicits false positive results.
2. Estimation of p24 antigen: This has high frequency of false positivity in the first month of life.
3. HIV DNA PCR, RNA PCR and Viral cultures: PCR is preferred over culture techniques. It invariably has a specificity of >95%. The sensitivity ranges from 38% within 48 hours of birth, to more than 93% at 14 days and 96% by 28 days of life.

Cord blood is not to be used for testing as there can be contamination. The negative ELISA done between 6 - 18 months in the absence of clinical disease will rule out HIV infection[in an infant who is not breast fed].

For infection in utero , the HIV DNA PCR or viral culture has to be positive in the first 48 hours.

For intrapartum infection the tests within 48 hours are negative but positive after one week.

If one PCR is to be done due to cost constraints then it is best performed between 3 to 6 months of age.

Reporting procedure

The results are kept confidential.

Negative – if the initial/screening test is nonreactive

Positive- if the sample shows reactive results by three screening tests.

Indeterminate- If the sample shows discordant results by three screening tests. Confirmatory assay is to be done. If the confirmatory test is indeterminate the follow up samples are retested at three, six and 12 months before the result is reported. If still indeterminate after one year, the person is declared negative.

In summary, to diagnose congenital HIV infection in early infancy ELISA is unreliable. The mainstay is by HIV PCR or rarely by viral culture. After 18 months of age three serial ELISAs can be done. The disease progress has to be monitored by assay of CD4 counts.

Test	Time required	Approximate cost (rupees)
ELISA	upto 3 hours	200
PCR	12 hours	3000
Viral culture	2-4 weeks	6000
CD4 counts	3 - 4 days	800

HIV INFECTION

GENERAL MANAGEMENT OF HIV IN CHILDREN

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Abstract: *The advent of potent antiretroviral therapy has enabled transformation of HIV infection from a fatal to chronic disease in the developed countries. However supportive care, appropriate prophylaxis and management of infections are equally important. In fact, they are the mainstay of therapy in developing countries like India where anti retroviral therapy is not affordable by most patients. This article attempts to provide an overview of the basic treatment principles of this increasingly common childhood illness.*

Key words: *HIV, Children, Management*

Early management of pediatric HIV disease is based on timely institution of chemoprophylaxis, immunization, management of opportunistic infections, nutritional support and anti retroviral therapy. However early management using appropriate measures are possible only if these children are diagnosed early. Spectacular advancement has been made in strategies to reduce mother to child transmission. The vertical transmission of HIV infection may occur in utero (30-50%), intrapartum (50-70%), or through breast feeding (about 15%). Of the HIV infected children about 20-30% are rapid progressors. Amongst the slow progressors 15% are asymptomatic even at 5 years of age. The slow progressors reveal a lower rate of fall of absolute CD4 counts and generally tend to have higher CD8 counts. The median survival time of vertically infected children is reported to be about 8-9 years. Plasma HIV RNA levels of more than 2,99,000 copies per milliliter in an infant has been correlated with rapid disease progression and death. In general, plasma HIV RNA load of more than 1,00,000 copies per milliliter and CD4 of less than 15% are considered as poor signs of survival.

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Breast feeding

There is a 14-16% risk of mother to child transmission of HIV through breast milk. In a developing country like India where the breast feeding safeguards against risk for diarrhoea and respiratory infections, which by themselves are associated with high morbidity and mortality, the risk from breast feeding needs to be individualized. Whenever safe, cost effective and alternative sources of milk are available the HIV infected women need to be counselled not to breast feed their infants. Mother and family participation in the decision making is imperative.

Nutrition

Factors like repeated infections, poor intake, malabsorption, increased requirements and emotional deprivation make a HIV positive child more prone to develop malnutrition. Malnutrition can itself augment the immuno deficiency of HIV infected children. The diet should consist of high calories, proteins and vitamins preferably from home made foods. Treatment of opportunistic infections, oro-pharyngeal and esophageal

candidiasis, diarrhoea and respiratory infections is necessary to help in keeping the oral intake adequate. Health education and economic support may be necessary for better nutrition. In extreme or terminal cases tube feeding or total parentral nutrition may become necessary for a short period of time. Emotional and psychological support for the family is required.

Anti retroviral therapy

Three classes of anti retroviral therapies (ART) are available for HIV. Two of these target, the reverse transcriptase enzyme, the nucleoside (NRTI) and non-nucleoside (NNRTI) reverse transcriptase inhibitors. The third class of drug is the protease inhibitors, which target the viral protease enzyme. Drug absorption, metabolism, pharmacokinetics and interactions should be understood well before undertaking therapy. Compliance is also difficult as the drugs are expensive and some are unpalatable. Treatment with ART needs proper patient selection, appropriate choice of drugs, monitoring and evaluation to look for need for change in treatment regimens.

Management of opportunistic infections

Prior to use of ART the gains in survival of HIV infected children were mainly due to chemoprophylaxis of opportunistic infections. Pneumocystis carinii pneumonia (PCP) is the most common infection seen in about a third of pediatric HIV infected patients and is an important indicator for AIDS. PCP prophylaxis is done using Trimethoprim – sulphamethoxazole (TMP-SMX). Fungal infections are common in HIV/AIDS children. Oral or topical drugs are used in early cases and intravenous antifungal agents in non-responders and in wide spread disease. Cryptococcal meningitis, cytomegalo virus retinitis, varicella zoster, herpes simplex virus infection and measles are uncommon in children.

Monitoring of growth and development

Anthropometric measurements at regular intervals are essential for early recognition of growth failure and malnutrition. Height, weight, head circumference and skin fold thickness measurements can be used to predict disease progression and overall effectiveness of ART. Mental development should be monitored as it can be affected due to encephalopathy and opportunistic infections.

Counselling

Counseling to the patient and the family should be an essential ongoing process throughout the course of the disease. The mother or care giver should be counselled regarding diagnosis, treatment, follow up, prophylaxis against opportunistic infections, immunization, breast feeding, prevention of transmission of HIV and socio-economic consequences of the infection.

Schooling

Children with HIV infection should not be excluded from school for the protection of other children or personnel since HIV does not spread through types of contact that may occur in the school. The family of an affected child has the right, but is not obliged to inform the school about the infection status of the child. All schools should adopt the standard procedures for handling blood or contaminated fluids regardless of the HIV status.

Home care

The family should follow standard guidelines to prevent exposure to HIV infected material. Sharing of toothbrushes, razors etc should be avoided. Hands and body parts should be washed readily after contact with blood. Routine changing of diapers and nose wipes should be followed by hand washing. When blood or blood-contaminated fluids are spilled the

surface should be cleaned and then disinfected with freshly prepared 1: 10 dilution household bleach.

HIV infected travellers

Some countries prohibit the entry of HIV infected travellers. They should be vaccinated early in the disease and prior to travel. Insect repellents should be used and strict food and water hygiene should be observed. Isoniazid prophylaxis may be required for a long-term traveller to a high endemic zone of tuberculosis.

Immunization

Immunization in the HIV positive children differs from the routine schedule of vaccination as live vaccines are contraindicated with some exceptions. There may be a sub - optimal sero conversion after vaccination.

Table 1. Recommendations for immunization in a developing country

Vaccine	Recommendation
BCG	Recommended by WHO, as tuberculosis is rampant and neonates are asymptomatic.
OPV	Ideally IPV should be given. Since it is not available OPV is recommended, as evidenced by absence of complications in those who were given OPV in early epidemics.
Measles MMR	Measles and MMR vaccines are contraindicated only in children who are severely immunocompromised. (category C)
DPT Hepatitis B Hemophilus influenza type B	These vaccines are recommended because they do not contain any live agent. Hepatitis B immunoglobulin should be given within 7 days of exposure.
Varicella	Recommended only for the asymptomatic or mildly symptomatic (CDC classification N1 or A1 with an age specific CD4 of > 25%). Immunoglobulin should be given within 4 days of exposure.
Pneumococcal	All HIV infected children who are 2 years or older should receive the vaccine, with a booster 5 years later.
Influenza	HIV positive children should receive yearly vaccine after 6 months of age.
Hepatitis A	Recommended for those living in endemic areas.
Typhoid	Vi polysaccharide vaccine is recommended. Oral typhoid vaccine is contraindicated.
Rabies	Vaccine and immunoglobulin can be given for post exposure prophylaxis.

HIV INFECTION

COUNSELLING IN PEDIATRIC HIV/AIDS

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Abstract: *HIV/AIDS is here to stay. In the fight against AIDS more than all the drugs and intervention it will be a test of human resilience, human support system which will decide how this battle will be fought. In this respect counselling is indispensable. In the present scenario of HIV/AIDS in India, with antiretroviral therapy being only a dream for most patients, counselling remains the backbone for management of HIV/AIDS patients. In order for the individual to accept the infective status, carry on with life, plan the future, prevent transmission and continue to function as a useful member of the community counselling is a must. Counselling induces a positive attitude and a high life force in the individual helping him or her to carry on as before in spite of and irrespective of the HIV infection.*

Counselling is required when a physician orders a HIV test i.e. pre test counselling and when the results are told to the patient i.e. post test Counselling. This is mandatory as laid down by WHO/UNAIDS. Government of India is also actively emphasizing the need for HIV counselling Preventive counselling is also required for the community at various levels to understand and prevent the disease by preventing transmission of HIV infection. It is done for individuals both with or without risk behaviour. Supportive counselling facilitates an individual, family or a group to cope with circumstances arising as a result of HIV status who need psychosocial support.

Keywords: *Counselling, HIV, AIDS*

In the present scenario of HIV/AIDS in India, with antiretroviral therapy being only a dream for most patients, counselling remains the backbone for management of HIV/AIDS patients. Counselling is required when a physician orders a HIV test i.e. pre test counselling and when the results are told to the patient i.e. post test counselling. Counselling is the mainstay of management of a patient who has been diagnosed as HIV positive or who has already gone into full blown AIDS. The family of the patient requires extensive counselling to cope up with the ramifications of the disease. Counselling is also required for the community at various levels to understand and prevent the disease i.e. preventive counselling. Counselling is also needed for the community to look after the HIV affected persons in a humane way. Counselling may be done as one to one, that is individual counselling or as a group.

Counselling plays a major role in HIV/AIDS prevention and management. It aims at preventing transmission of HIV infection. It is done for individuals both with or without risk behaviour. Supportive counselling facilitates an individual, family or a group to cope with circumstances arising as a result of HIV status who need psychosocial support .

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Counselling skills

Counselling is not about telling a client what to do nor is it a forum for presentation of the counselor's views. In fact a counselor should resist making assumptions or jumping to conclusions. Counselor should avoid comparing one client's problem to other client's similar problem

Skills are required to understand a problem. These are necessary for any doctor or health professional. Counselling is an 'art' because it has a blend of the skill and personality of the counselor and a 'science' because of its underlying principles. In counselling language, the patient is referred to as a client.

What to say ?

Verbal skills are extremely important for proper rapport building and for explaining to the client.

What to do?

Non- verbal skills. Acquiring and maintaining client's confidence.

How to be?

Body language of the counselor should not be threatening or disapproving. Counselor must correctly interpret body language of patient. One should not show shock or disapproval at any comments of the patient. Do not go by the attitude portrayed. Clinic atmosphere should be friendly.Environment should not be intimidating. There should be informative reading material lying around.

The key factors are: assurance, confidentiality, privacy, easy accessibility

Elements of counselling

- Greet patient
- Make the patient comfortable
- Create the confidence of the patient and assure confidentiality.
- Listen carefully to patient's problems.
- Do not interrupt while patient is talking.
- Try to elicit more information while patient is talking.
- Counsel over a number of sessions and be empathetic.
- Provide information over the issue the patient has come.
- Help the patient to decide for him or herself.
- Explain how to carry out patient's decision.
- Time to time reassurance and follow up regarding health condition of the patient is often needed.

Interviewing skills

- listening,
- observing
- assurance,
- acceptance
- being patient and trust worthy
- receiving information
- probing
- clarifying doubts
- give simple direct answers
- assurance
- emotional support
- anticipatory guidance
- decision making
- empathy
- confidentiality
- reality orientation
- motivation
- skills for solving the problem
- understand how the problem has risen

After initial assessment the counselor has to decide the following

Direct Treatment

Futher counselling sessions have to be planned

Referral

Appropriate referrals should be planned

Followup and Homevisit

These are extremely important if one desires good results from counselling

Interviewing skills for adolescents

This requires special skills and different approach

- be open
- be flexible
- be understanding
- be approachable
- stress confidentiality
- show respect

Meeting counselling challenges

Client is Silent

Use various methods to coax a repsonse. Do not show anger, frustration or intimidation

Client crying

Give him or her time to get over her emotions. Be empathetic without getting emotionally involved

Counsellor does not know answer to the question

Be frank in saying I do not know and will try to find out.

Counsellor makes a mistake

Be honest and courageous to accept the mistake

Client asks a personal question

Gently explain that the discussion is about the client and his or her problems

Client asks counsellor to make a decision

Emphasize that the client has to make decision himself or herself.

Counselling in HIV/AIDS

Why is HIV counselling necessary?

HIV/AIDS counselling is mandatory for providing voluntary HIV testing services. This is because diagnosis of HIV in an otherwise healthy individual induces a series of psychological reactions like denial, anger, anxiety, depression, to finally acceptance.

So far there is no successful cure or vaccine available for HIV infection. In order for the individual to accept the infective status, carry on with life, plan the future, prevent transmission and continue to function as a useful member of the community counselling is a must. Counselling induces a positive attitude and a high life force in the individual helping him or her to carry on as before, inspite of the HIV infection. HIV/AIDS counselling is mandatory (pre and post tests) as laid down by WHO/UNAIDS. Government of India is also actively emphasizing the need for HIV counselling

The important facts for HIV counselling are

Infection with HIV is lifelong, so the person requires lifetime counselling

1. A person can avoid acquiring HIV infection or transmitting it to others by changing behaviour (primary prevention)

2. Motivation for change in high risk behaviour (secondary prevention)

There is so much fear, misunderstanding and discrimination provoked by HIV epidemic that it needs appropriate handling. Suspicion, recognition or diagnosis of HIV infection or AIDS can lead to emotional, social, behavioral and medical consequences leading to immense psychological pressures.

What is HIV Counselling?

WHO defines HIV/AIDS counselling as a dialogue between a client and a care provider aimed at enabling the client to cope with stress and take personal decisions relating to HIV/ AIDS. The counselling process includes the evaluation of personal risk of HIV transmission and the facilitation of preventive behavior

HIV counselling is an on-going dialogue and relationship between client or patient and counsellor. The aims are preventing HIV transmission and providing psychosocial support for those affected directly and indirectly by HIV. AIDS/HIV counselling consists of preventive counselling and supportive counselling

Difference between counselling and health education

- Counselling differs from health education in many ways
- Counselling is usually a one to one process where as health education addresses a group of people.
- Counselling is useful not only for giving information but also changing attitudes and motivating behavioral change. Health education is used mostly for assessing information sharing
- Counselling sessions involve personal problem solving. In health education general issues are discussed
- Counselling is more focused, specific, and goal targeted where as health education is much more generalized.
- Counselling evokes strong emotions in both counsellor and client whereas health education sessions are generally emotionally neutral in nature

For whom is HIV/AIDS Counselling Done?

This is very important for those persons who

- Are already identified as having AIDS or being infected with HIV
- Those being tested for HIV (pre and post)
- Experience discrimination due to HIV infection
- Family and friends of people with HIV infection
- Those seeking help because of past or current risk behavior and planning for their future
- Those not seeking help but practising high risk behavior
- Health workers/others in regular contact with HIV infected persons

Where can HIV/AIDS Counselling be provided?

HIV/AIDS counselling can be provided in any setup including hospital wards, STD clinics FP. clinics ,ANC/PNC clinics, blood donation centers, drug deaddiction centers, primary and secondary health posts, community based programs.

Who should provide HIV/AIDS Counselling

HIV AIDS counselling can be provided by any one who has a sympathetic ear, can give time to listen, has knowledge of accurate scientific facts about HIV/AIDS and undergoes systematic and periodic training in counselling.

In addition to doctors, nurses, social workers, psychologists, psychotherapists, even teachers, health educationists, community and peer leaders and youth and self help groups can undertake preventive and supportive counselling

Main Function of HIV/AIDS Counselling

1 Preventive counselling

Preventing infection with HIV and its transmission to other people

2 Supportive counselling

Providing psychosocial support

Preventive counselling: Main steps

1 Assessing high risk behaviour in individuals or group

2 Convincing individual/group to acknowledge risks associated with such behaviour

3 Rationalizing the linkage of their life style and self image to this behaviour

4 Supporting individuals to make rational decisions for changing behaviour

5 Working with them to sustain the modified behaviour.

Primary preventive counselling

For people at risk of HIV infection but not known to be infected - Aware/Unaware. It aims at creating this change focussing on behaviours that present a risk for HIV infection and reviewing ways of managing individual changes.

Secondary preventive counselling

For persons known or considered likely to be HIV-infected. They should be given specific instructions as to ways by which they can prevent spread to others. An attitude of understanding should be adopted, as the fact that the person is positive is traumatic enough to accept. Since behavioral change is difficult at least she/ he should be asked to take precautions: use condom, while having sexual intercourse, do not share needles and syringes and do not donate blood.

Supportive Counselling

1 For people with diagnosed HIV infection and HIV related illness - AIDS Relafed Complex / AIDS

2 For relatives/friends close to HIV/AIDS persons

Counselling for HIV/AIDS is the process of

Empowering the person with HIV/AIDS Mobilizing the person's own strengths and resources to face and manage the various concerns and problems

Essential Features of HIV/AIDS Counselling

- Time : A lot of time must be spent to absorb information/news and to develop rapport
- Acceptance and remaining non judgmental by counsellor irrespective of the life style of client
- Accessibility and availability of counselling facilities
- Consistency and accuracy of any information
- Confidentiality and Trust (Exceptions ?)

Content of pre test counselling

This is aimed at preparing an individual for HIV test result

It consists of the following

- Assessing an individual's risk profile to take the test
- Obtaining information on the personal history of the client

- Sexual behaviour – multiple partners, unprotected sex, homosexuality, bisexuality, prostitutes; drug users, blood transfusion, organ transplant.
- Assessing the risk of having been exposed to HIV.
- Exploring why the client wants the test.
- Understanding what the client already knows.
- What behaviour and symptoms are of concern to patient
- Giving appropriate and relevant information on HIV/AIDS and on how to prevent transmission/infection.
- Providing accurate information as to the difference between HIV (as causative organism) and AIDS as the terminal stage of illness.
- Explaining the test procedure and waiting for the result.

