A Review of Paediatric Acquired Immunodeficiency Syndrome

By

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INTRODUCTION

The first description of the acquired immune deficiency syndrome (AIDS) in children was in 1982[1, 2], a year after the disease was first reported in the adult population among male homosexuals in Los Angeles, California, United States of America[3]. Since then, the human immune deficiency virus (HIV) pandemic has undergone four main phases of evolution viz. emergence, dissemination, escalation and stabilization[4, 5].

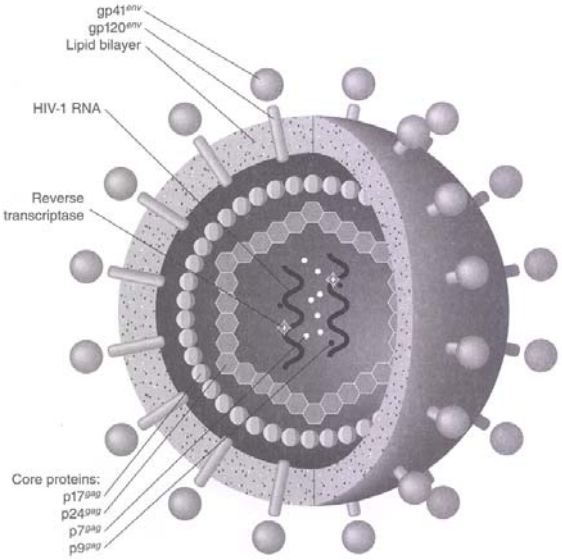
The first report of paediatric AIDS in Nigeria was in 1986 in a 13 year-old female hawker in Calabar, Cross River State[6, 7]. Children can be infected with the virus through a human immune deficiency virus positive mother (Mother-to-child-transmission or MTCT), transfusion with contaminated blood or its products, sexual contacts and the use of non-sterile sharp objects such as needles, blades and knives[6]. The commonest route of HIV infection in the paediatric population is the MTCT[6, 7]. However, HIV infection through blood transfusion remains a risk[6, 8]. Improved donor selection and serologic screening have greatly diminished but not eliminated the overall risk for recipients of blood and blood products. After screening, HIV-1 has been reported to be transmitted in approximately 1 out of 60,000 transfused units[9, 10]. Despite various publications concerning paediatric acquired immunodeficiency syndrome the awareness of the impact of this problem is still poor in our environment. Also the complexity of the ever evolving management of this condition is such that every physician needs to be constantly reminded of the details of its management. This review article is aimed at both continuing to increase the awareness and providing up-to-date information as regards the management of AIDS in children.

THE HIV VIRUS

The human immunodeficiency virus is the primary aetiologic agent for the acquired immune deficiency syndrome (AIDS) [11]. AIDS has no precedent in medical history. Though it was first widely recognized in 1981, evidence of the virus has been found in blood collected in 1959[12], and so it seems to have been in existence for longer than was first thought[12].

The human immune deficiency virus (HIV) is a ribonucleic acid (RNA) virus of the sub family, lentiviridae within the retroviridae family[1]. It is an approximately 100nm icosahedral structure with an outer lipid envelop containing two glycoproteins (gP 120 and gP 41)[1, 11]. It has a characteristic dense, cylindrical nucleocapsid containing core proteins (P24 and P17), genomic single stranded RNA and reverse transcriptase[1]. There is some strain variability especially for the surface glycoproteins[1, 8]. HIV-2 is mostly seen in Western Africa and differs in protein structure and antigen from HIV-1 which is seen worldwide[1, 8]. Schematic diagram of HIV 1 virus is shown in figure 1. HIV –2 presents a longer period of asymptomatic status runs a slower disease course and is more prevalent in Southern Nigeria[8]. However HIV-1 variant is the predominant AIDS virus found in Nigeria accounting for 80%–90% of infection in the country[8, 13]. A third variant, HIV –1 group O is rare in Nigeria[13].