Obtaining motivated consent

- Anticipatory preparation of the result of the test and response
- Assessing an individual's coping mechanism and existing support systems specially role of the family, as a preparation for subsequent management plans

Content of post test counselling

This should be planned based on the individual's coping capacity

- Helping client to respond to the result.
- Assess the level of the individual's knowledge about HIV/AIDS so that the counselling is tailor made to suit her /his needs. The positive results should be given directly
- Assisting him/her to understand the meaning of the result (and what it does not mean).
- Appropriate "warm pause" should be provided to enable individual to understand and absorb the meaning of positive test result.
- Considering whom to tell and how to tell.
- Imparting relevant medical knowledge appropriately.
- Counsellor should provide adequate time for an effective dialogue and not be in a hurry to provide all information in one sitting.
- Giving accurate information on how to prevent HIV transmission.
- Considering long term implications
- Counsellor should identify major psychological issues (such as anxiety, depression) and social issues(discrimination, interpersonal relationship). This will help to plan an appropriate intervention for providing psychological/social and emotional support.

Some special issues

Pregnancy: Females of childbearing age found HIV positive should be told to avoid pregnancy, as there is a risk of vertical transmission from mother to child

If pregnant: There is one in three chance of having an infected child. Termination of pregnancy to be discussed. Counselling will depend upon personal, religious and cultural is factors of the patient. Both partners need to be counselled

Infants: Should be kept under medical observation and treated with care and affection. Parents and siblings need to be counseled. Though the risk of acquiring infection from

infant's body fluid is minimal, nevertheless people with cuts should avoid contact with fluids. Hygienic precautions should be emphasized upon.

Breast feeding: May result in transmission of HIV from mother to child. In our country stoppage of breast-feeding may deprive the newborn of protective immunity from mother. Counselling will require a balance between the two. The possibility of acquiring HIV infection and lack of immunity and other benefits of human milk if not breast-fed. One should impart all scientific knowledge to the mother and she should take the final decision

Counselling after a negative result

Usual response is relief or euphoria. However the patient has to be cautioned that there is a window period for 3 months, during which a negative result cannot be considered reliable. A negative test carries greater certainty if six months have passed from the last exposure. A negative test should not give a false sense of security. In general, patient should be advised safer sex practices. Prevent further exposure by avoiding high risk behavior, avoidance of needle sharing. Provide other information on avoidance of HIV infection.

Counselling after a positive result

- Usual response is a mixture of negative emotions
- Fears are related to illness, death, job, length of life etc
- Loss due to stigma attached by society and speculation in the minds of people regarding the behavior of those affected by HIV
- Anxiety regarding all aspects of life guilt , grief, denial, anger, depression, suicidal activity

Issues after positive results

- First discussion - private and confidential
- Time given for patient to adjust to the news and understand all implications of being HIV positive. i.e. meaning and social/medical implication of the result.
- No speculation of prognosis of estimate of time left to live but providing support
- Information of how to prevent further transmission
- Information where resources are available and possible treatment of some of the symptoms of HIV infection and efficacy of anti-retroviral treatment.
- Psychosocial support
- Besides the individual who has been tested and found to be positive, counselling is also needed for others around him i.e. the health workers and family to face and share of fears and uncertainties regarding their getting the infection. All have to be given full and proper information so that they can provide support, which the individual requires to be able to face his/her problems.

Counselling after an equivocal test result

(10% samples in some areas)

- Meaning of the result
- Test is cross-reacting with a non-HIV protein
- Insufficient time for full seroconversion - since HIV exposure
- Options
- Use other methods to get a reliable result
- Stop further testing for the moment - advise repeat test after three months

- Issues
- Information on prevention of transmission
- Support while waiting for an unequivocal result

HIV/AIDS is here to stay. It is slowly but surely spreading its tentacles and pervading all sections of society. No one can remain isolated from this menace. Each individual in today's society will be called upon to play some role sooner or later. In the fight against AIDS more than all the drugs and intervention it will be a test of human resilience, human support system which will decide how this battle will be fought. In this respect counselling is indispensable.

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NEWS AND NOTES

SNIDs AND NIDs FOR POLIO – 2003-2004

Government of India has organized Subnational Immunization days (SNIDs) on 14Th September 2003 and 9th November 2003 and National immunization days (NIDs) on 4th January 2004 and 22nd February 2004 for polio immunization. SNIDs will be conducted all over the state in the states of Uttar Pradesh, Bihar, Delhi, Gujarat, Haryana, Rajasthan, Jharkhand and West Bengal and in 31 districts of MP and 4 districts of Uttaranchal. NIDs will be conducted all over India. All IAP members are requested to keep their clinics open and advice parents to bring their children on these dates for polio immunization.

T. Jacob John — Chairperson

Naveen Thacker — Convener

Polio Eradication Committee, IAP

A.P.PEDICON – 2003

HOSTED BY IAP NELLORE DIST. BRANCH

Date: November 15th & 16th 2003

Venue: Nellore, A.P.

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HIV INFECTION

OPPORTUNISTIC INFECTIONS IN PEDIATRIC HIV DISEASE

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Abstract: *Opportunistic infections (OI) are the hallmark of the immunodeficiency associated with HIV infection in children. As HIV infection affects the cellular as well as the humoral arms of the immune system all types of organisms, viruses, bacteria, fungi, protozoa and mycobacteria, are responsible for OI. The pattern of OI in children differs from that in adults. The type of OI encountered in children is dependent upon the patient's age as well as on the degree of immunosuppression. Opportunistic infections should be managed with vigor. Efforts should be made to identify the causative organism, so that early treatment can be instituted. Prophylactic regimens, both primary and secondary, are available for most OI. They have decreased the morbidity and mortality associated with HIV infection and have improved the quality of life of HIV infected children. Prophylaxis does not mean prescribing medications alone. The pediatrician has a much wider role in prevention of OI that includes giving counseling regarding hygienic practices, offering appropriate vaccinations and giving advice regarding maintenance of nutrition and avoiding infections. Effective anti-retroviral therapy (ART) helps arrest to immune function deterioration and may even lead to improvement in immune function; thereby decreasing the incidence and severity of OI. The diagnosis, prophylaxis and treatment of OI are an integral component of comprehensive HIV care. Given the wide spectrum of health services available in the developing countries, including India, there is a need to evolve standard protocols for management of OI taking into consideration the facilities available at different grades of healthcare system.*

Keywords: *Opportunistic Infection, HIV, Children, Prophylaxis*

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HIV infection primarily affects the immune system. Hence, opportunistic infections (OI) are commonly encountered in individuals infected with HIV[1]. It is important for the pediatricians to know about OI for the following

a. Frequently, OI may be the first manifestation of pediatric HIV infection. pneumocystis carinii pneumonia (PCP) or persistent oral thrush can be the first manifestation of the disease in infancy. The treating physician should be aware of this fact and thus investigate such a child for HIV infection.

b. Many a times these infections present with unusual and/or severe manifestations. For example, cytomegalovirus (CMV) does not give rise to severe manifestations in the post-neonatal age group. However, when associated with HIV infection, it can present with features such as retinitis, colitis and hepatitis.

c. Even infection with the usual pathogenic organisms can present with unusual or severe

clinical features. For example, chickenpox is an inconsequential illness in most young children. However, in HIV infected children it has a higher probability of presenting with severe life-threatening manifestations (progressive varicella syndrome) such as pneumonitis, hepatitis and encephalopathy. Similarly, Candida albicans commonly causes oral thrush that responds well to conventional measures. However, in HIV infected children, oral thrush can cause esophagitis and the infection could be resistant to the commonly used anti-fungal agents.

d. The pediatrician should be well versed with the clinical features and diagnostic studies of these infections so that early treatment can be instituted. This improves the prognosis. For example, if the treatment of PCP is commenced early, the prognosis is much better than if the diagnosis itself is delayed.

e. Prophylactic regimens can be used to prevent a number of opportunistic infections. This has improved the prognosis for HIV-infected children. If the primary diagnosis is established, secondary prophylactic regimens can be started. This holds true, among others, for PCP, disseminated Mycobacterium avium complex (MAC) infections and toxoplasmosis.

Infectious agents take the opportunity of defective immune system to cause opportunistic infections. The type of opportunistic infection encountered depends on the type of immune defect. For example, fungal infections are common in diseases with defective cellular immunity while bacterial infections are common in diseases affecting humoral immunity (e.g. hypogammaglobulinemia). The primary immune defect in HIV infection is related to destruction of CD4 cells. Hence, it is not surprising that opportunistic fungal, viral and parasitic infections are seen with HIV infection. However, CD4 cells and T-helper cells are also required for proper functioning of humoral immunity. Hence, HIV infection is also associated with recurrent and severe bacterial infections[2]. Iatrogenic factors like the use of immunosuppressive anti-retroviral drugs and insertion of catheters that breach natural barriers like skin, further accentuate the immune defect caused by HIV. The probability of an organism causing an infection is dependent upon its virulence and is inversely proportional to the host resistance. When the immune function is normal, only the organisms with high virulence are able to cause infection. When immune function is deficient, as in patients with HIV infection, organisms with low virulence (which are abundant in environment) are also able to establish an infection and cause disease. In fact, as these organisms with low virulence far outnumber those with high virulence, infections with less virulent organisms are commonly encountered in HIV infected children.

Profile of Opportunistic Infections

Although any and all organisms can cause infection in these children, certain infections are commonly encountered. Table 1 shows the opportunistic infections that have been reported in various Indian studies. The type of infection is related to the patient's age as well as to the degree of immunosuppression. For example, HIV infected infants are prone to develop symptomatic Pneumocystis carinii pneumonia (PCP). Persistent and recurrent oral thrush that does not respond easily to anti-fungal treatment is seen with minimal immunosuppression and MAC infections are encountered with severe immunosuppression. There are infections that occur without any relation to degree of immunosuppresion. The classical example of such a relationship is tuberculosis.

The Center for Disease Control (CDC) has given a revised clinical classification for

Table 1. Incidence of opportunistic infections in children infected with HIV

AUTHOR	DETAILS ON OPPORTUNISTIC INFECTIONS
Merchant et al[3]	24% of children admitted for chronic diarrhea were seropositive.
Daga et al[4]	Recurrent diarrhea was the most frequent manifestation of HIV infection in children and was present in 42.7% in ELISA– positive symptomatic patients.
Dhurat et al [5]	In 55 HIV infected children, tuberculosis (67.5%), oral candidiasis (23.6%) and chronic diarrhea (18.2%) were the commonest manifestations encountered.
Karande et al [6]	Oral candidiasis was a significant independent risk factor for predicting HIV infection.

designating children with symptomatic HIV infection[7]. Children with opportunistic infections like persistent oropharyngeal candidiasis, CMV infection (with onset at age less than one month), Herpes simplex virus (HSV) infection and disseminated varicella are included in category B. Those with recurrent bacterial infections, esophageal candidiasis, CMV after 1 month of age, tuberculosis, atypical mycobacterium infections, PCP and chronic diarrhea are grouped in Category C.

There are certain differences between OI occurring in adults and those occurring in children. In adults, OI usually represent reactivation of a latent infection acquired early in life. In contrast, young children generally have primary infections with these organisms and since they lack prior immunity, often have a more fulminant course. Certain infections such as PCP and recurrent bacterial infections, which are features of pediatric HIV disease, are rarely encountered in adults with HIV infection.

Table 2. Relationship between opportunistic infections and CD4 counts in older children

Stage of HIV Infection	CD4 cell count (Cells per mm^3)	Prevalent Opportunistic Infections
Initial infection	Much above 500	OI rarely reported
Early HIV disease	Just over 500	Pulmonary tuberculosis, MAC, histoplasmosis, Herpes simplex labialis
Intermediate stage	200-500	Recurrent bacterial infections, Pulmonary tuberculosis
Late stage	50-200	PCP, Toxoplasma gondii, Esophageal candidiasis, Pulmonary tuberculosis
Advanced stage	<50 cells	MAC, Cryptococcal meningitis, CMV retinitis, Pulmonary tuberculosis

MAC: Mycobacterium avium complex; PCP: Pneumocystis carinii pneumonia

*Modified from Reference 8

Increased viral load and low CD4 count have been shown to predict the development of opportunistic infections in children[8]. Table 2 shows the correlation of the CD4 counts and the occurrence of specific opportunistic infections.

Clinical manifestations of opportunistic infections

It will not be possible to describe clinical manifestations and diagnostic investigations of all OIs encountered in HIV-infected children. This information is available in standard texts[1,2]. Table 3 shows the clinical manifestations and diagnostic features of certain important OIs.

Tuberculosis and HIV

Tuberculosis is a common HIV-related OI[10]. HIV infection increases the susceptibility to primary infection, as well as to reactivation of tuberculous infection due to depressed cellmediated immunity[2,9]. Children with low CD4 counts may be at higher risk for development of tuberculosis, but as stated earlier, children at all stages of HIV infection can develop the infection [2,9]. Some authorities are of the opinion that HIV is associated with a high incidence of drug resistance as well[2,10]. The progressive depletion and dysfunction of CD4 cells and defective functioning of macrophages and monocytes in HIV infected children are responsible for the development of extensive tuberculosis.

Co-infection of HIV and tuberculosis impacts both the disease processes. In the presence of HIV infection, extra-pulmonary and disseminated forms are more common[2,9,10] and HIV infection can induce latent infection to progress to a clinically active disease[9]. In turn, active tuberculosis accelerates the progression of HIV disease. Tuberculosis causes activation of cytokines especially tumor necrosis factor (TNF). Increased elaboration of cytokines and increased stimulation and enhanced multiplication of lymphocytes increases HIV replication and plasma HIV–RNA levels[8].

The co-infection of HIV and tuberculosis poses diagnostic problems for the clinician. HIV infected children may develop extra-pulmonary disease and atypical symptoms. Pediatricians give considerable importance to results of Mantoux test while diagnosing tuberculosis. The test is not perfect at best of times. The interpretation becomes much more problematic in the presence of HIV infection as even with tuberculous infection and disease, the test is likely to show a falsely negative result. Hence, it is advocated that an induration of 5mm or more, be taken as indicative of a positive test. The treatment of tuberculosis in HIV infected individuals does not differ greatly from that in immunocompetent hosts. Children with pulmonary disease should be treated for 6-12 months, whereas extra-pulmonary disease requires 12 months of treatment[2]. Rifampicin is a potent inducer of cytochrome P-450 enzyme system. It, therefore, enhances the metabolism of protease inhibitors or non-nucleotide reverse transcriptase inhibitors used in the treatment of HIV infection. In adults receiving these drugs, some clinicians substitute rifabutin for rifampicin. However, paucity of data precludes offering any definite guidelines regarding treating children on similar grounds[2,9]. It is vital to trace the adult contact responsible for transmitting tuberculosis. If the adult has been incompletely or inadequately treated or is infected with multi-drug resistant (MDR) infection, the child would have to be treated as a case of MDR-TB.

Management of opportunistic infections

Opportunistic infections should be managed with vigor. Affordable treatment is available for many OI, which are described in standard reviews[2,11]. India's National AIDS Control (NACO) Program offers free treatment and

Table 3. Common opportunistic infections: Clinical manifestations and diagnostic modalities[2,8,9]

Infectious agent	Clinical manifestations	Diagnostic tests
Pneumocystis carinii	Pneumonia is the commonest presenting feature. Manifests with fever, cough, breathlessness, cyanosis, tachypnea, fine rales	Demonstration of trophozoite on specimen obtained by BAL or in sputum or tracheal secretion; lung biopsy
M. tuberculosis	Organ-specific manifestations	Demonstration of organism, specific histopathological features and supportive evidence in the form of contact tracing, chest radiograph and Mantoux test
Atypical mycobacteria	Pulmonary and disseminated disease	Isolation of organism by blood culture, typical histopathological features on biopsy of lymph node, bone marrow or other tissues
HSV	Orolabial ulcers, genital ulcers and HSV encephalitis	Isolation of virus in culture. Detection of HSV 1 or 2 antigens from skin or mucosal scrapings by immunofluorescent technique HSV DNA in CSF depending upon the site of infection
VZV	Severe infection, recurrent, persistent and chronic infections	Clinical picture is classical. VZV specific IgM and PCR can help confirm infection
CMV	Retinitis	Fundoscopy: Yellowish white area of retinal necrosis with peri-vascular exudates and hemorrhage at the periphery.
	GI Involvement, colitis	Mucosal biopsy and demonstration of CMV inclusion bodies
	Esophagitis	Endoscopy: small confluent ulcers
Cryptococcus neoformans	Subacute or chronic meningoencephalitis	CSF: Cryptococcal antigen detection and culture
Candidiasis	Oral	Pseudohyphae on KOH stained specimens
	Esophageal	Endoscopy and biopsy
Toxoplasma	Congenital: low birth weight, microcephaly hydrocephalus, chorioretinitis	IgM, IgA antibodies in serum

contd.

		Presence of IgG antibody in CSF and intra-cranial granulomas and calcification on CT scan
Recurrent bacterial infections	Two or more bacteriologically documented systemic bacterial infections in 2-year period in the form of bacteremia, pneumonia, meningitis, osteomyelitis, sinusitis and skin, ear and upper respiratory infections	Relevant investigations to be carried out depending upon the site of infection. All efforts should be made to isolate the causative organism
Chronic diarrhoea*	Passage of 3 or more loose stools for more than 14 days	Microscopic examination of the stool sample (special stains), Immunological tests: IF, antibody, LA, Serology: ELISA for IgG, IgM, IgA levels.

CMV: cytomegalovirus, LA: latex agglutination, IF: immunofluorescence, CNS: Central Nervous system, HSV: Herpes simplex virus, VZV: Varicella zoster virus, BAL: Broncho-alveolar lavage

*** Caused by- Protozoa**: Isospora belli, Cryptosporidium parvum, Microsporidia, Entemoeba histolytica, Giardia lamblia; **Bacteria**: Salmonella, campylobacter, shigella, Clostridium difficle and MAC; **Viruses**: CMV, adenovirus, HIV, HSV and rotavirus; **Fungi**: Histoplasma

prophylaxis for opportunistic infections. Early institution of treatment gives gratifying results in terms of decreased mortality and morbidity. Certain principles in management of OI are worthy of consideration[2]:

a. It is important to develop a broad and inclusive differential diagnosis while approaching a case of OI.

b. Maximum possible efforts should be made to obtain tissue and or body fluid specimens to establish a definitive diagnosis. Many infective episodes have to be followed by secondary prophylaxis. This will not be possible unless the etiology of infection has been determined.

c. Complications of drug therapy, especially adverse drug reactions should be considered while treating children with HIV infection.

d. Multiple studies have demonstrated a direct relationship between high viral load, low CD4 count and the risk for progression and development of OI. The incidence, frequency and severity of OI are decreased as immune function improves. This is possible only with institution of effective anti-retroviral therapy (ART). Therefore, the possibility of institution of ART should always be explored.