Figure 1 Schematic diagram of the HIV-1 Virion



[Adapted from Care and Management of Patients with HIV infection by Bartlett J. A. (Ed)]

The human CD4+ T lymphocytes is the central regulatory cell controlling monocytes, macrophages, cytotoxic T cell, natural killer cell and suppressor T cell responses to antigen[8]. The human immunodeficiency virus is trophic for cells bearing CD4 molecules on their cell membranes which act as a receptor for attachment of the envelope protein[13, 14, 15]. Although the $CD4^+$ subset of T lymphocytes is the prime target on entry into a host; HIV, also infects other cell lineages such as macrophages, monocytes, glial cells, Langerhans cells and colorectal epithelial cells which express CD4 molecules at lower densities[8, 16]. These cells play a key role in maintaining a person's immunity to disease. As a result, HIV infected people become susceptible to illnesses caused by the collapse of body's immune system[12]. Individuals infected with the virus can transmit infections for the rest of their lives[12]. There is no difference between strains prevalent in children and those in adult.

PATHOPHYSIOLOGY

HIV-1 is more virulent and worldwide in distribution than HIV-2. Two sub-types of HIV-1 are recognized in Nigeria, viz, A and G[6]. There are three principal genes that code for the functional and structural components of HIV[3]. These are *gag, pol* and *env*. The gag gene encodes core proteins; pol encodes the enzymes reverse transcriptase, protease and integrase, while env encodes for the HIV structure components[6, 17]. HIV infection attacks dendritic cells in the mucous membrane and skin in the first 24 hours of exposure, and within days, the virus makes its way to the lymph nodes and peripheral blood where replication becomes very rapid[6, 8]. The attachment of the HIV virus on the $CD4^+$ molecule is through its gp 120.Following its attachment, the enzyme reverse transcriptase then transcribes the virion RNA into viral DNA, producing double stranded circular DNA[18]. The circular DNA is transported into the nucleus where it is integrated into chromosomal DNA and referred to as the provirus. Subsequently the proviral DNA encode production of the viral RNA genome, which in turn leads to the production of viral proteins necessary for viral assembly. Finally the RNA genome is incorporated into the newly formed viral capsid. As the new virus is formed, it buds through the cell membrane and is released. The initial infection with HIV results in both antibodies and cytotoxic T cells responses. The anti-HIV antibodies have no neutralizing property due to the intrinsically unstable epitopes of HIV envelope glycoproteins and therefore do not protect the infected person[19].

MODES OF TRANSMISSION

HIV is transmitted only through the exchange of infected body fluids whereby a substantial quantity of virus gains access to the T4 cells in a susceptible individual[12]. The main modes of transmission of paediatrics AIDS include

1. ***Mother to Child Transmission (MTCT)***

This is the commonest route of infection in children and accounts for about 90% of Paediatric AIDS in most African nations[6]. Mother to child transmission is vertical transmission and includes:
Peri-partum (during pregnancy or during labour and delivery, when the baby comes in contact with the infected mothers' blood) and post-partum (through breastfeeding, from the infected mothers' milk).

2. ***Infected Blood and Blood Products***

This is an efficient way of transmitting the virus[6] and the second most important route of AIDS transmission in Africa and Haiti[17]. Transfusion of infected blood and blood products accounts for between 5% – 15% of AIDS in Africa[8, 13] and as high as 25% of paediatric cases of AIDS may be from transfusion of unsafe blood in the continent[5, 13].

3. ***Sexual Intercourse***

This route is especially important among adolescents and sometimes, sexually abused children

4. ***Contaminated Sharp Instruments***

Transmission of HIV infection through contaminated needles and syringes is also important in our environment because of the high indulgence of the populace in unnecessary injections, unsafe circumcision and the high prevalence of unqualified health practitioners[20, 21]. The percentage of sero-conversions following HIV contaminated needle-stick accidents varies between 0.2% and 0.5% with a median of 0.3% in the general populace[21]. The exact prevalence in children is not known.

SYMPTOMS AND MODES OF PRESENTATION

Clinical presentation of HIV infection is highly variable and progresses more rapidly in children than in adults[22, 23]. The initial symptoms may be subtle and non specific to HIV. Symptoms are distinguishable only by their persistence.

Clinical symptoms common in HIV patients but uncommon in HIV-negative patients especially children

Recurrent infections: three or more severe episodes (bacterial and/or viral such as pneumonia, meningitis, sepsis, cellulitis) within a 12 month period, oral thrush(lasting >30 days despite treatment or recurrent after neonatal period), chronic parotiditis(unilateral or bilateral for >14 days, with or without associated pain or fever), generalized lymphadenopathy (without any apparent underlying cause), hepatosplenomegaly (non-malaria areas), persistent and/or recurrent fever (>38°C), neurological dysfunction, persistent dermatitis[22,24,25].
Others include recurrent common bacterial infections (otitis media, sinusitis), Chronic parotid swelling, Lymphocytic interstitial pneumonitis, and early onset of progressive neurologic deterioration (delayed or regression) of developmental milestones. Growth failure, failure to thrive, or wasting syndrome may indicate HIV infection if other common metabolic and endocrine disorders do not appear to be the etiology[22, 23]. Behavioural abnormalities, such as loss of concentration and memory, may be an

indicator of HIV encephalopathy in older children[24].