Prophylaxis

Opportunistic infections are responsible for a considerable proportion of mortality and morbidity in pediatric HIV infection. Prophylactic regimens can be used to prevent a number of opportunistic infections[1,11]. Table IV and V show prophylactic regimens for prevention of OI. In general, prophylactic regimens are divided as primary and secondary. Primary prophylaxis is advised on the basis of depression of CD4 counts and other factors even before the child has suffered from an episode of the OI. Prophylaxis to prevent PCP in infants is an example for primary prophylaxis being offered irrespective of CD4 count. In contrast, primary

prophylaxis against Mycobacterium avium complex (MAC) is offered on the basis of depression in CD4 counts. Secondary prophylaxis is instituted for many infections after one or more episodes of an infection. Once begun, the prophylaxis has to be given life-long unless the immune function improves in response to effective ART. More clinical studies are required to address the specific questions regarding timing of withdrawal of the prophylaxis[1]. The guidelines issued by the US Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA) for primary and secondary prophylaxis are summarized in Tables 4 and Table 5. Table 6 outlines the treatment of common opportunistic infections in HIV.

Although prophylactic regimens are effective in preventing several episodes of OI, they are not always effective. Most patients need to continue them life-long. Probability of drug interactions, possibility of adverse events, complex drug regimens and high cost are its other limitations[2]. It is, therefore, important to emphasize that offering effective anti-retroviral therapy is the best way to prevent OI[2,9]. The future epidemiology of OI is linked inextricably with the effectiveness of future antiretroviral treatments. Nonetheless, the prophylaxis, diagnosis and treatment of OIs are likely to remain integral component of HIV care[2].

Important issues in management of OI

It is alright to say that one should diagnose the causative agent of all OIs. However, this may not always be possible. Even in the tertiary care centers where all investigative modalities are available, physicians may be reluctant to do invasive procedures for diagnosis. If this reluctance stems out of fear of acquiring HIV infection, they need to be informed about the ways of protecting themselves. At times, the reluctance may originate from concerns about the ability of the ill child to tolerate the procedure.

The situation is vastly different when a pediatrician or a doctor has to manage a case of OI in a primary health care setting, where hardly any investigations are available. It is necessary that professional bodies develop guidelines regarding management of OI in these situations. The guidelines could be based on "syndromic approach", wherein the clinician is able to make a diagnosis on the basis of clinical manifestations and minimal number of investigations. The purpose of such an exercise would be to enable the primary care physicians to offer appropriate care to HIV infected children with the resources at their disposal. The guidelines should be based on situation on the ground and should clearly delineate the indications for referral to a higher level of care.

Role of a pediatrician

The treating pediatricians should be aware of the fact that OI may be the first manifestation of pediatric HIV infection. They should investigate for HIV infection if the patient presents with unusual and severe manifestations of OI. HIV infection should be suspected in patients with:

1. Unexplained cyanosis, which may point towards diagnosis of PCP,
2. Chronic diarrhea along with failure to thrive, persistent fever, oral thrush,
3. Persistent and/or extensive oral thrush,
4. Persistent fever, not responding to anti-malarial drugs or antibiotic therapy,
5. Unexplained encephalopathy,
6. Severe, extra-pulmonary, multi-drug resistant (MDR) tuberculosis,
7. Recurrent bacterial infections

Table 4. Primary prophylaxis for opportunistic infections in HIV-infected infants and children[11]

Pathogen	Indication	Agents used for primary prophylaxis
Pneumocystis carinii	HIV-infected or HIV-indeterminate, infants aged 1-12 mo, HIV-infected children with CD4 count < 15%	TMP-SMZ, Dapsone, aerosolized pentamidine or Atovaquone
MTB (isoniazid-sensitive)	MT ³ 5mm or contact with any case of active tuberculosis	Isoniazid or Rifampicin
MTB (Isoniazid-resistant)	Same as above; high probability of exposure to isoniazid-resistant tuberculosis	Rifampicin
MTB (Multidrug-isoniazid and rifam picin resistant)	Same as above; high probability of exposure to multi-drug resistant tuberculosis	The agent to be used as per the sensitivity of the organism
MAC	For children aged ³ 6 yr: CD4+count <50/µL; Age 2-6 yr: CD4+count <75/µL; Age 1-2 yr: CD4+count <500/µL; Age < 1yr: CD4+count < 750/µL	Clarithromycin, Azithromycin or rifabutin
VZV	Significant exposure to varicella or shingles with no previous history of chickenpox or shingles	VZIG within 96 hr
Vaccine preventable pathogens	HIV exposure / infection	Routine immunizations
Toxoplasma gondii	IgG antibody to Toxoplasma and severe immunosuppression	TMP-SMZ or dapsone plus pyrimethamine plus leucovorin or atovaquone
Influenza virus	All patients (annually, before influenza season)	Inactivated split trivalent influenza vaccine, Oseltamivir, Rimantadine or amantadine
Invasive bacterial infections	Hypogamma-globulinemia (i.e. IgG < 400 mg/dL)	IVIG
Cryptococcus neoformans	Severe immunosuppression	Fluconazole or Itraconazole
Histoplasma capsulatum	Severe immunosuppression, endemic geographic area	Itraconazole
Cytomegalovirus (CMV)	CMV antibody positivity and severe immunsuppression	ganciclovir

Abbreviations: MTB: Mycobacterium tuberculosis, MAC: Mycobacterium avium complex, MT: Mantoux test; TMP-SMZ: trimethoprim-sulfamethoxazole

Table 5. Secondary prophylaxis to prevent recurrence of opportunistic infections in HIV-infected infants and children[11]

Pathogen	Agents Used for Secondary Prophylaxis
Pneumocystis carinii	TMP –SMZ, dapsone, aerosolized pentamidine or atovaquone
Toxoplasma gondii	Sulfadiazine plus pyrimethamine plus leucovorin or clindamycin plus pyrimethamine plus leucovorin
Mycobacterium avium complex	Clarithromycin plus ethambutol with or without rifabutin or azithromycin plus ethambutol with or without rifabutin
Cryptococcus neoformans	Fluconazole, amphotericin B or itraconazole
Histoplasma capsulatum	Itraconazole or amphotericin B
Coccidioides immitis	Fluconazole, amphotericin B or itraconazole
Cytomegalovirus	Ganciclovir or foscarnet
Salmonella species (non-typhi)[3]	TMP-SMZ
Invasive bacterial infections	TMP-SMZ or IVIG
Herpes simplex virus [Frequent /severe recurrences]	Acyclovir
Oropharyngeal Candida [Frequent/severe recurrences]	Fluconazole
Esophageal Candidiasis [Frequent/severe recurrences]	Fluconazole, intraconazole

Abbreviations: IVIG = intravenous immune globulin; TMP–SMZ = trimethoprim ≠ sulfamethoxazole.

No efforts should be spared to establish the etiology of the OI. This is vital as it is difficult to institute secondary prophylaxis without the correct primary diagnosis. Having said this, it is also important that in certain OI, treatment should not be withheld just for the sake of lack of conclusive evidence. For example, treatment of PCP is an emergency. The prognosis is worse if treatment is delayed by 48 hours. Hence, treatment should be started and simultaneously efforts be made to determine the causative agent. High viral load and low CD4 counts are associated with increased frequency of OI. Hence, the pediatrician should explore the possibility of institution of effective ART.

The role of pediatricians in prevention of OI does not end with prescribing medications. All efforts should be made to emphasize the importance of maintenance of nutrition, balanced diet and good personal hygiene. They should advise the parents that the child should receive freshly cooked food, should not swim in river water and should avoid contact with infected individuals to the extent possible. They should also give advice regarding appropriate immunizations for prevention of vaccine-preventable diseases.

Table 6. Treatment of common opportunistic infections[2,3]

Condition	Standard treatment		Alternative Treatment	
	Drug	**Dosage**	**Drug**	**Dosage**
PCP	TMP-SMZ	20mg/kg/d of TMP po or iv in 4 div doses for 21 d	Pentamidine	4mg/kg/day iv as a single dose for 21 days
	Steroids	For 7-10 d		
Recurrent bacterial infections	Broad-spectrum antibiotics till isolation of organism. This may be followed by specific antimicrobial agent depending upon response to therapy and antimi crobial sensitivity report			
MAC Complex	Clarithromycin or Azithromycin with Ethambutol and/orRifabutin		15mg/kg in 2 divided doses 10mg/kg once daily 15-20 mg/kg/d 5-10 mg/kg/d	
MTB	Isoniazid Rifampicin Pyrazinamide Ethambutol or Streptomycin		10-20 mg/kg/d, max.300 mg/d 10-20 mg/kg/d, Max. 600mg/d 30 mg/kg/d 15 mg/kg/d 20-30 mg/kg/d	
Candidiasis Oral	Topical nystatin	100,000 - 500,000 U 4 times a day	Oral fluconazole	3-6 mg/kg/d Once daily for 14 days
Oesophageal	Fluconazole	3-6 mg/kg d po /iv for 21 days	Amphotericin	0.5-1 mg/kg/d for 14-21 days
Cryptococcosis	Amphotericin	0.5-1 mg/kg/d for 14-21 days	Fluconazole	400-800 mg/d
Toxoplasmosis	Sulphadiazone,	85-120 mg/kg/d in 2-4 divided doses		
	Pyrimethamine,	1mg/kg/d, single dose		
	Folinic acid	5-10 mg every 3 days		
CMV	Gancyclovir	10mg/kg/d in 2 divided doses for 14-21 days	Foscarnet	180 mg/kg/d in 3 divided doses IV for 14-21 days
Varicella zoster	Acyclovir	1500 mg/m^2/d iv	Foscarnet	180 mg/kg/d in 3

contd.

If CD4 count is low: Mild infection and relatively good immune system	Acyclovir, oral	in 3 divided doses for 10 days. 80mg/kg/d in 4 divided doses		divided doses IV for 14-21 days
Herpes Simplex Virus	Acyclovir	80mg/kg/d in 3 –4 divided doses for 10 days	Foscarnet	180 mg/kg/d in 3 divided doses IV for 14-21 days

Note: TMP-SMZ: Trimethoprim-Sulfamethoxazole; MTB: Mycobacterium tuberculosis; CMV: Cytomegalovirus

Acknowledgement

The authors thank Dr. N.A. Kshirsagar-Dean, Seth G.S. Medical College & KEM Hospital, Parel, Mumbai 400012 for granting permission to publish the manuscript.

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HIV INFECTION

ANTIRETROVIRAL THERAPY (ART)

**** Archana Kher***

Abstract: *Effective antiretroviral therapy [ART] has improved the mortality and morbidity due to HIV infection in the developed nations. Potent regimens require a combination of three or more drugs to suppress the viral replication to very low levels. Before commencing therapy, various issues such as guidelines for initiation of treatment, monitoring, toxicity, resistance, compliance and adherence to treatment need to be adequately addressed. Cost and access to health care are other limiting factors. Due to these complexities, the ART should be initiated by physicians with expertise in the use of these agents. Long term benefit and safety must be considered. This review aims to provide the primary care physicians with practical information on antiretroviral drugs that are available for treatment.*

Key words: *Antiretroviral therapy - Guidelines*

Drug therapy for HIV infection has changed rapidly in the last few years. As early as 1987, pharmacotherapy included zidovudine monotherapy[1]. Today it is recognized that combination therapy with at least three antiretroviral drugs is far superior. Combination therapy such as Highly Active Antiretroviral Therapy [HAART] can suppress viral replication, improve immunological status, reduce opportunistic infections and delay the development of resistance. In 1993, the Working Group on ART and Medical Management of HIV infected children was convened by National Pediatric and Family Resource Center [NHFRC][2]. Dramatic advances in laboratory and clinical research have evolved and recommendations have undergone appropriate revisions. Presently, 15 ART drugs are approved by FDA, of which 11 have been recommended for use in children.

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Pathogenetic features of Pediatric HIV infection

Two major developments in the mid 1990s have contributed to the understanding and therapy of HIV infection in children[3].

a) Advent of many potent ART drugs available for combination therapy.

b) Facility to accurately quantitate the virus within the blood component.

It is important to recognize the biology of the HIV virus for a better understanding of pharmacotherapy of HIV infection[4]. HIV is an enveloped single stranded RNA virus. It contains the genes for gag, env, pol that encode for the core nucleocapsid polypeptides, surface coated proteins and viral enzymes reverse transcriptase, protease respectively. The virus enters the host cells by an interactive process between the envelope glycoproteins, host cell CD4 molecules and chemokine receptors. After entry into the CD4 cell, the single stranded viral RNA is transcribed by reverse transcriptase enzyme into double stranded DNA. The viral DNA thus enters the host cell nucleus and new virions are generated. Immature virions cleave gag-pol gene

products with the protease enzyme during their maturation process. The mature virions are then able to infect other host cells. An average of 10 billion virions are produced daily, with a half life of 6 hours in infected individuals. The rate of replenishment is high as the infected T lymphocytes have a half life of 24 hours. Higher number of CD4 T cells in infants and young children provide a larger target population for the virus thus accounting for a higher viral load in children. The viral pool has an extensive capacity for mutation and recombination in response to the individual's immunity and pharmacotherapeutic agents. Mutations occur when errors are introduced in the viral genome during replication. The polymerase reverse transcriptase has 10,000 nucleotides and there is one error for every 10,000 nucleotides. A large pool of viral variants exists at the beginning of the disease, many of the variants are defective and incapable of producing infection; however, they can be responsible for drug resistance. This fact is accounted by using multidrug therapy early in the course of the infection to achieve suppression of viral replication and avoid development of drug resistance[3]

Important considerations for treating HIV infected infants and children [2,3,4]

- Acquisition of infection through perinatal exposure for many infected children.
- In utero exposure to zidovudine (ZDV) and other retroviral agents in many perinatally infected children
- Differences in evaluation of perinatal infection
- Differences in immunologic markers (e.g. CD4+ T lymphocyte count) in young children
- Evaluation of drug dosages as changes in pharmacokinetic parameters occur with age due to continued development, maturation of organ systems involved in the drug metabolism and clearance, especially in preterm babies and neonates.
- Differences in the clinical and virologic manifestations of perinatal HIV infection due to occurrence of primary infection in immunologically immature individuals.
- Special emphasis for adherence to treatment in children.

Important considerations for treating HIV infected adolescents[2]

- Adolescents may have acquired the infection recently through intravenous drug abuse or the sexual route and are ideal candidates for ART.
- Special consideration for compliance and adherence to treatment.
- Doses should be prescribed based on Tanner's stages and not the age. For those with stages I and II are given pediatric doses. Females with stage III and males with stage IV are given adult doses.
- Females develop more fat and males develop more muscle mass, this could alter the drug pharmacokinetics.

Initiation and continuation of ART should be undertaken only by personnel who have gained expertise in the management of HIV infections and in centers where there is a infrastructure to manage opportunistic infections and monitor therapy.

Antiretroviral agents

Currently available antiretroviral agents act by inhibiting the activity of two major viral enzymes namely reverse transcriptase (RT) and the HIV protease. Other targets under evaluation include the integrase inhibitors, inhibition of viral entry (especially fusion) and viral activation [4,5,6,7] (Table 1).

Table 1. Antiretroviral drugs available for therapy

Drugs	Formulation	Pediatric dosage	Side effects	Remarks
Nucleoside Analogue Reverse Transcriptase Inhibitors[NRTIs]				
1. Zidovudine [AZT, ZDV]	Syrup 50mg/ml Cap 100mg, Tab 300mg IV Infusion 10mg/ml	90 -180 mg/m^2/dose QID Neonates: Oral 2mg/kg q 6hrs	Anemia, leucopenia, nausea, headache, liver toxicity, myopathy	Take with food, do not use with d4T, reduce dose in hepatic and renal dysfunction.
2. Lamivudine [3TC]	Syrup 50mg/ml Tab 100mg, 150mg.	4mg/kg/dose BD, max 150mgBD.	Headache, diarrhoea pancreatitis, peripheral neuropathy.	Prevents ZDV resistance, reduce dose with renal dysfunction.
3. Stavudine [d4T]	Solution 1mg/ml Cap 15,20,30,40 mg.	1mg/kg/dose BD [upto 30kg] 30 -60 kg - 30 mg BD	Peripheral neuropathy, pancreatitis, steatosis, mitochondrial toxicity.	Elevation of hepatic enzymes, do not combine with AZT.
4. Didanosine [ddI]	Solution 10mg/ml Chewable tabs 25, 50, 100, 150 mg.	90 -150 mg/m^2/dose BD	Nausea, diarrhoea, peripheral neuropathy pancreatitis.	Rapidly degraded in acidic environment, To be taken on empty stomach.
5. Zalcitabine [ddC]	Tab 0.375mg, 0.75 mg	0.01mg/kg/dose TDS	Fever, rash, stomatitis, esophageal ulcers, pancreatitis, peripheral neuropathy,	Do not use with ddI, d4T, to be taken on empty stomach. Reduce dose in renal dysfunction.
6. Abacavir [ABC]	Solution 100mg/5ml Tab 300 mg	8mg/kg/dose BD	Gastrointestinal, rash, fever, hypersensitivity, lactic acidosis, respira tory symptoms.	Allergic reactions may appear within 6 weeks of starting therapy and resolve within 24 - 48 hours of stopping therapy.
NonNucleoside Reverse Transcriptase Inhibitors[NNRTIs]				
1. Nevirapine [NVP]	Suspension: 50mg/ 5ml Tab 200 mg.	120 -200 mg/m^2/dose BD use OD for first 14 days.	Rash, fever, nausea, headache, hepatitis	Discontinue drug in case of severe rash
2. Delaviridine [DLV]	Tab 100mg.	Not known precisely	Rash, headache	Should be taken with an acidic beverage.
2. Efavirenz [EFV]	Cap 50, 100, 200 mg.	Wt10 -15 kg , 200mg Wt 15 - 20 kg, 250mg Wt 20 - 25 kg, 300mg Wt 25 - 32 kg, 350mg Wt 32 - 40kg, 400mg Wt > 40 kg , 600mg Taken OD	Rash, insomnia, confu sion, euphoria, hallucina tions, poor concentration, stomach discomfort, elevated liver enzymes.	Avoid high fat foods, should be given at bed time.

contd.