Some other features are very specific for HIV infection and they include oesophageal candidiasis, Herpes zoster (shingles) across several dermatomes, invasive salmonella infection, Pneumocystis jirevoci pneumonia (PCP), lymphoid interstitial pneumonia (LIP), extrapulmonary cryptococcosis, Lymphoma and Kaposi's sarcoma[24, 25].

Few physical findings are specific to HIV, and many of the physical findings are caused by opportunistic infections. Lymphadenopathy, hepatomegaly, and splenomegaly are fairly common findings in HIV infection[22, 25].

NATURAL COURSE AND HISTORY

There is no evidence from the literature that the natural course and history of HIV infection in children differ from that in adults. However the disease progression in children is faster than in adults.

When an individual is infected with the HIV virus the individual, is said to be HIV positive. Once infected, the virus invades the immune system of the individual especially the T4, CD4 or helper T cells. The virus, through its replication gradually destroys these important cells until the immune system of the individual starts to malfunction. This gradual process occurs in 3 major phases:

A. The Acute Retroviral Syndrome

This initial phase of Acute Retroviral Syndrome is due to intense primary viraemia. During this period, 50-70% of the patients may present with non-specific 'flu-like' symptoms such as fever, fatigue, pharyngitis, lymphadenopathy, and rash. The initial infection of CD4 cells and macrophages at site of exposure leads to the dissemination of infection to lymph nodes. This results in widespread viral seeding to various organs including brain & lymphoid tissues. This antigen-driven migration and accumulation of CD4+ cells within the lymphoid tissues leads to the initial dramatic decrease in the number of circulating CD4+ cells and the generalized lymphadenopathy noted during this phase. There is then the development of humoral immunity (HIV specific antibodies) and cellular immunity (HIV-specific CD4 and CD8 cells) within 2-4 months leading to substantial decline in circulating virus. The patients then enter an asymptomatic phase with return of CD4+ cells to only moderately decreased levels.

B. Period of clinical latency

The period of clinical latency varies greatly in children but may be as long as 8-12 years in adults, during which time there is a high turnover of virus and CD4+ cells (more than a billion cells per day). Viral replication occurs in monocytes.

C. Progression to Chronic HIV-1 Infection and AIDS

With the high turnover of CD4 cells, there is continuous destruction and compensatory increase in production of CD4 Lymphocytes. This causes the viral load to plateau at viral set point, thus leading to non-specific, generalized, immune activation that result in immune dysfunction. Reduction in the CD4 cell number and the effects on their function reduces the capacity of the body to fight infectious diseases. Individuals with HIV infection are therefore increasingly susceptible to many infections especially at later stages of HIV infection. AIDS refers to a stage in the HIV infection when a group of illnesses develop when

the immune systems have been severely impaired by HIV infection.

HIV DISEASE PROGRESSION IN CHILDREN

The biggest challenges with HIV-infected children are early diagnosis and institution of proper care and support as children differ in how early they become symptomatic. Vertically transmitted HIV disease has a trimodal distribution in terms of progression[24] hence different categories depending on the timing.

Category 1: The rapid progressors, who die by age 1 (median age 6-9mo) and are thought to have acquired the infection in utero or during the early perinatal period (about 15-25%). This early severe form is characterized by low birth weight, developmental delay, persistent oral candidiasis, recurrent/persistent diarrhoea, recurrent bacterial/fungal infections, severe encephalopathy before 18 months, high viral load at birth and rapidly decreasing CD4 counts.

Category 2: Majority (about 60–80%) of children develop symptoms early in life, followed by a downhill course and death by age 3 to 5 years.

Category 3: The long-term survivors or slow progressors (<5%), whose median age of survival is 8 years but may live beyond age 8 years They have minimal or no clinical disease, relatively normal CD4 count and low viral load. They are probably infected through breastfeeding.