Table 1 - contd.

Drugs	Formulation	Pediatric dosage	Side effects	Remarks
Protease Inhibitors[PI]				
1. Ritonavir [RTV]	Solution 400mg/5ml. Cap 100 mg	350 - 400mg/m^2/dose BD	Nausea, vomiting, bitter taste, abdominal pain, paresthesia, elevated liver enzymes and cholesterol.	Should be taken with food, increase dose slowly, drug should be refrigerated.
2. Saquinavir [SQV]	Hard gel cap 200mg Soft gel cap 200mg	33mg/kg[max 1200mg of soft gel] TDS	Diarrhoea, nausea, in somnia, headache, hepatotoxicity	Take within 2 hours of a full meal. Refrigerate for long term storage.
3. Nelfinavir [NFV]	Oral powder 50mg/ scoop ful Tab 250mg.	25mg/kg TDS or 55mg/kg BD	Diarrhoea, nausea, flatulence, abdominal pain,diabetes,	hyperglycemia, rash. Hepatotoxicity, To be taken with a light snack/meal.
4. Indinavir [IDV]	Cap 200, 400 mg.	500mg/m^2/dose TDS. Max 800mg TDS.	Stomach discomfort, headache, crystalluria, nephrolithiasis, raised indirect bilirubin, hemolytic anemia.	Take on empty stom ach or low fat snack. Ensure good hydration.
5. Amprenavir [VX478]	Soln 75mg/ml Cap 50,150 mg.	Soln 22.5 mg/kg BD Cap 20 -25 mg/kg BD	Gastrointestinal , rash , paresthesia, depression	Not to be given with antacids, enquire about sulfa allergy prior to starting the drug.
6. Lopinavir +Ritonavir	Oral soln 400mg Lopinavir + 100mg Ritonavir /5 ml Cap 133.33mg Lopinavir + 33.3 mg Ritonavir	Wt <15 kg 12mg/kg of Lopinavir BD Wt > 15 kg 10mg/kg of Lopinavir BD 300mg/m^2 Lopinavir BD-	Gastrointestinal, rash, elevated serum lipids, liver enzymes, amylase and glucose.	Rifampicin increases the metabolism of lopinavir , not to be used concomittantly.

Long term side effects of NRTIs have been associated with damage to the mitochondria. This damage may cause low red and white cell counts, muscle pain, wasting. New NRTI Emcitrabine and NNRTI Emivirine are being evaluated. Adefovir and Tenofovir diisoproxil fumerate are nucleotide agents. They inhibit HIV RT enzyme without the initial step of phosphorylation. Long term side effects of PIs include changes in blood sugar levels, development of diabetes, elevations in blood fat levels, lipodystrophy. There could be fat deposits in the abdomen, back of shoulders as well as loss of fat in the arms, legs and face. Perianal abscesses are also known to occur.

1. Reverse Transcriptase Inhibitors (RTIs)

The RTIs primarily act via inhibition of HIV reverse transcriptase, the enzyme that catalyses the conversion of HIV RNA into double stranded DNA. Enzyme inhibition results in termination of the DNA chain and therapy reduces viral replication. This class of agents is further divided into nucleoside RTIs, non-nucleoside RTIs and nucleotide RTIs.

a) Nucleoside RTIs (NRTIs)

They contain faulty versions of nucleotides, which are used by RT enzyme to convert RNA to DNA. The new DNA cannot build correctly and virus production is arrested. Resistance to

this class of drug is due to the development of mutations in codons of the RT gene. Cross resistance among this group of drugs results from multiple mutations in the RT gene.

b) Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

They bind at different sites on the RT enzymes, and are potent inhibitors of the RT enzyme. They are active against the nucleoside reverse transcriptase inhibitor-resistant strains.

2. Protease Inhibitors (PIs)

They inhibit the HIV protease, an enzyme required for cleavage of viral polyprotein precursors and subsequent generation of functional HIV proteins. The virus copies its own genetic code into the host cell's DNA, thereby creating new copies of HIV virus. Once the viral DNA is inside a T cell DNA, the cell produces a long strand of genetic material that must be cut and put together correctly to form new copies. Cutting this strand requires protease.

Principles of treatment of pediatric HIV Infection

Determine the goals/ of therapy and discuss them with parents and the patient (if old enough) clearly before initiation of therapy. The aim is to make the plasma viral load undetectable so that maximal inhibition of viral replication is achieved, to slow the disease progress and to minimize the development of drug resistance [8,9,10]

1. Ideally all children with HIV infection should be offered specific ART irrespective of their clinical status, CD4 counts or HIV RNA copies . Immediate side effects of the drugs, long term toxicities, high cost of therapy and monitoring are major limiting factors.
2. All drugs approved for adults, can be used in children; though specific pediatric pharmacokinetic studies and effects on growth and development are not clearly defined.
3. Early initiation of appropriate therapy is beneficial as it slows the deterioration of immune function, delays progression of the disease and reduces the incidence of opportunistic infections.
4. Monotherapy is contraindicated as it may result in incomplete suppression of HIV replication and thereby promote development of drug resistance. ZDV monotherapy as prophylaxis, is indicated for 6 weeks in neonates born to HIV positive mothers, but once the presence of HIV infection is proven in the baby, monotherapy is changed to combination therapy.
5. ART is most beneficial in patients who are treatment naive and are initiated with the most potent regimen. The combination of two nucleoside RT inhibitors and a protease inhibitor has become the gold standard of therapy.
6. Although complete suppression of viral replication in the plasma can be achieved with most potent drug combinations, plasma represents only 1% of the total body viral burden. In some patients one may only manage to keep the viral load below 5000 copies/ml.
7. Therapy is not curative and has to be continued life long even if the CD4 T lymphocyte counts are normal and HIV RNA is undetectable in the blood. When therapy is discontinued, there can be a resurgence of the viral load from the long lasting cellular reservoirs of the virus.

When to initiate ART ? (Table2)

Most decisions regarding the initiation of ART are based on viral load and CD4 cell

determination. Potent therapy can at least partially restore pathogen specific immunity to recall antigens and naive CD4+ cells can be restored gradually with prolonged virus suppression.

Therapy is recommended for[10]

a) All patients with symptomatic established HIV infection and advanced HIV disease (CD4 cell count < 200 cells/mm^3).

b) CD4 cell counts < 350 cells/mm^3 irrespective of HIV RNA level.

c) Plasma viral load of > 30,000 copies/ml regardless of CD4 cell count.

d) Both plasma HIV RNA levels in the 5000 to 30,000 copies/ml range and CD4 cell counts between 350 to 500/mm^3 .

e) When CD4 cell counts > 500 cells/mm^3 and viral load < 5000 copies/ml, the risk of disease progression is slow over next 3 to 5 years. Such patients should be monitored closely for CD4 cell counts and HIV RNA to diagnose disease progression.

f) Consider therapy when CD4 cell count > 500 cells/mm^3 but viral load is 5000 to 30,000 copies/ml.

g) No definite recommendations can be made for those with intermediate viral load levels and CD4 cell counts between 350 and 500 cells/mm^3.

Acute treatment of a serious opportunistic infection takes precedence over ART initiation.

Recommendations by the Working Group on ART and Medical Management of HIV Infected Children are summarized in Table 2.

Table 2. Indications for initiation of ART in children with HIV infection[2]

- Clinical symptoms associated with HIV infection (i.e., clinical categories A, B, or C)
- Evidence of immune suppression, indicated by CD4+ T cell absolute number or percentage (i.e., immune category 2 or 3)
- Age < 12 months - regardless of clinical, immunologic, or virologic status **.
- For asymptomatic children aged > 1 year with normal immune status, two options can be considered:

  Option 1: Initiate therapy - regardless of age or symptom status.

  Option 2: Defer treatment in situations in which the risk for clinical disease progression is low and other factors (i.e., concern for the durability of response, safety, and adherence) favor postponing treatment. In such cases, the health-care provider should regularly monitor virologic, immunologic, and clinical status. Factors to be considered in deciding to initiate therapy include the following:

  - High or increasing HIV RNA copy number.
  - Rapidly declining CD4+ T cell number or percentage to values approaching those indicative of moderate immune suppression (i.e., immune category 2)
  - Development of clinical symptoms.

** The Working Group recognizes that clinical trial data documenting therapeutic benefit from this approach are not currently available, and information on pharmacokinetics in infants under age 3-6 months is limited. This recommendation is based on expert opinion.

Table 3. Recommended Antiretroviral Regimens for initial therapy of HIV infection in children

Strongly recommended

Clinical trial evidence of clinical benefit and/or sustained suppression of HIV replication in adults and/or children.

- One highly active protease inhibitors (nelfinavir or ritonavir) plus two nucleoside analogue reverse transcriptase inhibitors.
    - Recommended dual NRTI combinations: the most data on use in children are available for the combinations of ZDV and ddI, ZDV and lamivudine (3TC), and stavudine (d4T) and ddI. More limited data are available for the combinations of d4T and 3TC and ZDV and ddC.
- For children who can swallow capsules: the non-nucleoside reverse trasncriptase inhibitor (NNRTI) efavirenz (SustivaTM) plus two NRTIs , or efavirenz (Sustiva™) plus nelfinavir and one NRTI.

Recommended as an alternative

Clinical trial evidence of suppression of HIV replication, but 1) durability may be less in adults and/or children than with strongly recommended regimens or may not yet be defined; or 2) evidence of efficacy may not outweigh potential adverse consequences (i.e., toxicity, drug interactions, cost, etc); 3) experience in infants and children is limited.

- NVP and two NRTIs.
- ABC in combination with ZDV and 3TC.
- Lopinavir/ritonavir with two NRTIs or one NRTI and NNRTI.
- IDV or SQV soft gel capsule with two NRTIs for children who can swallow capsules.

Offered only in special circumstances

Clinical trial evidence of either 1) virologic suppression that is less durable than for the strongly recommended or alternative regimes; or 2) data are preliminary or inconclusive for use as initial therapy but may be reasonably offered in special circumstances.

- Two NRTIs.
- APV in combination with two NRTIs or ABC.

Not recommended

Evidence against use because 1) overlapping toxicity may occur; and/or 2) use may be virologically undesirable.

- Any monotherapy. [except in neonates born to HIV positive mothers, ZDV is given for 6 weeks.]
- d4T and ZDV
- ddC and ddI
- ddC and d4T
- ddC and 3TC

ddC is not available commercially as a liquid preparation. There are currently no data on appropriate dosage of EFV in children under age three years.

What drug combinations to use [2,3,8,9,10] (Table3).

Monotherapy usually results in only a 0.5 to 1.5 log reduction of plasma RNA and due to rapid development of resistance, is never recommended. Nucleoside analog combinations rarely achieve durable suppression of viral replication and are therefore not recommended. Dual nucleoside combinations are the backbone of most potent regimens. The combinations used are ZDV + 3TC, d4T + ddI, d4T + 3TC, ZDV + ddI. The three nucleoside RT inhibitor combination of 3TC, ZDV and Abacavir has been found to be potent initially, though long term studies are awaited. These three drugs can be given as a single pill. The combination of two nucleoside RT inhibitors and a PI has become the gold standard of treatment. The initial mutations seen with Nelfinavir failure are not associated with resistance to other PIs and Ritonavir – Saquinavir and Ritonavir – Indinavir can then be used. Addition of a small dose of Indinavir improves the pharmacokinetics of Saquinavir and Amprenavir. The combination of two nucleoside RT inhibitors and Efavirenz or two nucleoside RT inhibitors and Nevirapine is equally potent as 2 NRTIs + PI. There is less information using Delavirdine as initial therapy.

Monitoring during ART [8,9,10]

An adherence rate of at least 95% is essential for optimal results. Barriers such as number, timing of dose, number and size of pills, food restrictions and adverse effects should be considered when planning drug regimens. Minimum of two CD4+ cell counts and two HIV RNA measurements done a month apart should be obtained prior to initiation of therapy. Infections and vaccinations can lower the CD4 counts. The tests should be done from the same laboratory. A one to two log decrease in viral load is taken as an indication of positive drug effect. A decrease of > 0.5 logs (three fold change) is needed to overcome variability of test. Failure to achieve the target level of < 50 copies/ml or 10 fold decrease from the base line by 8 - 12 weeks should raise concerns about poor adherence, improper drug absorption or drug resistance. HIV RNA levels are to be monitored within 1 month of initiation of therapy or change, monthly until the goal of therapy is reached and then every 3 to 4 months. Rise in the CD4+ cell count during therapy reflects at least partial immune system reconstitution.

When to change therapy ? [2,8,9,10]

Reasons for changing drugs in ART are

a) Drug failure, b) Adverse effects, c) Regimen inconvenience.

Drug failure is defined as:

- Less than a 10 fold decrease (one log) from baseline HIV RNA levels in spite of receiving potent treatment for 8 to 12 weeks of therapy.
- Detectable HIV RNA levels after 4 to 6 months of therapy.
- Repeated detection of HIV RNA in patients who had undetectable levels following initiation of therapy.
- Levels of HIV RNA between 50 and 500 copies/ml are associated with higher risk of resistance than levels below 50 copies/ml. Therapy change based on only CD4+ cell response is not recommended.

Drug failure is essentially seen with non-adherence, sub-therapeutic drug levels, non potent regimens.

If an individual drug in a regimen is changed to reduce toxicity or for convenience, the full regimen must be reviewed for potency, resistance and drug interactions.

Table 4. Considerations for changing Antiretroviral therapy for HIV infected children[2]

Virologic considerations *

- Less than a minimally acceptable virologic response after 8 to 12 weeks of therapy. For children receiving antiretroviral therapy with two NRTIs and a PI, such a response is defined as a less than tenfold (1.0 $\log_{10}$) decrease from baseline HIV RNA levels. For children who are receiving less potent antiretroviral therapy (i.e., dual NRTI combinations), an insufficient response is defined as a less than fivefold (0.7 $\log_{10}$) decrease in HIV RNA levels from baseline.
- HIV RNA not suppressed to undetectable levels after four to six months of antiretroviral therapy.†
- Repeated detection of HIV RNA in children who initially responded to antiretroviral therapy with undetectable levels.§
- A reproducible increase in HIV RNA copy number among children who have had a substantial HIV RNA response but still have low levels of detectable HIV RNA. Such an increase would warrant change in therapy if, after initiation of the therapeutic regimen, a greater than threefold (0.5 $\log_{10}$) increase in copy number in children aged > 2 years and greater than fivefold (0.7 $\log_{10}$) increase is observed in children aged < 2 years.

Immunologic considerations *

- Change in immunologic classification .¶
- For children with CD4+ T cell percentages of < 15% (i.e., those in immune category 3), a persistent decline of five percentiles or more in CD4+ T cell percentage (i.e., from 15% to 10%).
- A rapid and substantial decrease in absolute CD4+ T cell count (i.e., >30% decline in < 6 months).

Clinical considerations

- Progressive neurodevelopmental deterioration.
- Growth failure defined as persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation.
- Disease progression defined as advancement from one pediatric clinical category to another (i.e., from clinical category A to clinical category B). **

* At least two measurements (taken one week apart) should be performed before considering a change in therapy.

† The initial HIV RNA level of the child at the start of therapy and the level achieved with therapy should be considered when contemplating potential drug changes. For example, an immediate change in therapy may not be warranted if there is a sustained 1.5 to 2.0 $\log_{10}$ decrease in HIV RNA copy number, even if RNA remains detectable at low levels.

§ More frequent evaluation of HIV RNA levels should be considered if the HIV RNA increase is limited (i.e., if when using a HIV RNA assay with a lower limit of detection of 1,000 copies/mL, there is a <0.7 $\log_{10}$ increase from undetectable to approximately 5,000 copies/mL in an infant aged < 2 years).

¶ Minimal changes in $CD4^+$ T cell percentile that may result in change in immunologic category (i.e., from 26% to 24%, or 16% to 14%) may not be as concerning as a rapid substantial change in $CD4^+$ percentile within the same immunologic category (i.e., a drop from 35% to 25%).

** In patients with stable immunologic and virologic parameters, progression from one category to another may not represent an indication to change therapy.

Changing the regimen: (Table 4)

In the absence of virologic failure

- For adverse effects or intolerance substitute the individual drug.
- In case of NNRTI induced rash, substitution with other NNRTIs must be monitored because of risk of shared toxicity.
- In case of Abacavir induced hypersensitivity, the drug should be discontinued and rechallenge deferred due to severe toxicity and fatal reactions.

Due to virologic failure

- In patients having detectable, but low levels of HIV RNA after a few months of potent therapy and without identified resistance to drugs in the current regimen, addition of a new drug (i.e. intensification) could be an alternative to complete change.
- Whenever a decision is made to change a given regimen, at least 2 drugs (preferably all 3) should be replaced.
- While the NRTIs can be replaced by other drugs from the same class, the same does not hold true for the PI or NNRTIs because of significant cross-resistance amongst other drugs of these classes.

Three options are another PI, combination of 2 PIs, an NNRTI and another PI.

Should therapy be stopped ?

Based on clinical and immunologic benefit, it is reasonable to continue treatment as long as possible.

Indications for changing therapy are as follows:

a) Toxicity or intolerance

- HIV RNA suppressed below target (< 50 copies/ml) or still above target but fewer than 8-16 weeks of therapy. (Change the offending agent)
- HIV RNA above target (> 50 copies/ml) more than 8-16 weeks on therapy or prior success.(Change the entire regimen)

b) Difficulty with adherence

- HIV RNA suppressed below target, but adherence problems present, or HIV RNA above target but less than 8-16 weeks of therapy. (Change to simplified regimen with equal potency, may substitute single drug.)
- HIV RNA above target, more than 8-16 weeks therapy or prior success, change entire regimen.

c) Virologic failure

- Failure to reach target viral load within 8-16 weeks of therapy, continue current regimen, assess adherence, consider intensification.
- Failure to reach target viral load within 24 to 36 weeks of therapy or prior success but now confirmed drug failure. Change entire regimen, 3 new drugs and a new class of antiretrovirals should be used.

Resistance testing and Cross Resistance [10]

Two measures are available for resistance testing:

- **Genotyping testing**: These assays amplify the HIV-1 PR and RT genes from viral RNA in plasma and then use automated DNA sequencing of the entire PR and RT genes.
- **Phenotyping testing**: Susceptibility of the HIV -1 to inhibition by a particular drug is determined.Drug required to inhibit the viral production in vitro by 50%, 90%, 95%, is tested, such assays can easily determine cross resistance

Cross resistance within the three classes of medications is usual. Cross-resistance among PIs is important; strains resistant to Indinavir tend to be resistant to Ritonavir. Two new PIs should be used. Patients who have received Nelfinavir may respond well to Ritonavir – Saquinavir or Ritonavir – Indinavir. There is almost complete cross resistance among available NNRTIs. Cross resistance among the NRTIs is more variable. Resistance to 3TC appears rapidly, point mutation at position 184 of the RT gene confers high level resistance. Resistance to ZDV is a gradual process, appearance of multiple ZDV resistance mutations confers high level resistance; these strains are also resistant to d4T. Viruses with high level resistance to ZDV and 3TC are usually resistant to Abacavir. There is little cross-resistance among ddI, ddC and ZDV. It is difficult to demonstrate d4T resistance. Broad resistance among nucleoside analogs is seen with mutation at codon 151 and insertion mutation at codon 69.

TB medications – ART Drug Interactions:[10]

The most problematic drug interactions occur between Rifampicin and PIs or NNRTIs. Interactions are less pronounced with Rifabutin and therefore it is a safe alternative to Rifampicin. No significant drug interactions are noted between TB medications and NRTIs, except that ddI should be dosed 1 hour apart due to its antacid buffer. There is an increased risk of neuropathy if ddC and INH are used together. Ethambutol, Pyrazinamide and the Flouroquinolones have no known cyp3A4 effect and hence no major interactions with antiretrovirals.

Other modalities of therapy and newer drugs [2, 9]

Newer treatment options under trial are as follows:

- Integrase Inhibitors e.g. ARITT and Fusion Inhibitors e.g. Pentafuside (T-20) which prevent fusion of the HIV virus with target cells by binding to surface protein gp41 are being studied at length.
- Hydroxyurea is a ribonucleotide reductase inhibitor. It reduces the cellular pool of endogenous deoxynucleotide triphosphates and improves the uptake and utilization of nucleoside analogs. It inhibits HIV DNA synthesis and is myelosuppressive and reduces CD4 cell counts.
- Benzamide compounds interfere with zincfinger proteins that are essential for viral packaging and replication.
- Chemokines which interfere with co-receptors involved in HIV infection e.g. CCR5, CXCR4 are being evaluated.
- The immune system can be assisted using broad-spectrum recovery with cytokines such as Interleukin IL2 or Proleukin. This stimulates the production of T4 cells. The cytokines regulate the immune system and stimulate or inhibit the growth and activity of various immune cells. Proleukin is used in the form of high (15 million units everyday IV), intermediate (9 million units everyday IV) and low (3 million units everyday IV) dose regimens for 5 days. The course is repeated every 3 weeks.
- Another approach uses therapeutic vaccines. This approach attempts to teach a person's immune system to fight a virus long after it has infected the host. The candidate for this kind of therapy is Remune or Salk Vaccine (HIV-I Immunogen) or AG1661. The HIV virus has been altered and killed so that it will not cause damage to the immune system. It is a dead form of the virus and the key protein gp120 is missing. It can enhance the immune response when given in the dose of 1 ml every 3 months.

- Routine intravenous immune globulin (IVIG) therapy is also recommended in combination with antiviral agents for children only for the following :-

  [i] hypogammaglobulinemia (IgG < 250 mg/dl, 2.5 g/L)

  [ii] recurrent serious bacterial infections (defined as 2 or more serious infections in one year).

  [iii] children who fail to form antibodies to common antigens.

  [iv] treatment of parvovirus B_{19} infections.

  [v] treatment of thrombocytopenia

  [vi] single dose for children exposed to measles.

Dose used is 400 mg/kg/dose every 4 weeks, and 600 mg/kg/dose every 4 weeks for bronchiectasis.

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NEWS AND NOTES

PALS COURSE

Date: 6th and 7th December 2003

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HIV INFECTION

PREVENTION OF MOTHER TO CHILD TRANSMISSION OF HIV

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Abstract: *Nearly 4 million people are living with HIV infection in India today. Six states namely Maharashtra, Tamil Nadu, Andhra Pradesh, Karnataka, Manipur and Nagaland have high prevalence rates for HIV infection defined as more than 1% HIV prevalence amongst pregnant women tested during sentinel surveillance conducted in the ante-natal clinics. 28 million deliveries occur in India annually. At a national average of 0.5% HIV prevalence in mothers attending the ANC clinics, 1.4 lakhs of deliveries occur in HIV infected mothers annually and without any intervention 30% of these exposed babies will become HIV infected. This means approximately 40000 babies get HIV infection through vertical route in India annually. This figure could be more if the national average prevalence is more than 0.5%. What is required is an effective and feasible program to prevent mother to child transmission. Voluntary testing and counseling must be available to all the mothers attending the ANC clinics. Those who are detected HIV infected must receive anti-retroviral prophylaxis, safe delivery care and counseling on the feeding of the baby. Besides this, the focus must be turned on primary prevention of HIV infection in the wouldbe mothers with mass education and last but not the least care and concern towards those who are already infected. This article discusses further the various modalities available for prevention of mother to child transmission (PMTCT).*

Key words: *Childhood HIV, Mother to child transmission, Indian feasibility study*

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Magnitude of the problem

World over, 30-40 million people are expected to be HIV infected. 30-40% of HIV cases are in women of childbearing age and 10-15% of cases occur in the pediatric age group. It is estimated that daily 2000 new pediatric HIV cases occur world over, of which 200 cases occur in India. Mother to child transmission accounts for 80-90% of pediatric cases, which can be easily prevented[1]. Of the 28 million deliveries occurring in India annually, 0.84 lakh deliveries occur in HIV positive mothers at a national average of 0.3% prevalence of HIV in pregnant women. Without any intervention, 30% of these babies will become HIV infected i.e. annually 24,000 babies are HIV infected in India by vertical transmission. If this prevalence reaches 1%, it will lead to a lakh of babies infected at birth.

Efficacy of vertical transmission

Vertical transmission occurs due to infection of the baby by maternal blood, cervico-vaginal secretions or via breast milk. The baby gets infected either due to transplacental hemorrhage or due to infection via umbilical cord or via oral

and GI (gastrointestinal) mucosa while swallowing infected amniotic fluid. The incidence of vertical transmission is 20% in western world, whereas it is as high as 30-40% in developing countries. In India it has been shown to be 30%. With the use of interventions like elective caesarean section, antiretroviral drugs and replacement feeding instead of breast-feeding, the incidence of transmission has dropped from 20% to 8% or even less in the western world.

Factors that affect the efficacy of vertical transmission

The efficacy of vertical transmission depends on various factors. These include maternal factors, type of delivery, factors in newborn, breast-feeding and the type of interventions used to decrease the rate of transmission.

Maternal factors

Vertical transmission rate is high when the mother has recently seroconverted or in those who are in late stage of HIV disease, as both are likely to have high viral load. More the viral load in the mother, more is the rate of vertical transmission. Except one study, all others have shown that transmission does occur even when maternal viral load is low or is undetectable. Hence, no level of viral load is safe as far as vertical transmission is concerned. Presence of high titre of anti-HIV antibodies in mother protects the newborn from HIV infection to some extent, as these antibodies pass transplacentally to the baby. Many studies have shown higher chances of vertical transmission when mothers were malnourished as they have low anti-HIV antibody levels. Vitamin A deficiency in mother is also associated with increased chances of vertical transmission. Presence of other STDs especially with bleeding lesions of cervix or vagina lead to increased chances of contamination of birth canal and increased chances of vertical transmission. Some viral characteristics, like highly replicating virus in mother, are associated with increased vertical transmission. In western countries mothers who used illicit intravenous drugs are known to have increased vertical transmission.

Type of delivery

Infected vaginal and cervical secretions as well as the maternal blood have been the source of HIV infections for the baby. HIV has been isolated from vaginal as well as cervical secretions of at least 50% of HIV- infected women. Logically longer the time the baby remains in contact with birth canal, more will be the chances of HIV infection. Various studies have shown increased vertical transmission rates in babies delivered vaginally, especially with prolonged labour and rupture of membrane for more than 4 hours. It is also more in the presence of chorioamnionitis, traumatic delivery, instrumentation during delivery and episiotomy. In mothers with sexually transmitted diseases, the risk is more due to increased contamination due to open bleeding lesions. The incidence of transmission has been shown to be 25% with rupture of membrane for more than 4 hrs as compared to 14% with rupture of membrane for less than 4 hrs. This has prompted many investigators to study the effect of elective LSCS on HIV transmission.

Prematurity

Prematurity is associated with an increased rate of vertical transmission. This is probably related to the thin skin, susceptible mucous membranes and immature immune functions with lesser transfer of maternal antibodies transplacentally (before 34 weeks of gestation).

Postnatal factors

The main post-natal factor involved in transmission is breast milk which is expected to

lead to 14% extra risk of transmission over and above other factors.

Timing of vertical transmission

Exact timing of vertical transmission varies from case to case. It can occur in utero as early as 15-20 weeks (as aborted fetuses have been shown to be infected with HIV). In addition, some workers have described HIV dysmorphism in some cases characterized by craniofacial dysmorphisms and congenital heart disease. But the fact that most of the HIV infected babies are normal at birth, suggests that the infection is transmitted most commonly in the last trimester, during labour and via breast milk postnatally. This is also evident by the fact that interventions to decrease vertical transmission are able to block it by 50-65%.

The relative frequency of timing at which transmission occurs is as follows. Of the 30% of babies who get infected vertically, 2% get infected early in gestation and 3% late in gestation mainly in last month of gestation, 15% get infected during labour, 5% get infected in early post partum period and 5% in late post-partum period[2]. The Pediatric Virology Committee of the AIDS Clinical Trial has proposed definitions for determining the timing of infection (in-utero versus intra-partum). It is considered that a child with a positive PCR within 48 hours of birth has been infected in utero[3]. If a non- breastfed baby who is PCR- negative at birth demonstrates a positive PCR at 7- 90 days, the baby is considered to have been infected during delivery. Most of the interventions to decrease the transmission target the late prenatal period, labour and postnatal period to block transmission.

Prevention of mother to child transmission (PMTCT)

PMTCT involves four strategies:

a) Measures to decrease maternal HIV cases
b) Measures to decrease viral load in HIV infected mothers e.g. AZT to mother.
c) Measures to decrease exposure of baby to maternal fluids e.g. elective lower segment caesarean section (LSCS) or avoiding breast-feed.
d) Measures to decrease chances of HIV in exposed babies e.g. AZT to baby.

Interventions to decrease MTCT

Different interventions undertaken to prevent vertical transmission include: -

a) Antiretroviral drugs
b) Infant feeding issues
c) Elective LSCS
d) Cleaning of birth canal during delivery
e) Vitamin A prophylaxis
f) Immunotherapy

A) Anti-Retroviral Drugs

The most successful intervention decreasing vertical transmission is the use of antiretroviral drugs during pregnancy, labour and post-natally to the mother and baby. Most extensively and successfully used drug is AZT (used as mono-therapy since 1994). Even nevirapine has been used successfully as mono-therapy since 1999. Of late, combination of two drugs or more has been used successfully bringing down the vertical transmission to below 2%. These drugs act by reducing the viral load in the mother and act as post exposure prophylaxis in the newborn. There are ethical dilemmas like creating orphans by preventing HIV in the peri-natally exposed babies by these measures. However 70% of babies born to HIV infected mothers naturally escape the infection and are at the risk of being orphans sooner or later. It will be more unethical to let a child contract HIV when it could have been prevented.

There are many trials done in this regards like PACTG 076 protocol, Thai-CDC protocol, Uganda protocol using nevirapine, French perinatal cohort study, Cote d' ivoire study, PETRA study, SAINT Study, etc. We will discuss some of the important studies. Most studies target the last months of gestation, labour and post-partum period of 1 week for the mother and for 6 weeks to the baby postnatally.

1) PACTG 076 Protocol

This multicentric study by the Pediatric AIDS Clinical Trial Group was done in 1994 in USA and France[4]. HIV positive mothers who were AZT (Zidovudine) naive had CD4+ counts more than 200 were enrolled between 14-35 weeks of gestation. They were not enrolled before 14 weeks due to fear of teratogenicity of AZT and not enrolled after 35 weeks as it was considered too late to start AZT. All enrolled mothers were given AZT in the dose of 100 mg 5 times a day from the day of enrolment till the onset of labour. On the day of delivery they were given intravenous AZT in the dose of 1 mg/kg/hr in drip form till delivery. After delivery the baby was put on oral AZT in the dose of 8 mg/kg/day in 4 divided doses, starting the first dose within 12 hrs of birth and it was continued for 6 weeks. All babies were born by elective LSCS at 38 weeks of gestation and all the babies were given formula feeds and breast-feeding was not allowed at all. The results of vertical transmission were compared with matched control group of mother and child pairs who were given placebo instead of AZT in the same schedule. The results at 18 months showed the transmission rate to be 26% in placebo group and 8% in AZT group, this means 68% efficacy of AZT in preventing mother to child transmission. This has been the best efficacy reported by any study so far. In fact with the interim reports, the trial was stopped prematurely as it was unethical to continue placebo group. All the subsequent trials are compared with the 076 trial.

Though 076 protocol is ideal, it has many practical problems for developing countries. Firstly, it is a lengthy protocol both for mother and baby. It will lead to increased cost, decreased compliance and hence failure in majority. In developed countries the cost of this protocol is estimated to be US$ 1000/- per patient. It starts very early in gestation which means mothers have to register early and all mothers need to be tested for HIV, which are difficult in developing countries. It not only needs intravenous AZT during labour, a formulation which is not available in India, but also elective LSCS, which is not available and safe all over the country. Only top feeding in babies is allowed which may not be desirable, safe, affordable and acceptable to mothers. Hence there is a need for shorter, less complicated protocols for developing countries.

2) Thai-CDC Protocol (short course AZT protocol)

This protocol was tried in Bangkok, Thailand in 1998, in collaboration with CDC keeping in mind the need for simple, short term AZT protocol for developing countries[5]. In this protocol, HIV positive mothers were enrolled at 34 weeks of gestation and were given AZT orally in the dose of 300 mg BD till the onset of labour. During labour, they were given oral AZT in the dose of 300 mg 3 hourly till delivery to a maximum of 4 doses. LSCS was not mandatory. However, all babies were given formula feeds and breast-feeding was not allowed. Baby was not given AZT at all. At 3 months after birth the transmission rate was 18.9% in placebo group and 9.4% in AZT group. It means AZT in such a short course still had 50% efficacy in preventing vertical transmission. This may appear 15% less than 076 protocol but it has many advantages. Firstly, it is a short protocol and that too only for mother for just one month. This is affordable, and acceptable to many leading to better compliance. Mother could be enrolled even if she

is registered as late as 35 weeks of gestation. It was not mandatory to do LSCS. Only oral AZT was continued during labour and not IV AZT. The only drawback was avoidance of breast-feeding. Yet this protocol is ideally suited for developing countries.

In India during phase I feasibility study of AZT, this protocol was used with only modification being that informed choice was given to the mother to decide the type of feeding to the baby after counseling. It was a multi-centric study done in 11 medical colleges in 5 states of high prevalence involving 192,474 deliveries, of which 171,471 (89.1%) were offered pretest counseling, 103,681 (60.5%) accepted screening, 1,724 (1.7%) were found HIV positive, of which 726 (42.1%) were put on AZT. 427 newborns were tested for PCR and 43 (10%) of them were found positive by 2 months of age (personal communication). Only 22% of the mothers chose to breast-feed their babies. This proves that in a short term follow up, this protocol had efficacy of 66% as it brought down the transmission from 30% to 10%. It will be interesting to know the transmission on long term follow up till 18 months as those who are infected via breast-feed will be picked up later.

Problems with Thai protocol: Though this protocol brought down the cost from US$1000/- for the 076 protocol to US$ 50/- for this protocol, it still has its own problems in countries like ours. We still need to give AZT for one month, which may be difficult as the compliance may not be good. It also makes it expensive to supply drug for one month. The other thing is that the mother still needs to enroll in the antenatal clinic before 35 weeks of gestation, which is not always the case, as many mothers come late or even during labour straightaway. Lastly breast-feeding was not allowed in Thai protocol, which again poses problem in a country like ours where replacement feeding may be dangerous and where breast-feeding is the norm. Hence, there is a need to have alternate protocol, which further decreases the period of medication and may be useful even in those who present straight in labour and secondly a protocol that may allow breast-feeding to be continued.

There are various protocols which have looked at the efficacy when breast-feeding is allowed. There are two protocols that have looked at this problem, the Cote d lvoire Abedjan study and the Cote d lvoire and Buskina Faso study (DITRAME study)[6,7]. Both the protocols in essence used AZT for a month as in the Thai protocol and allowed breast-feeding to continue in addition. Both the protocols showed similar efficacy of 37%-38% on long term follow up, which is less than with the Thai protocol.

Nevirapine protocol (HIV NET 012)

Nevirapine as mono-therapy was used in this protocol in Uganda in 1999[8]. Nevirapine was compared against short course of AZT (as trying placebo will be unethical). Nevirapine was given as single dose of 200 mg orally at the onset of labour to be taken at home with onset of first labour pain. The baby was given single dose of nevirapine in the dose of 2 mg/kg orally within 48-72 hours of birth while in hospital. This was compared with another group given AZT in the dose of 600 mg at onset of labour followed by 300 mg 3 hourly till delivery and then to the baby in the dose of 4 mg/kg/dose BD for 7 days. Elective LSCS was not mandatory and breast-feeding was allowed. The initial results are very encouraging. At 6-8 weeks the HIV transmission rate was 21.3% in AZT group and 11.9% in nevirapine group and at 14-16 weeks it was 25.1% in AZT group and 13.1 in nevirapine group. This gives efficacy of around 50%, which is same as Thai protocol. However, at 12 months the transmission in nevirapine group was 16% and in AZT group 24% showing only 35%

efficacy. Yet there are many advantages of this protocol. Firstly it involves only a single dose to mother at the onset of labour and a single dose to baby while in hospital. This makes the protocol very cost effective and acceptable with good compliance. It can also be administered to mothers who register at the last moment or even to unregistered cases. In fact some think that in areas with HIV prevalence as high as 15-25%, like in some African countries, this protocol should be offered to all those come for delivery and who are not tested so that it will benefit many. However, it may be unethical to do so. Elective LSCS is not mandatory and breast-feeding is allowed in this protocol. This makes it acceptable to many in developing countries. One needs to await further results on long- term follow-up. Secondly, the success of this protocol needs to be duplicated at some other centers to prove the efficacy and safety.