The slow progression is characterized by opportunistic Infections after 2 - 10 years, no encephalopathy but growth stunting, common lymphoid interstitial pneumonitis (LIP), parotitis, skin problems, AIDS related cancers, low viral loads at birth, stable CD4 counts for 2 - 10 years then slow decline

Factors that influence HIV Transmission include

Social Mobility: Global economy-HIV/AIDS follows routes of commerce

Stigma and Denial: Denial prevents acknowledgment of risk; and with stigma, people may feel isolated and rejected, and this prevents risk reduction efforts and care-seeking.

Cultural Factors: Traditions, beliefs and practices affect understanding of health and disease and acceptance of conventional medical treatment. Culture can create barriers which prevent people, and especially women, from taking precautions e.g. pressure to breastfeed may expose more infants, spousal inheritance and pressure to bear children inhibits condom promotion

Poverty: Lack of information needed to understand and prevent HIV, poor nutritional status, reduced access to health care services all contribute in increasing the transmission of HIV Infection.

Gender inequalities: In many cultures men are expected to have many sexual relationships, women suffer gender inequalities, often economic in nature, women may not feel empowered to negotiate whether sex happens at all or to negotiate condom use and this exposes women more to HIV infection.

DIAGNOSIS OF HIV

Clinical Diagnosis:

According to the World Health Organization (WHO) diagnostic criteria for paediatrics AIDS, a child who has two major and two minor criteria is diagnosed as having AIDS[6].

Major Criteria includes weight loss of 10% or more; prolonged fever more than one month; chronic diarrhoea and tuberculosis.

Minor Criteria includes oropharyngeal candidiasis; persistent cough for over one month; night sweats; loss of appetite; generalized skin infections; generalized lymphadenopathy; herpes zoster; chronic herpes simplex infection; pneumonia; and Kaposi sarcoma.

WHO Clinical staging

WHO Clinical staging is used in the assessment of paediatric AIDS patient.
All children with HIV infection should be staged, even in the absence of equipments in resource poor countries. The WHO clinical stage should be re-evaluated at every clinic visit.
There are 4 stages:

Clinical Stage 1 in which the child may be asymptomatic or may have generalized lymphadenopathy

Clinical Stage 2 in which the child may present with hepatosplenomegaly, papular pruritic eruptions, seborrhoeic dermatitis, extensive human papilloma virus infection, extensive molluscum contagiosum, fungal nail infections, recurrent oral ulcerations, lineal gingival erythema (LGE), angular cheilitis, parotid enlargement, herpes zoster, recurrent or chronic URTIs (Otitis media, otorrhoea, sinusitis)

Clinical Stage 3

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigation ; These include moderate unexplained malnutrition not adequately responding to standard therapy, unexplained persistent diarrhoea (14 days or more),unexplained persistent fever (intermittent or constant, for longer than one month), oral candidiasis (outside neonatal period), oral hairy leukoplakia, acute necrotizing ulcerative gingivitis/periodontitis, pulmonary Tb and severe recurrent presumed bacterial pneumonia

Conditions where confirmatory diagnosis testing is necessary. These include lymphoid interstitial pneumonitis (LIP), unexplained anaemia (<8g/dl), and or neutropaenia (<1000/mm3) and or thrombocytopenia (<50 000/mm3 for more than one month, chronic HIV- associated lung disease including bronchiectasis

Clinical Stage 4

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations. These conditions are also known as AIDS defining conditions and they include unexplained severe wasting or severe malnutrition not adequately responding to standard therapy; pneumocystis jiroveci pneumonia; recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia); chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration); extrapulmonary Tb; Kaposi's sarcoma, oesophageal candidiasis; CNS toxoplasmosis (outside the neonatal period) and HIV encephalopathy.

Laboratory Diagnosis:

(a) HIV Antibody Tests

These antibody tests detect HIV IgA antibodies in the blood or serum. These antibodies develop from 1-3 months after the initial infection. Examples include:

- HIV ELISA (Enzyme Linked Immunosorbent Assay) Test. The ELISA test is performed on patient's blood or serum. The test becomes positive 6-12 weeks after an infection has occurred. It is highly sensitive.

False positive ELISA test results from autoimmune diseases, certain viral infections, syphilis, haematological malignancies and pregnancy. A positive result from ELISA should therefore be confirmed using Western Blot test. If this is not available, another ELISA of different antigenic origin can be used to confirm infection[4].