In India, during phase II feasibility study, nevirapine was used as stated above giving informed choice to the mother to decide the type of feeding to the baby after counselling. It is a multi-centric study done in 11 medical colleges in 5 states of high prevalence involving 45,924 deliveries, of which 38,984 (84.9%) were offered pretest counseling, 35,472 (91.0%) accepted screening, 464 (1.6%) were found HIV positive during ANC and 81 (4.5%) were found positive during labour (who benefited from this protocol). 305 (70.6%) mother-child pairs were put on Nevirapine. 48 newborns were tested for PCR and 4 (8.3%) of them were found positive by 2 months of age. This proves that in a short term follow up this protocol had efficacy of 66% as it brought down the transmission from 30% to 8.8%. It will be interesting to know the transmission on long term follow up till 18 months as those who are infected via breast-feeds will be picked up later. 54.9% of mothers opted for breast-feeding and only 20.8% were breast-feeding at 4 months (personal communication).

Long term safety of AZT

Short-term follow up during O76 protocol has shown less than 4% chances of toxicities like anemia, neutropenia or skin rash in mothers as well as babies given AZT. These side effects like anemia are transient and disappear by 4-6 weeks. In France, mitochondrial dysfunction has been reported to occur in a small number of infants exposed in-utero or neonatally to nucleoside reverse transcriptase inhibitor[9]. Such a side- effect has not been noted in any other study or reviews of earlier studies. Lastly though there is theoretical fear of inducing drug resistance by using a single agent for a short study period, the advantages of these protocols far outweigh such miniscule risks. Many times there is ethical dilemma when the mother is offered the drug under the protocol to prevent MTCT but once the drug is stopped after the protocol is completed, she is not offered any treatment free and she cannot afford to take the anti-retro viral drugs on her own. It appears that the mother is solely given the drug for the sake of prevention of HIV in the babies and she herself is not looked after. However, it is worth it even ethically, as we are preventing HIV in the newborn.

PACTG 219 is a long term follow up study of the babies enrolled in 076 protocol originally and are planned to be followed up till 21 years of age[10]. The interim results show that at median follow up of 4.6 years the growth parameters, cognitive function, ophthalmic evaluation; immunological function and ECG are similar in AZT group as in placebo group. This proves long -term safety of AZT.

Protocols containing combination drugs

In the West, protocols containing 2 or more drugs are used and that has reduced the vertical transmission rate to < 5%. PETRA study had 4 arms using AZT plus 3TC in various combination for the mother and the newborn[11]. The efficacy

at best was 21% when minimum 1-month of drugs were given to the mother. The efficacy fell to 7% when shorter courses were used. SAINT trial was done in South Africa in 2000[12]. HIV positive mothers were assigned to one of the two treatment arms. In Arm A, mothers were given nevirapine in dose of 200 mg orally at onset of labour and at 24-48 hrs after delivery and the baby was given 2 mg/kg orally at 24-48 hrs after delivery. In Arm B multiple doses of AZT + 3TC were given during labour and for 1 week and also to baby for 1 week (like in PETRA Arm B). The results at 6-12 weeks showed transmission rate of 12.7% in Arm A (similar to Uganda Protocol HIV NET O12) and 9.5% in Arm B (similar to PETRA Arm B).

B) HIV and infant feeding - A big dilemma Breast-feeds (BF) or Replacement feeds (RF)

The biggest dilemma faced by a pediatrician in managing HIV patients is to decide whether to allow breast-feeding by HIV positive mothers. Various questions that come in mind include what is the risk of HIV infection with breast- feeding? How long to breast-feed? What is the alternative and what are the risks of replacement feeds in our set-up? Whose right is it to choose what feeds the newborn should receive?

HIV and breast-feeding

HIV is transmitted by breast milk as proved by many studies. Firstly both the free and cell bound HIV has been isolated from human breast milk. Free HIV can infect CD4+ cells lining the GI tract of baby. Infected maternal mononuclear cells present in breast milk can pass through mucous membranes of baby and infect the baby. Transmission to child is shown to occur from the mother infected with HIV post-natally and who breast-fed the infant. Lastly, studies done have compared rate of vertical transmission in those babies who were breast- fed compared to those who were exclusively top- fed and showed that there is 14% extra risk related to breast-feeding over and above other factors.

HIV in human breast milk

HIV has been shown in high titers in colostrum as well as in breast milk for first 4 days after delivery. Some have shown it to be present for as long as 4-6 months or even beyond that after delivery. Vitamin A deficiency in mother leads to increased titers of HIV in breast milk. Other conditions like breast abscess, mastitis or sore nipple can lead to contamination of breast milk with mother's blood.

As against this, there are some protective factors present in human milk that protect the baby against HIV infection. Goldman et al have shown presence of glycoproteins and other substances like mucins, lysozymes, lactoferrins, T cells, complements and secretory leukocyte protease inhibitor (SLIP) etc that decrease binding of pathogenic organisms to GI tract epithelial cells and decrease chances of transmission via breast milk, including that of HIV. Presence of anti-HIV antibodies especially anti-gp120, anti-gp40, IgG as well as anticore IgM and IgA antibodies in human milk have been shown by Western Blot technique. This can also decrease the infection of baby.

HIV infected mothers and breast-feeding

Most studies have shown that there is 14% extra risk of HIV transmission by breast milk, which means that it almost, doubles the rate of vertical transmission. The risk depends on various factors. Colostrum has higher viral load and higher risk of infection. But it also contains higher antibody level. The risk is increased by obvious contamination by maternal blood due to cracked or sore nipple. But the most important factor is the length of breast-feeding.

There is a cumulative increase in transmission of HIV, as length for which breast-

feeding increases, as shown in the Malawi study done in 1999[13]. The risk was estimated to be 0.7% per month for 0-6 months i.e. cumulative risk of 4.2% in this period. It was 0.6% per month between 6-12 months i.e. cumulative risk of 3.6% during this period. It decreased to 0.3% per month between 12-18 months i.e. cumulative risk of 5.8% in this period and 0.2% per month between 18-26 months i.e. cumulative 1.2% for that period. The total cumulative risk is 10.2% if breast-feeding is continued till 2 years and is 4.2% if breast-feeding is continued till 6 months. Hence it will be optimal to exclusively breast feed till 6 months and then abruptly wean off completely in next 10-15 days.

Exclusive breast-feeding will avoid problems of infection related with top feeding. It is cost effective, ideal in developing countries. It will also avoid stigma associated with not breast-feeding due to HIV. It is accepted by > 90% in developing countries. However, as discussed later mixed feeding should be avoided and the compliance to absolutely exclusive breast-feeding in general population is estimated to be only 22-35%. Hence, it is the duty of counselor and pediatrician to ensure that it is exclusive breast-feeding and not mixed feeding.

HIV and replacement feeding (RF)

Replacement feeding may appear as a logical choice in HIV infected mothers. However, it has its own problems. Replacement feeding, especially bottle-feeding, is associated with higher infections like acute respiratory infections (ARI) and diarrhea, especially in countries with high infant mortality rate (IMR). A study in Brazil showed that the overall mortality due to ARI was 4 times more and that due to diarrhea 14 times more in top-fed babies as compared to breast-fed babies[14]. A recent study done in South Africa compared babies born to HIV positive mothers who were breast fed with those who were formula fed[15]. This was done in urban set up with under five mortality rate (UFMR) of 70/100,000. The mothers were educated to an average of 8th standard and they all had access to safe water supply. This was very similar setting as ours. 2 year follow up results showed that the transmission of HIV at 2 years was 19.1% in formula fed babies and 35.7% in breast fed babies, yet the mortality at 2 years was 20% in formula fed babies and 24.4% in breast fed babies. This proves that the gains in the form of less HIV infection in top fed babies was set off by higher mortality due to ARI and diarrhea in both HIV infected and non-infected babies.

Besides this there is problem of breast milk spillage and leakage if mother chooses to give replacement feeds. There is social stigmatization if the mother does not breast feed the baby in countries where breast-feeding is the norm. It also involves issues of education of mother, socio-economic condition and access to potable water to make safe and correct replacement feeds. Lastly, comes the question of affordability. The mother may tend to dilute feeds, which is dangerous. At national level in India, it will be enormous task to spend 75 million rupees per month to provide formula feeds to all babies born to HIV positive mothers. Hence, if the mother chooses not to breast- feed, it is better to give cow's milk with spoon rather than formula feeds, as it is cheaper, easily available and more acceptable. One should again ensure 'exclusive' replacement feeding if it is chosen by mother and not mixed feeding.

HIV and mixed feeding

A study done in Durban, South Africa in 1999 compared HIV transmission in exclusively breast fed babies, exclusively top fed babies and babies given mixed feeding i.e. babies given breast feeds plus any other liquids, born to HIV infected mothers[16]. The results at 3 months

showed that the HIV transmission was 14.6% in exclusively breast fed babies, 18.8% in exclusively top fed babies, and 24.1% in babies given mixed feeding. At this stage, it appeared that the transmission was less in exclusively breast fed babies than in exclusively top fed babies and both were significantly better than mixed feeding. Long term follow up results at 15 months showed that HIV transmission was 24.7% in exclusively breast fed babies, 19.4% in exclusively top fed babies and 35% in babies given mixed feeding. This showed that over long term the advantage of exclusive breast-feeding seems to be negated as compared to exclusive top feeding. However both were significantly better than mixed feeding.

HIV is absorbed via the gut of newborn. A baby on top feeding has leaky gut allowing increased chance of HIV absorption. Hence, a child who is on mixed feeding will have worst outcome. Besides such a child is exposed to evils of both HIV as well as other infections related to top feeding. Hence, HIV infected mother should not give mixed feeding. If she decides to breast feed, it should be exclusive breast-feeding and if she decides to give replacement feeding, it should be exclusive replacement feeds.

Policy

Policy regarding infant feeding by HIV infected mothers at individual level and at national level should take into consideration the merits and the demerits of breast milk replacement feeds, education level, socio-economic status, health statistics, accessibility to safe water, affordability and HIV prevalence. It should be an informed choice made by the mother after proper counseling. This process should start right during pregnancy and continue after delivery. The role of counselor and pediatrician should be to give correct information on various options and they should not be biased or judgmental towards any option. The informed choice opted by the mother should be respected even if it appears incongruent socio-economically. In the West, mothers prefer not to breast-feed. In India, the choice should be left to mother. But whatever the choice be, it should either be exclusive breast-feeding or exclusive replacement feeding and not mixed feeding.

C) Safe delivery practices

i) Elective LSCS: Many studies have shown that elective LSCS done at 38 weeks before rupture of membrane or onset of labour reduces the risk of HIV transmission by 20-50%. One recent study done by Swiss group compared the effect on vertical transmission of AZT alone as per O76 protocol, elective LSCS alone, combined elective LSCS and AZT and no interventions. They found that the chances of HIV transmission with combined AZT and elective LSCS were 0%, with elective LSCS alone 8%, with AZT alone 17% and with no intervention at all 20%[17].

Elective LSCS reduces the transplacental hemorrhage occurring during labour, reduces the length of exposure of the baby to vagino-cervical secretions or maternal blood, reduces the quantum of infective material, reduces swallowing of infected material by baby and reduces chances of ascending infection to baby. All this reduces HIV transmission.

However, elective LSCS in all HIV infected mothers is an enormous task. It may increase maternal mortality, as it may not be safe in some parts of our country. It will also increase the cost of therapy. Hence, the decision has to be individualized depending upon the set-up and stage of HIV in the mother.

ii) Vaginal delivery: Vaginal delivery leads to more chances of HIV infection. The Swiss study showed that the risk of transmission of HIV was 6% with LSCS and 20% with vaginal delivery.

The chances increased to 29-31% if interventions are done during vaginal delivery like traumatic delivery or episiotomy. Hence episiotomy and other procedures should be avoided during vaginal delivery in HIV infected mothers.

iii) Miscellaneous: Cleaning of birth canal with virucidal / antiseptic agents like chlorhexidine led to a decrease in the rate of vertical transmission in a study done in South Africa.[18]. However other studies have failed to get the desired results. Hence, a search for the ideal agent still continues. Interestingly, all these studies showed decrease in mortality in babies due to decreased incidence of neonatal sepsis. Hence cleaning of birth canal is beneficial both ways. Vitamin A was found to be beneficial in an earlier study, however a recent study from Malawi in South Africa has shown no benefit of vitamin A supplementation in HIV infected mothers on vertical transmission[19]. Similarly the use of anti-malarial drugs in endemic areas have shown benefits in some studies.

Phases of PMTCT

PMTCT involves 5 phases:

Phase I: This phase involves giving information on voluntary counseling and testing, infant feeding, option of medical termination of pregnancy, family planning measures, problems of orphans, etc. to mother who is HIV positive. This will go a long way in preventing pregnancies or decrease the exposure of babies to maternal HIV.

Phase II: This phase involves giving prophylaxis to mother and child, which includes antiretroviral drugs to mother and baby and use of safe delivery practices like elective LSCS and non-traumatic vaginal delivery.

Phase III: This phase involves issues related to replacement feeds versus breast feeds.

Phase alpha: This phase involves primary prevention of HIV in mothers and society. This includes HIV education, avoiding high-risk behaviors, treatment of sexually transmitted diseases, imparting life skills etc.

Phase omega: This phase includes care and support of already HIV infected mothers and babies, social support and economical support, etc.

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NEWS AND NOTES

XXIII ANNUAL CONVENTION – NATIONAL NEONATOLOGY FORUM

ORGANISED BY N.N.F, A.P. CHAPTER

Date: 18th to 21st December 2003

Venue: Gandhi Medical College (probable), Hyderabad, Andhra Pradesh.

Address for correspondence:

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Hyderabad – 500 659.
Phone: 24530194.

(or)

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Joint Organising Secretary
Prof. of Pediatrics
Department of Pediatrics
Gandhi Hospital, Hyderabad - 500 003.
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Email: dr_malireddy@yahoo.com
Website: www.neocon2003.org

RADIOLOGIST TALKS TO YOU

ABDOMINAL MASS

**** Vijayalakshmi G***
***** Natarajan B***
****** Ramalingam A***

Abdominal mass is a serious problem in children. About 40 % of abdominal masses were malignant in a series in Institute of Child Health and Hospital for Children which included obstructive renal lesions, polycystic disease of the kidneys and other inflammatory masses. Quite often the mass has presented late to the pediatrician and the symptoms may be vague and non-specific. There is no substitute for a good abdominal palpation. This may bring to light some mass so that there is no delay in detection or investigation which may affect the clinical course of the child. Once a mass is suspected the first imaging is with ultrasound. Ultrasound (US) in most cases offers adequate information that makes other intensive radiological investigations superfluous.

Once the screening ultrasound has demonstrated a solid tumor, a CT may be done. CT is a useful baseline and follow-up examination.Its main disadvantage is the radiation involved. If CT is not available, an IVU can be done that will demonstrate renal function, involvement of pelvicalyceal system and therefore the plane of swelling –whether retroperitoneal or not.

Ultrasound will give you a number of answers:- First of all whether a mass is present or not. There are times when a colon loaded with fecal matter has been mistaken for a mass. Secondly, if a mass is present, what organ is involved, what cavity is involved or whether a mass extends across the diaphragm as in the case of certain neuroblastomas. Then it will also show content of the mass –whether cystic or solid. Ulrasound will also alert you to what vital organs or blood vessels are at risk. In addition, it will indicate presence or absence of hepatic spread and involvement of lymph nodes. So, you can reason out if the tumor can be safely removed or should the child be first treated with chemotherapy or radiation before surgical intervention? Ultrasound can also be useful for screening high-risk individuals who may develop malignancies like Beckwith-Wiedemann Syndrome.