- Simple Rapid HIV Tests (Antibody detection in blood or plasma). This test is easily and more rapidly conducted. If the result is positive, it should be repeated using another rapid test kit that tests for another antibody. The colour reaction occurs rapidly within minutes and can be read visually without the need for a spectrophotometer[26]. They are of comparable specificity and sensitivity to ELISA, and are very convenient and reliable for screening smaller number of samples [26].
- Western Blot Test. This is an electrophoretic test using polyacrylamide gel. It detects protein bands specific to HIV antibodies. Confirmation with Western Blot techniques requires the demonstration of antibodies reactive with at least two of the virus-specific proteins P18, P24, P32, P41, P51, P55, P65 gp 20 and gp 160 for HIV-1 and P16, P26, gp 36, P56, gp 105 and gp 140 for HIV-2, [26,27] It is most widely used in Nigerian blood banks[26,27]. It is used in confirming positive results from ELISA or Rapid Simple tests, or where two ELISA tests are discordant, or when simple rapid tests are discordant.

It is very specific but its high cost is a limiting factor. Furthermore, it is not used for confirmation of diagnosis in children under 18 months of age. Below 18 months, most antibodies in children are maternal in origin and western blot is an antibody based test. Other forms of confirmatory tests are immunofluorescence and radio-immunoprecipitation assay[28].

(b) Viral Load Assay

- P24 Antigen Test, and immune complex – dissociated P24 antigen (ICD-P24). These are very useful in young infants allowing a definitive diagnosis in most infected infants by 1-6 months of age. This is done using an antigen detecting enzyme-linked immunosorbent assy[28].
- Polymerase Chain Reaction (RNA or DNA PCR). HIV DNA PCR is the preferred virologic assay in developed countries with more than 90% of infected individuals testing positive by 2 weeks of age[18]. The HIV RNA PCR is more sensitive than the former for early diagnosis but data are limited. These techniques are often complex and expensive, and are at the moment largely used for research purposes.

(c) Viral Culture

HIV viral culture has similar sensitivity to HIV DNA PCR but more technically complex and expensive and results are often not available for 2-4 weeks compared with 2-3 days for PCR[18].

(d) **Haematological laboratory values**:

CD4 lymphocyte count is a surrogate marker for disease progression and should be monitored closely. CD4 count should be obtained prior to starting therapy. A rapid decline in CD4 count, especially in the first year of life, is a poor prognostic sign and should prompt initiation or alteration of therapy.

TREATMENT

Treatment of paediatric AIDS is divided into specific treatment with anti - retroviral drugs, treatment of opportunistic infections and other supportive treatment

Antiretroviral therapy

Specific treatment is achieved by the use of highly active antiretroviral therapy (HAART) which is defined as any antiretroviral regimen that will prevent disease progression, optimize opportunity for recovery and prevent drug resistance[29]. HAART usually requires combination of 3 or more drugs in at least 2 different classes. ARVs, when taken correctly, can tremendously enhance a patient's life and dramatically halt progression of disease[30]; however, in order to derive the most benefit from the medications, ADHERENCE must be excellent. For better visual understanding, the points of actions of the various antiretroviral drugs are shown in figure 2.

Classes of ARVs

The following are classes of ARVs

- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**: These stop viral replication by binding directly onto the reverse transcriptase enzyme preventing the transcription of RNA to DNA. Examples include Nevirapine (NVP), Efavirenz (EFV) and Delaviridin (DLV).[30]
- **Nucleoside reverse transcriptase inhibitors (NRTIs)** incorporate themselves into the DNA of the virus, stopping the building process. The resulting DNA is incomplete and cannot create a new virus. Examples include Zidovudine (ZDV, AZT), Lamivudine (3TC), Stavudine (d4T), Abacavir (ABC), Didanosine (ddI), Zalcitabine (ddC) and Emtricitabine (FTC).
- **Nucleotide reverse transcriptase inhibitors (NtRTIs)**: Act at the same stage of the viral life cycle as the NRTIs, but do not require to be phosphorylated for effective antiretroviral activity. Examples include Tenofovir (TDF).
- **Protease inhibitors (PIs)**: These work at the last stage of the virus reproduction cycle. They prevent HIV from being successfully assembled and released from the infected CD4+ cell. Examples include Lopinavir-ritonovir (LPV/r), nelfinavir (NFV), Saquinair (SQV), Indinavir (IDV), and Amprenavir (APV).
- **Entry inhibitors** (also called HIV fusion inhibitors): Prevent HIV particles from infecting the CD4+ cell. Drugs in this group include Enfurvitide and Maraviroc.
- **Integrase inhibitors**: They interfere with the ability of the HIV DNA to insert itself into the host DNA and thereby copy itself. Raltegravir is the only drug in this group[30].

Fig. 2. Life cycle of HIV showing the points of action of the ARVs

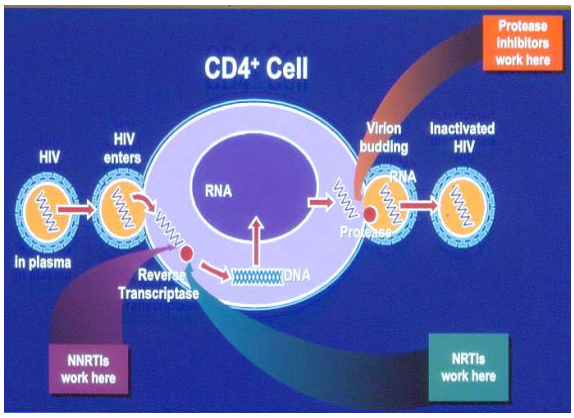
Initiating antiretroviral therapy in infants and children

The decision to start ART in children is complex. It depends on the age of the child, clinical stage and immunological assessment. Dosing in children is usually based on either surface area or weight[31].

Considerations for ART in children include:

- Multidisciplinary approach involving doctors, pharmacists, nurses, Medical laboratory scientists, counsellors, social workers, psychologists, nutritionists, data entry clerks, outreach workers and others
- Identification of a primary caregiver who understands the disease and implications of ART which include life long therapy, adherence issues, drugs storage and toxicities.

- Access to nutritional support and family support groups including identification of an informed secondary caregiver.



- The status of disclosure to the child and other members of the family.
- The choice of antiretroviral regimen should take into consideration possible limitation of future treatment options and potential for drug resistance.
- Factors influencing adherence to therapy,
  - Availability and palatability of paediatric formulations
  - Impact of the medication schedule on quality of life, such as number of medications, frequency of administration and the need to take with or without food
  - Potential for drug interactions (including traditional medicines)
- Access to laboratory monitoring.
- Prevalent coexisting conditions (e.g. malaria, malnutrition, TB, hepatitis B and C).
- Toxicity profile.

Pre-Treatment Evaluation includes confirmation of HIV infection; clinical evaluation of the child; detailed history and physical examination; determination of immunization status; anthropometry (weight, height/length, MAC, head circumference); neuro-developmental assessment; immunological evaluation of the child (CD4+ count/CD4+%); review of tuberculin skin test, chest x-ray, sputum/gastric aspirate for AFB (acid fast bacilli) to exclude tuberculosis; review of other laboratory results including liver function tests, urinalysis, electrolytes and urea, serum creatinine, full blood count (and Serum lipids, serum Amylase, viral load if available); and development of child-specific adherence strategy.

Indications for Initiation of Antiretroviral Therapy

a) WHO Recommendation for ART in children when CD4+ testing is available

i. Children with confirmed HIV infection with

WHO Paediatric stage 3 or 4 irrespective of CD4+% or WHO Paediatric stage 2 or 1 with

- CD4+ less than 25% (1500cells/µl) for children less than 12 months or
- CD4+ less than 20% (<750cells/µl) for children 12-35 months
- CD4+ less than 15% (350cells/µl) for children 36-59 months
- CD4+ less than 15% (200cells/µl) for children ≥ 5 years

All infants with a positive DNA-PCR should be closely monitored monthly for indications for early initiation of therapy. Decision to start treatment is particularly important for infants as probability of death in an untreated HIV infected children is high; mortality rate up to 40% by age of 1 year have been reported[32].

ii. Antibody positive children < 18months with no virological test, but with:

- WHO Paediatric stage 3 or 4 irrespective of CD4+ %
- WHO Paediatric stage 2 only if CD4+% is less than 20
- WHO Paediatric stage 1: do not treat if no virological tests are available

b) WHO recommendation for ART in children when CD4+ is not available.

i. Less than 18 months of age:

- WHO Paediatric stage 3 or 4, irrespective of total lymphocyte count (TLC).
- WHO Paediatric stage 2 only if TLC less than 4000/mm ^{3} (age <12 months); <3000/mm ^{3} (age 12-18months) or if mother has severe symptomatic disease (WHO adult stage 3 or 4), or died of AIDS.
- WHO Paediatric stage 1: don't treat if no virological test available (but monitor closely, monthly).

ii. More than 18 months of age

- WHO Paediatric stage 3 or 4 irrespective of TLC
- WHO Paediatric stage 2 only if TLC is
  - < 3000/mm^3 if aged 18-35 months;
  - <2500/mm^3 if aged 36-59months or
  - <2000/mm^3 if age is ≥ 5 years.