Fig 1 shows a kidney with a tumor mass confined well within. At this stage it is easy to make out the organ of origin. Organ capsule and fascial planes are not broken. Ultrasound shows the mass which is of a different echotexture than that of normal renal tissue. Look for the presence of normal renal tissue with normal pyramids. A mass will not show this normal appearance. Fig 2 is the CT of another patient showing a mass arising from the anterior surface of the right kidney. Compare the Pelvi Calyceal System on the right with the one on the left .Note the

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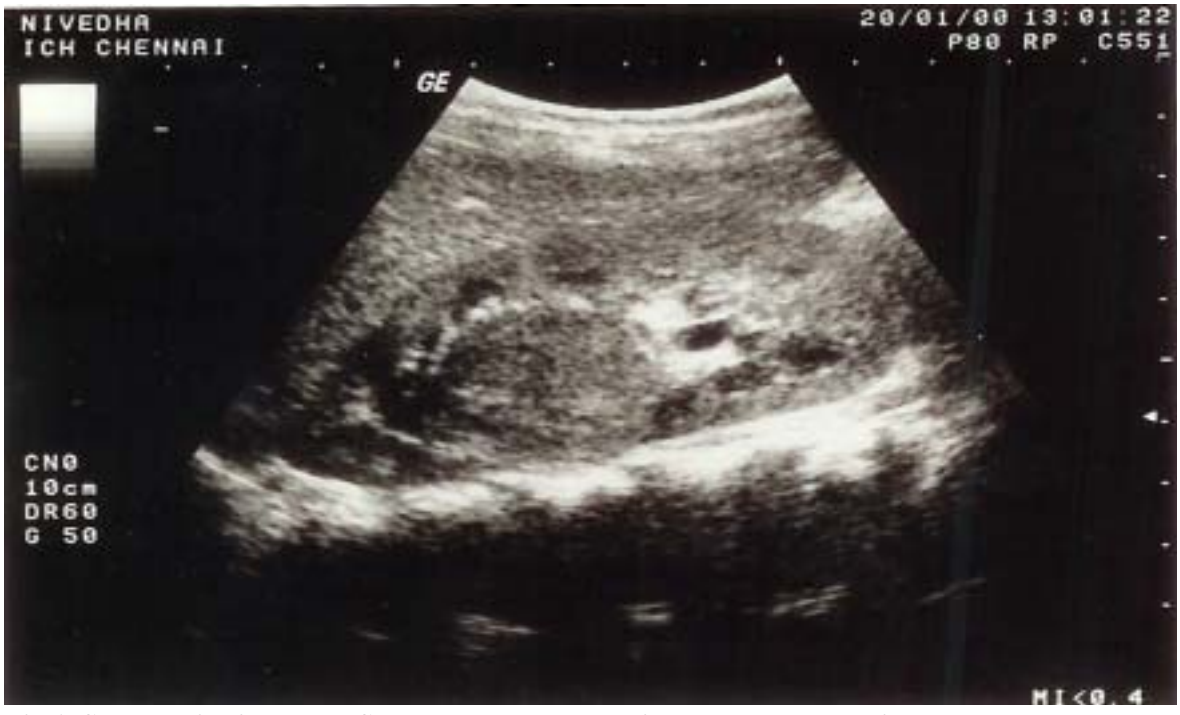

Fig 1. Small Wilm's tumor. See the rounded mass in the upper pole with normal parenchyma in the rest of the kidney

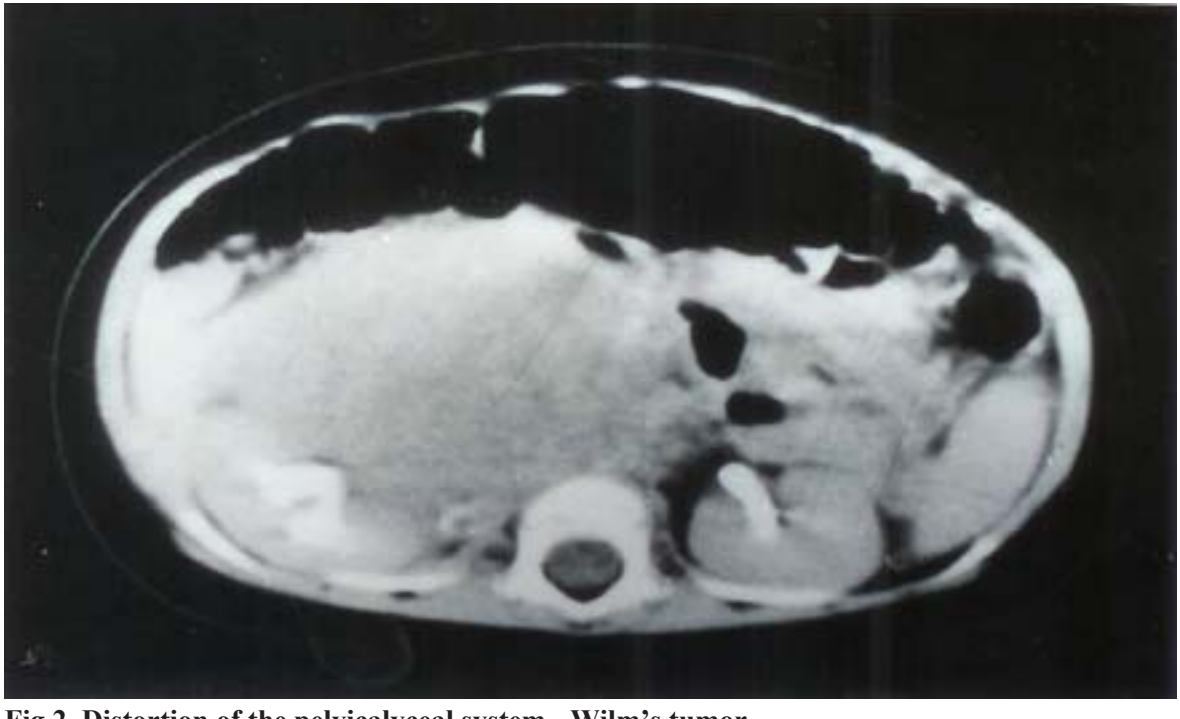

Fig 2. Distortion of the pelvicalyceal system.- Wilm's tumor

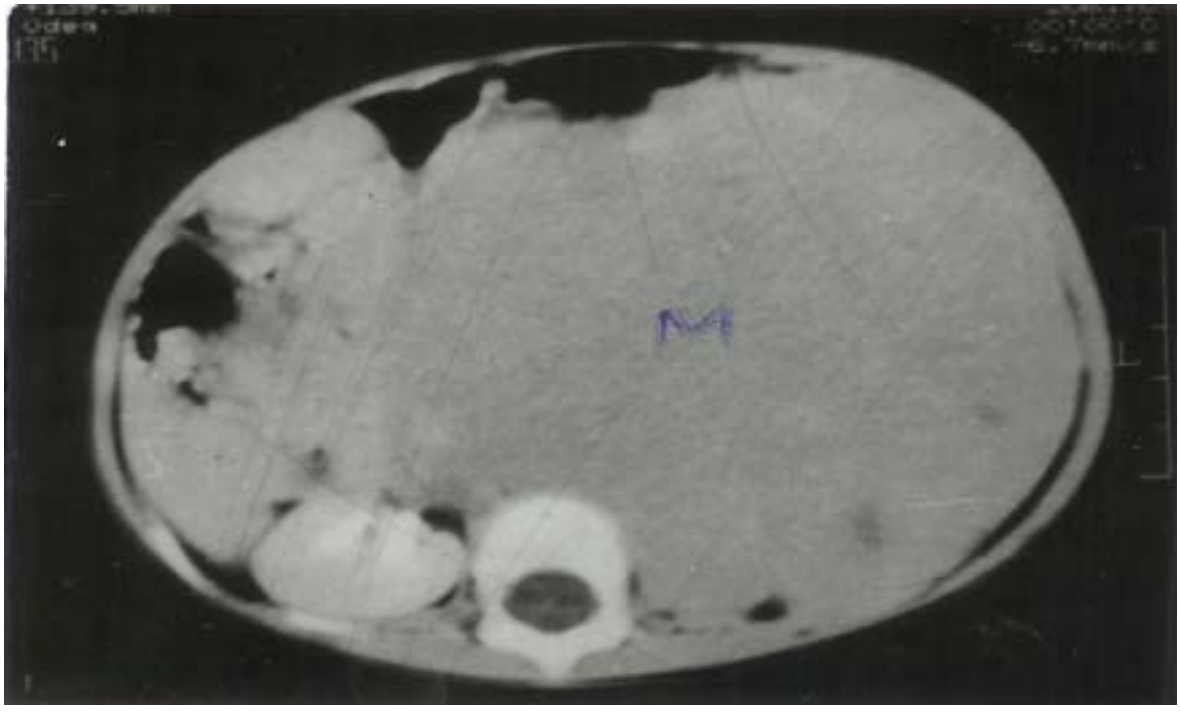

Fig 3. Large mass destroying the entire kidney

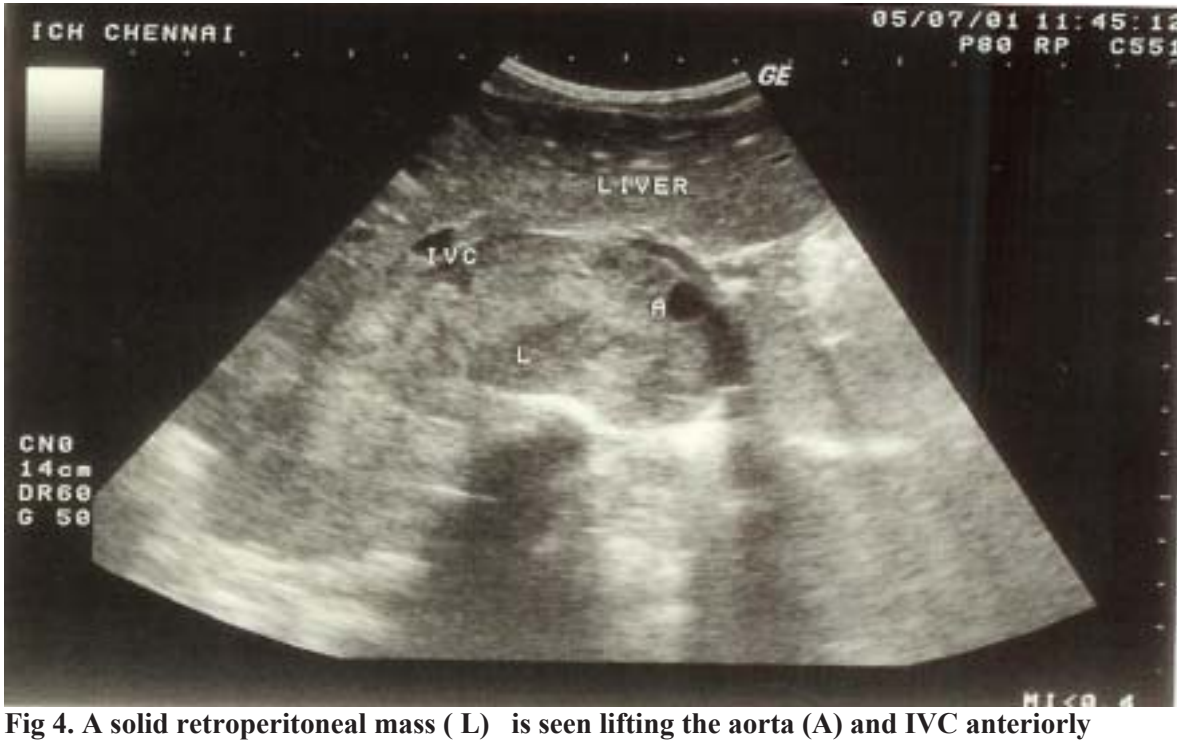

Fig 4. A solid retroperitoneal mass (L) is seen lifting the aorta (A) and IVC anteriorly

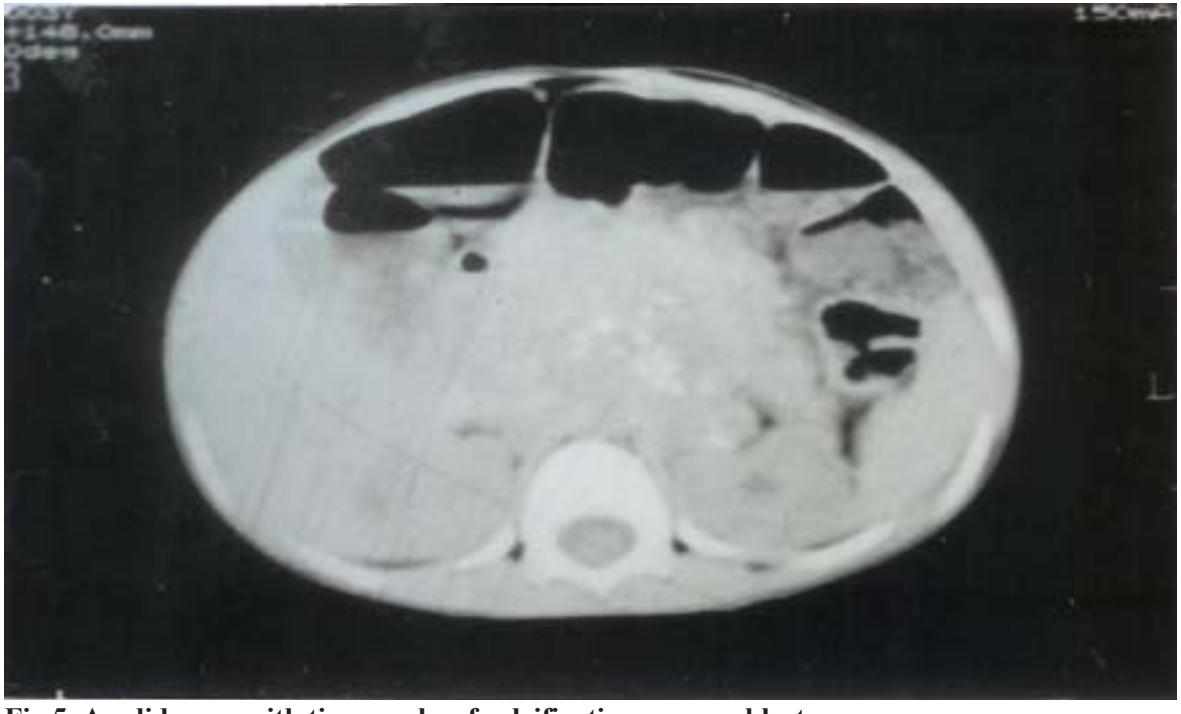

Fig 5. A solid mass with tiny specks of calcifications.- neuroblastoma.

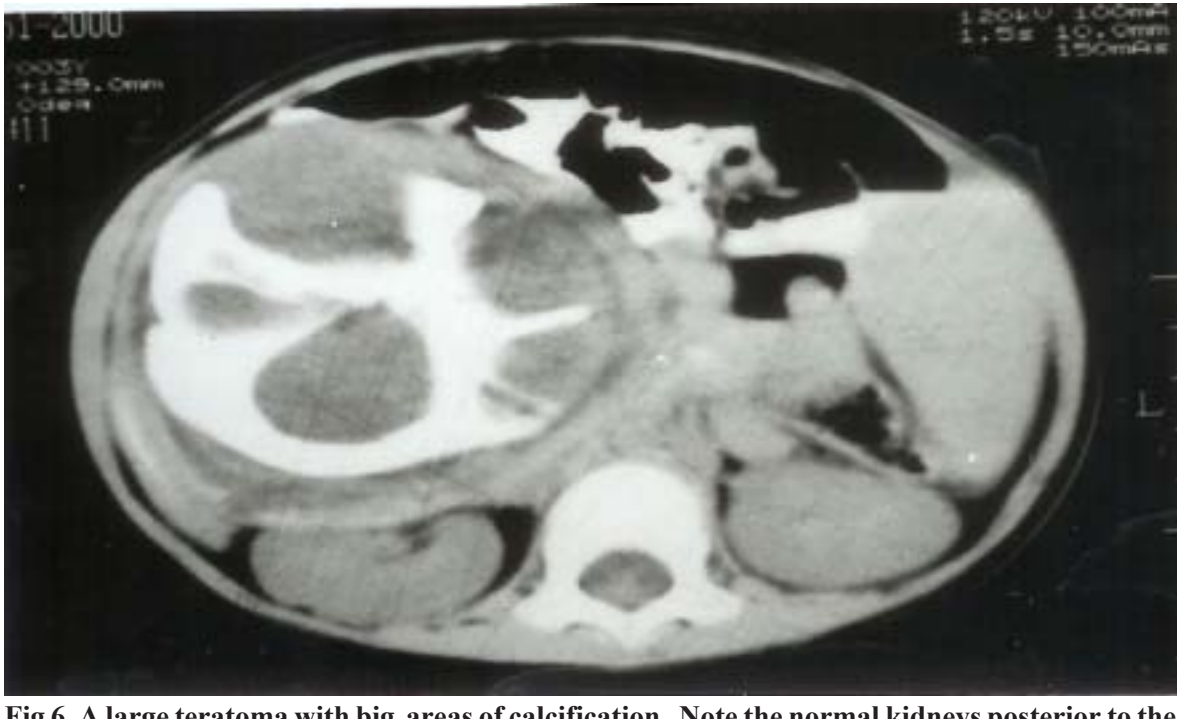

Fig 6. A large teratoma with big areas of calcification. Note the normal kidneys posterior to the mass.

distortion of the pelvicalyceal system on the right. This is an important feature you have to look for. It is seen in both IVU and CT, where the collecting system is outlined with contrast. This feature will tell you that the mass is renal.

But when the tumor is very large the entire kidney is destroyed .In the case of the patient in Fig 3., the kidney was not visualized in US. If the kidney is not visualized in US the next step is to do an IVU or a contrast CT to locate the kidney CT also showed a large mass on the left. The kidney or any part of its collecting system was not seen because there was no functioning renal parenchyma to excrete the contrast. In such a situation it is reasonable to assume that the mass is of renal origin. The commonest renal tumor is Wilm's tumor. This is usually a solid tumor. It may show areas of cystic degeneration. We have seen only two cases of the renal cell carcinoma which is extremely rare in the child .

The next common malignant tumor seen in children is the neuroblastoma. This usually arises from the adrenal gland but can also be seen anywhere along the sympathetic chain. The adrenal mass causes a characteristic displacement of the kidney-down and outwards. It rarely infiltrates the kidney. Look at the neuroblastoma in Fig 4. The mass has lifted the aorta and IVC anteriorly. Therefore this is a retroperitoneal mass. Displacement of neighbouring organs point to the plane of the swelling.

CT may outline the extent of masses better but small capsular breaches that would upstage the tumor are best seen only at surgery. Contour irregularity in CT may suggest extrarenal invasion. CT can also show lymphadenopathy due to tumor spread . CT is of value in identifying hepatic metastases while US remains the modality of choice for showing **tumor thrombus** in the IVC.

In US or CT the neuroblastoma has an irregular outline and tiny **calcifications** (Fig 5). Now look at Fig 6 .Is this a neuroblastoma ? There is a large well-defined mass with **gross calcific areas** in the subhepatic region. This is a typical picture of a teratoma – mass with thick calcifications. Contrast this with the fine calcification of neuroblastoma. The kidneys are intrinsically normal though the right kidney is seen flattened against the posterior abdominal wall. Again ,contrast this displacement with that of a neuroblastoma.

Now you can see that US is the first imaging modality that would help to localize the plane or origin and decide the nature of the mass.Detection is certain with US though extent and calcification is better with CT.

NEWS AND NOTES

1ST NATIONAL MEET ON FLUID, ELECTROLYTES AND BLOOD GASES
Organised by IAP 2003, Nagpur
Date: November 21st , 22nd & 23rd 2003
Venue: Hotel Centre Point, Nagpur.

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PRACTITIONER'S COLUMN

HEARING LOSS IN CHILDREN : NEED FOR EARLY DETECTION AND INTERVENTION

**** Abraham K Paul***

Hearing loss has considerable impact on the overall development of the infant – language development, development of cognition, development of social and emotional competence.

The first year of life is a critical period for brain development, especially development of the auditory pathway.[1] Auditory experience during this period has profound influence on functional development of auditory system and lack of auditory experience can have detrimental effects. This can be understood by this basic neuro developmental phenomenon. At birth, the brain has100 billion neurons and they form about 50 trillion connections.[2] The only way the connections can be strengthened is by stimulation – both auditory and sensory. The connections that are not used or stimulated wither away. Now we understand the need for a constant auditory stimulation for optimal development of auditory system, a prerequisite for optimal development of speech and language.