First line ARV regimen

First line ARV involves the use of 2 NRTI + 1 NNRTI.

Recommended for use in children are Zidovudine (ZDV, AZT) + Lamivudine (3TC) + Nevirapine (NVP)/Efavirenz (EFV). EFV is used only in children above age 3 years or >10kg.

Alternative regimen is the use of Stavudine +Lamivudine + Nevirapine/Efavirenz or Abacavir + Lamivudine + Nevirapine/Efavirenz

Antiretroviral Drug Toxicity

Most ART toxicities described in adults have also been reported in children; however there is limited data on toxicities compared to adults[33]. It is sometimes difficult to differentiate between complications of HIV infection, ARVs toxicity and drug-drug interaction. Alternative explanations for features suggestive of toxicities must be excluded before concluding that they are ARV-related. Alternative causes of these features include: concurrent infection e.g. malaria with severe anaemia; immune reconstitution inflammatory syndrome (IRIS); and a reaction to a non ARV drug such as Co-trimoxazole in a child receiving Co-trimoxazole preventive therapy.

Drug-related adverse events may be acute, occurring shortly after a drug has been administered, may be sub-acute, occurring within 1-2 days of administration or may be late occurring after prolonged drug administration. These adverse events may vary from mild to severe or life-threatening.

As a general principle mild toxicities do not require discontinuation of therapy or drug substitution. Symptomatic treatment may be given e.g. anti-histamine for a drug rash. Moderate/severe toxicities may require substitution by a drug in the same class but with a different toxicity profile. Severe life-threatening toxicity requires discontinuation of all ARV drugs and the initiation of supportive therapy.

Substitution within the first line ARV regimen

Substitution is the replacement of an identified offending drug causing toxicity with another drug from the same class that does not have the same adverse effects. This is different from switching which is the replacement of an ARV regimen because of treatment failure. An example of a substitution is replacing AZT with d4T because of anaemia while an example of switching is the replacement of a first line with a second line regimen.

Treatment failure

Treatment failure can be virological, immunological or clinical.

i) Virological indicators

Where CD4+ and clinical criteria for recognising treatment failure are conflicting, viral load assessment can add useful information. Detectable viral load in the absence of poor adherence to medication after 24 weeks of treatment is an indication of virological failure (for the purposes of treatment failure, undetectable levels is defined as viral load <400 copies/ml).

The viral load should not be measured during a concurrent infection; preferably, it should be measured at least one month after resolution of the infection.

ii) Immunological indicators

Treatment failure is characterised by a drop in the CD4+ cell count or %, to values at/or below the age-related threshold for the initiation of treatment after initial immune recovery following initiation of ART. Thus recognition of treatment failure on the basis of immunological values relies on comparison with previous CD4+ cell count or %. Immunological failure should be considered if CD4+ cell count or % falls to below:

- 20% for age <12 months
- 15% for age 12 – 35 months
- 10% for age 36 – 59 months
- 100 cells/mm^3 for ≥ 5 years.

Where CD4+ values are not available a new or recurrent stage 3 and 4 event is an indication of treatment failure. However, it is recommended that in the presence of pulmonary or lymph node TB or severe recurrent bacterial pneumonia, patients should receive appropriate treatment before treatment failure is considered.

iii) Clinical indicators

Clinical treatment failure should be considered when either new or recurrent stage 3 or 4 clinical events develop in a child on therapy.

Factors which contribute to treatment failure include poor adherence, inadequate level, prior existing drug resistance and inadequate potency of drugs chosen[34, 35, 33, 37]. Genetic differences in drug metabolism may also be important[38, 39].

Before treatment failure is considered in any child on ART, the following factors should be taken into account:

- Adherence to therapy should have been assessed and considered to be optimal
- Intercurrent opportunistic infections should have been treated and resolved
- The child should have received the regimen for at least 24 weeks
- Immune reconstitution inflammatory syndrome (IRIS) should have been excluded
- Adequate nutrition should have been ensured.