Even mild hearing loss if not detected early can significantly retard acquisition of language skill and untreated hearing loss of greater degree have a measurable, even devastating effect on speech and intellectual development.[3]

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In USA, UK and many other developed countries, routine screening for hearing of all newborns is made compulsory before discharge from hospital. If by chance, it is not accomplished, screening is done at the next visit, but never later than 2 months. The incidence of hearing loss is found to be in the range of 2 –4 per thousand. This is quite high as compared to all other screenable diseases put together (thyroid disorders, sickle cell anemia, phenyl ketonuria). When one takes into account the incidence of hearing loss in high-risk babies it may be to the tune of 1.5–15%.

Babies at high risk for Hearing impairment[5]

Neonates

1. Birth weight less than 1500 gms
2. Hyperbilirubinemia requiring exchange transfusion
3. Bacterial meningitis
4. Apgar scores of 0 to 4 at one minute, or 0 to 6 at 5 minutes
5. Mechanical Ventilation lasting 5 days or more
6. Ototoxic medications
7. Family history of hereditary childhood sensorineural hearing los
8. Intrauterine infections (TORCHS)
9. Craniofacial anomalies
10. Stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductive hearing loss.

Infants (29 days through 2 years)

1. Speech and language delay
2. Developmental delay
3. Concern regarding hearing by parents.
4. Bacterial meningitis.
5. Recurrent or persistent otitis media with effusion for at least 3 months.
6. Head trauma associated with loss of consciousness or skull fracture.

The importance of early detection of hearing loss will be understood when we explore the results of certain studies done in this field. One important study done is the one done at university of Colorado in 1998, which showed that early intervention before 6 months is critical for optimum development of speech and language. Even infants with severe hearing loss if intervention was done before 6 months showed near normal cognition and language development.[2]

Even minimal hearing loss (16 –25 dB loss) is educationally significant. This is because a youngster with mild bilateral hearing loss may miss 20% to 30% of vital speech information if unamplified. Many consonant sounds are heard inconsistently (eg. the word Cup, Cat, Calf may all be perceived as Ca) and faint and distant speech is difficult to be understood.[4] Children with hearing impairment typically demonstrate errors in the form, content, and the use of language. Early detection and intervention can reduce or prevent the impact of hearing loss on learning. Results of recent research has shown that many children with hearing loss are likely to achieve normal speech and language skills by 5 years when detection and rehabilitation are initiated before 6 months of age.

Infection used to be the major causative factor resulting in hearing loss. But with the widespread use of various preventive vaccinations (MMR, Hib) infection is no more the major cause. With survival of more number of preterm and high risk babies at neonatal intensive care services, they dominate as the most vulnerable group. Certain intra-uterine infections, otitis media, medications, sudden noise of high intensity, head trauma, infections and certain genetic diseases may all result in hearing loss.

Evaluation of hearing by BERA or Oto-acoustic emission (OAE) can be performed even in the newborn period. Various tests are also available appropriate for older infants and children of any age. Clapping of hands and observing the child's response is a very crude method and should never be resorted to as a reliable method of hearing assessment. A test may have to be repeated number of times or a battery of tests may have to be done. The skill and experience of the examiner plays an important part in the proper evaluation and judgement. One important point of emphasis is that all children with speech delay should have a hearing assessment as the preliminary test at the earliest.

The management primarily depends upon the cause. Once correctable and surgical causes are excluded, the cornerstone in management is amplification of sound by use of hearing aids (as early as 5-6 months of age). Children with profound deafness who derive negligible benefit from conventional amplification with hearing aids may be considered for cochlear implants (electronic prosthetic device that is surgically placed in the cochlear portion of inner ear to provide useful sound perception).

A total communication approach should be attempted blending the use of hearing aids,

auditory training, speech therapy and in selected cases, lip reading and sign language. By 3 years, educators and parents should plan the educational mode that will most suit the child – school for the deaf, special class in a regular public school or an ordinary school.

Key message: Never miss a hearing loss, identify hearing loss at the earliest, have hearing assessment done in all cases of speech delay.

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NEWS AND NOTES

37TH NATIONAL CONVENTION OF THE INDIAN COLLEGE OF ALLERGY, ASTHMA AND APPLIED IMMUNOLOGY

Date: 12, 13 & 14 December 2003

Venue: Bangalore, Karnataka.

Address for correspondence:

Dr.H.Paramesh
Chairman
Organising Committee

Prof. Shripad N. Agashe
Chairman
Scientific Committee

Ms.Elizabeth Cherian
Secretary
Organising Committee

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PEDINEUROCON-2003

V NATIONAL PEDIATRIC NEUROLOGICAL CONFERENCE

Date: 22nd and 23rd November 2003

Venue: SMS Convention Centre, Hotel Rambagh Palace, Jaipur.

Address for correspondence:

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Organising President

Dr.H.S.Bhasin
Organising Secretary

476 A/5, Vyas Marg, Raja Park, Jaipur, Rajasthan – 302 004.
Email: pedineurocon2003@hotmail.com, Phone: 0141-2621962, Mobile: 3126087

CASE STUDY

CLEIDOCRANIAL DYSOSTOSIS

**** Sujatha L***
***** Lakshminarayanan S***
Srivenkateswaran
Venkatesh AL

Cleidocranial Dysostosis is a disorder characterized by generalized dysplasia of osseous and dental tissues commonly resulting in defects in the skull, clavicle and teeth. Over 500 cases have been reported worldwide in literature[1].

A 6 year old male child was brought with history of failure to thrive, retarded growth and recurrent respiratory infections. There was no other positive history. On examination, the child had a large calvarium with a small face and shallow nasal bridge. Teeth abnormalities were present. Patient was able to closely approximate his shoulders over the chest. He was short statured.

X-ray studies: Skull-frontal and lateral view: large head, open anterior and posterior fontanelle and shows presence of wormian bones. Chest: complete absence of both clavicles, small and high scapulae, short ribs directed obliquely downwards.

Discussion

Cleidocranial Dysostosis is a familial – autosomal dominant dysplasia due to delayed ossification of midline structures particularly of membranous bone. It is a developmental defect characterized by absence or rudimentary development of the clavicles, abnormal shape of the skull and depression of the sagital suture, frontal bossing and many wormian bones. The

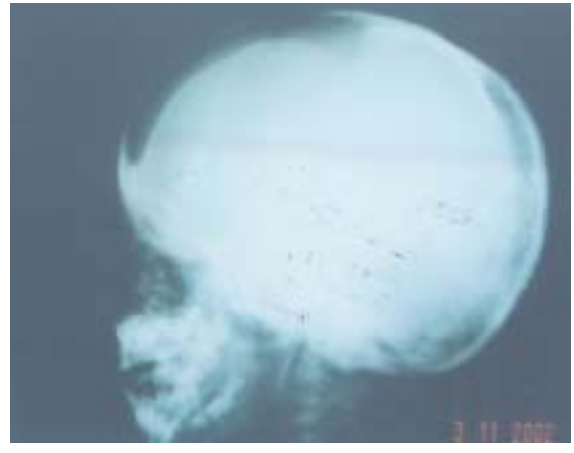

Fig. 1. Large calvarium, open anterior fontanelle and wormian bones.

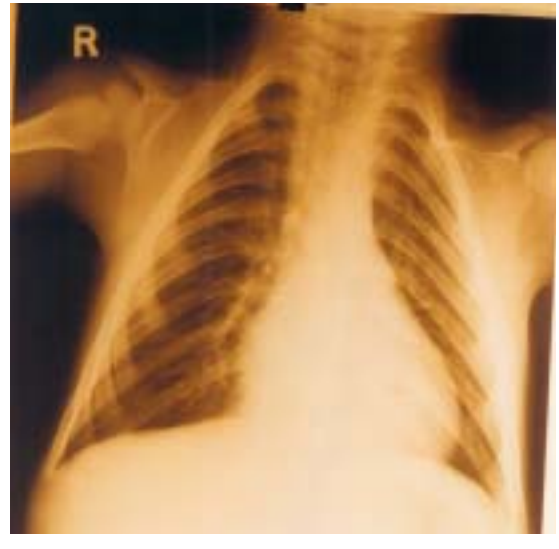

Fig. 2. Complete absence of clavicle. Small high scapulae. Short ribs directed obliquely downwards.

* Consultant Radiologist
** Consultant Pediatrician
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Tiruvarur,

fontanelle may remain open until adulthood. Dental features include maleruption, absent or delayed eruption of deciduous and permanent teeth and small maxillae[2]. There will be hypoplasia or absence of clavicle (defective development usually of the lateral portion or outer portion), narrow thorax which may cause respiratory distress in newborn and small scapulae, hemivertebrae and supernumerary ribs. There may be short and flat femoral neck and a wide pubis symphysis. The case is presented because of its rarity and its full fledged form.

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2. Lees W.R. Congenital skeletal anomalies; skeletal dysplasias: chromosomal disorders. In: Text Book of Radiology and Imaging. 6th Edn. Ed David Sutton, Churchill Livingstone, 1998: 12-13.

NEWS AND NOTES

XV NATIONAL PEDIATRIC NEPHROLOGY CONFERENCE

Date: November 21st and 22nd, 2003

Venue: Scudder Auditorium, Christian Medical College, Bagayam, Vellore, Tamilnadu.

Registration Fees:

Status	Before 15.08.03	Before 30.09.03	Spot
Delegate	900/-	1,200/-	1,800/-
Student*	800/-	1,100/-	1,600/-
Accompanying Person	700/-	1,000/-	1,500/-

* PG Students would be required to send a certificate from their professors that they are bona-fide students.

Address for correspondence:

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XV National Pediatric Nephrology Conference
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Christian Medical College, Vellore - 632 004. Tamilnadu, India.
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CASE STUDY

VAGINAL VOIDING AS A CAUSE OF RECURRENT URINARY TRACT INFECTION

**** Sripathi V***
***** Vijayakumar M***

Vaginal voiding (post void dribbling) is one among the minor dysfunctional disorder such as daytime urinary frequency syndrome, giggle incontinence and stress incontinence. This occurs in girls after they have finished voiding and is due to urine accumulation in the lower vagina. When the child stands up urine trickles out of the vagina into the undergarment. The problem is commonly due to poor posture during micturition, in obese children or in a child with female hypospadias wherein the urethra opens into the anterior wall of the vagina at a variable distance from the vulval outlet. Here we are presenting a clinical problem of a child with vaginal voiding presenting as recurrent UTI.

A 5-year-old female child presented with recurrent symptoms of low-grade fever, dysuria, increased frequency and hematuria of about 3 years duration. There has been episodes of frequent wetting of the undergarment after the completion of urination. It was attributed to the bladder infection. Renal function including urine analysis was unrewarding. Urine culture was positive for E.coli. Clinical examination revealed a dense adhesion of the labia minora, which was separated. A micturating cystourethrogram was done under image intensification. The voiding pictures showed widening of the urethra due to urine pooling in the vagina with a normal bladder (Fig. 1). Post void film showed retention of contrast in the vagina indicative of urine being retained (Fig. 2). The child was treated with appropriate antibiotics and educated to void urine

Fig. 1 Voiding phase of MCU showing widening of urethra. This is due to urine pooling in vagina

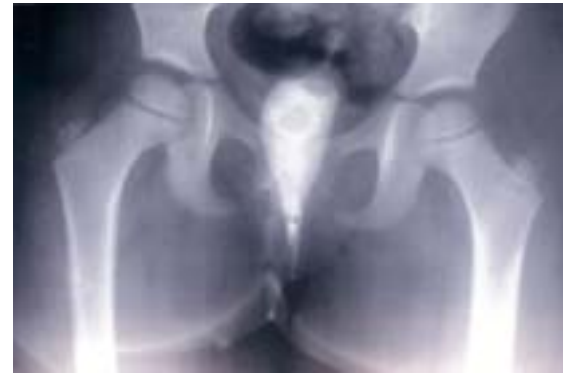

Fig 2. Post void film of MCU showing urine retained in the vagina after bladder empyting

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by keeping the thighs wide apart and to have complete voiding. The best way to achieve is to reverse the position of sitting on the Western or Indian toilet. This reverse position achieves separation of the thighs and avoids refluxing of the urine into the vagina, which could predispose to incontinence, stasis of urine and infection.

In conclusion, careful clinical examination for labial adhesion, urethral opening abnormalities and a history of urinary incontinence will help to identify the cause of UTI and minimize investigations.

BOOK REVIEW

Title : Clinical evaluation of newborns, infants and children

Author : Dr. S.Sushama Bai

Review : This book titled 'Clinical evaluation of newborns, infants and children' is an ideal book to be included in the armamentarium of books on clinical examination, where we have only very few books in this category. Book begins with a good start of how a doctor should be. The sections are well organized and all authors of these topics justified it to the fullest extent. The sections 'family interview' to start with and the concluding section 'How to communicate' deal with practical points. It is nice that examination of newborns also included. Authors have taken care to include relevant bedside tests also then and there. The interpretation of electocardiogram is one such attempt, which should be appreciated. We find this book as a good collection of certain reference values, measurements and differential diagnosis etc, for which we have to refer many books when in need. All the topics have been written in a simple and clear manner with many illustrations, which makes understanding better.

Publisher : Panicker Publications
Amalagiri P.O.,
Kottayam,
Kerala, 686 036.

Price : Rs.215/-

CASE STUDY

PODOPHYLLIN POISONING

** Harish V Sutrave*
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*** Kumarasamy K*
*** Sathyamurthy B*
*** Venkataraman P*
**** Vasanthamallika TK*

Introduction

Poisoning in children is a global problem. Morbidity and mortality due to accidental poisoning is a serious challenge to pediatricians. In India next to malnutrition and infection, poisoning poses a major threat to the lives of our children. Knowledge of the nature of the poison, lethal dose and antidotes is a must for every physician.

Podophyllin is a dried resin from the roots and rhizomes of Podophyllum peltatum (Mandrake or May apple plant) the North American variety; and Podophyllum emodi the Indian variety[1]. Active ingredients are lignans including podophyllotoxins, alpha-peltatin and beta- peltatin[1] .

Case report

A 2 year old female child presented to us with complaints of vomiting, fever, altered sensorium of one day duration. Alleged to have ingested 3-4 ml of podowart solution at her neighbours house the previous day. Child had repeated episodes of vomiting and altered sensorium after ingestion with one episode of loose stool. On admission she was withdrawing to pain only. Her vitals were stable and there was no shock or seizures. She was given supportive management and CSF analysis was done which was normal. Her sensorium improved to the extent of mild drowsiness with unsteady gait on day 2 of admission. Gait improved on day 4 and she was able to take oral feeds by then. Her hemoglobin was 9.6gm/dl with hypochromic microcytic anemia and liver function tests were normal. With no neurological deficit she was discharged on day 6. This will be the second reported case in Indian literature. Western literature has reported a 2 year child of podophyllin poisoning[2].

Discussion

Podophyllotoxin and its derivatives are potent cytotoxic agents that inhibit cell mitosis and deoxyribonucleic acid (DNA) synthesis in a manner similar to that of colchicines[2] a potent spindle poison[2]. Podophyllin is used as an ointment for plantar warts[1]. Routes of exposure are oral, dermal, inhalational and occular[1]. Local effects are pruritus, irritation, urticaria, skin necrosis, bleeding and scarring of tissue. Systemic effects of poisoning are tachycardia, cardiac arrhythmias, hypotension, cardiovascular collapse, tachypnoea, respiratory failure, pneumonitis, pulmonary oedema, confusion, lethargy, coma, convulsions, peripheral neuropathy, paralytic ileus, rhabdomyolysis, myoglobinuria, nausea and vomiting, abdominal pain, diarrhoea, elevation of hepatic enzymes,

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oliguria, cystitis, renal failure, fetal death, abortion, premature labour, fetal malformation, leucocytosis, followed by leucopenia, anemia, thrombocyto penia, pancytopenia and metabolic acidosis[1,2,3,4]. Death generally results from the cerebral, cardiovascular, renal, or haematological complications. Management involves performing gastric lavage if patient is seen early and administering activated charcoal. In case of topical contact wash with soap and water. Maintain vital signs. Hemoperfusion should be used for severe systemic poisoning since it has been shown to be effective in reducing the plasma fraction of podophyllum toxin[5]. No antidote is available[5].

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NEWS AND NOTES

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QUESTION AND ANSWER

Q. Various pharmaceutical companies are coming up with preparations containing both nimesulide and paracetamol. While promoting these, they talk of things like; 'paracetamol has faster onset of action but shorter duration of action, whereas nimesulide has delayed onset of action but longer duration of action. So when the effect of paracetamol starts waning, nimesulide takes up'. Is there any rationality in this combination or is this just another addition to the long list of irrational combination drugs available in the market?

Dr. Madhumita Nandi,
Shajahanpur, U.P.

A. Various drugs and drug combinations are used in the treatment of childhood fevers to restore the disturbed hypothalamic thermostasis. When antipyretics are indicated, traditional use has included aspirin, paracetamol, ibuprofen and more recently nimesulide. Even though nimesulide has a more potent antipyretic effect than paracetamol, combination of these two drugs (nimesulide –paracetamol) does not lead to a synergistic or potentiated therapeutic effect[1].

An ideal drug for the symptomatic treatment of fevers in children should be short acting which can be repeated as and when indicated , so as not to mask the signs and symptoms of serious illnesses in infants and children[2].Logically any drug/or combination with a prolonged antipyretic effect should rather be considered its limitation than an advantage. Such a fixed dose combination will also be associated with problems such as difficulty in dosing and a potential risks of adverse effects like hypothermia and abnormal liver enzymes. Thus there is no rational justification for the paracetamol and nimesulide combination and its use in children.

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1. Kulkarni SK, Jain NK. Is there a rationale for nimesulide paracetamol combination? Indian J Pharmacol 1999;31:444-445.
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Dr. Niranjan Shendurnikar
Associate Professor of Pediatrics
Medical College Baroda 390001

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Dr.Gautam Ghosh, Phone: 24553691 / 98301-71815, Email: ghoshped@cal3.vsnl.net.in
Dr.Santanu Bhakta, Phone: 26611413 / 23594294, Email: sbhakta@cal3.vsnl.net.in
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