Treatment failure needs to be differentiated from IRIS in the context of co-therapy. IRIS has been observed in patients receiving anti-TB therapy who were initiated on ART. It has been primarily reported in adults but it can also occur in children. It is defined as a paradoxical clinical deterioration after starting HAART, resulting from improving immune system interaction with organisms that have colonized the body during the early stages of HIV infection[40]. In spite of the clinical deterioration, there is improvement in CD4+ counts and suppression of viral loads.

IRIS is characterized by worsening of disease after initial clinical improvement, with onset of new systemic symptoms, especially fever. Other features include pulmonary infiltrates, the development of peripheral

and mediastinal adenopathy and worsening CNS manifestations in patients with tuberculoma. These reactions may occur during the first three months of ART, are generally self-limiting and last 10−40 days. Some reactions may be severe and require a short course of treatment with prednisolone at a dose of 1-2mg/kg/day for 4-6 weeks.

Initiation of ART can also unmask previously undiagnosed infections such as hepatitis B or C infections by improving the inflammatory response due to the improvement of the immune system. In general, ART should not be interrupted for immune reconstitution syndrome.

Switching ARV regimen

Switching is the replacement of a first-line regimen with a second line regimen because of treatment failure.

The second-line regimen should:

- Preferably include at least two new drugs, one or both of them from a new class in order to increase the likelihood of treatment success and minimize the risk of cross-resistance
- Be based on drugs expected to retain potency against the virus.

WHO recommends a regimen based on a PI, boosted where possible with ritonavir (RTV), and combined with two new NRTIs (usually based on didanosine [ddI]) as the second-line regimen for treatment failure. Example include the combination of

1. Didanosine + Abacavir +Lopinavir/ritonavir or Nelfinavir
2. Didanosine + Zidovudine + Lopinavir/ritonovir or Nelfinavir

Treatment interruption

Currently, there is limited data on treatment interruption in children. Interruption of ARV therapy should not be encouraged, but may be indicated in some situations which include serious treatment-related toxicity; acute illnesses (e.g. severe diarrhoea and vomiting); planned surgeries that preclude oral intake; patient or parent/caregiver requests after extensive counselling.

Nevirapine tail

When short term interruption is indicated all therapy should be stopped at once. This can be problematic with ARVs that have a long half-life for example NNRTIs (NVP, EFV). This results in functional monotherapy that may lead to NNRTIs resistant mutations. To avoid this, stop NNRTIs first and continue other ART drugs (NRTIs or PIs) for a period of one to two weeks to allow NNRTIs to be cleared from the body.

Discontinuation of therapy

Under exceptional circumstances it may be necessary to discontinue ART. Such circumstances include poor adherence and cases where the administration of medication is repeatedly interrupted. Continuing suboptimal ART is not useful

because it will lead to the emergence of viral resistance. Consider discontinuation only after exploring all potentially corrective measures, including intensive counselling, additional caregiver education, and family support.

Salvage therapy

A number of treatment approaches have been considered in clinical trial settings, although largely in adults and where virological monitoring is possible. These include the addition or substitution of new drugs (such as enfuvirtide [T-20]), mega-HAART (combination of five or more drugs, including two or more protease inhibitors), strategic recycling of drugs, structured treatment interruptions and the continuation of

current therapy until additional drugs become available. Refer patients to higher levels of care or ART specialists if necessary.

Drug resistance

Considerations on drug resistance

Infants and children may acquire resistant virus or develop resistance because of ARV exposure for prophylaxis or treatment. In perinatal acquisition the infant acquires resistant virus from the mother in utero, intrapartum or postpartum during breastfeeding.

The transmission of a resistant virus can occur from an ARV-naïve mother infected with resistant virus, a mother exposed to ARVs before becoming pregnant or a mother who has been exposed to ARVs during pregnancy either for her own health or for prophylaxis of MTCT.

Treatment-related development of resistance in children is, as in adults, frequently related to the use of suboptimal suppressive regimens or suboptimal dosing or sub-therapeutic drug levels because of either poor adherence or pharmacokinetic problems including drug interactions.

Considerations for minimizing the emergence of drug resistance

The emergence of HIV drug resistance (HIVDR) is of increasing concern in countries where ART is widely used and represents a potential impediment to the achievement of long-term success in the rapid scale-up of ART in resource-limited settings. Minimizing the emergence and transmission of HIVDR is therefore essential in order to ensure the efficacy of the limited number of ARVs available in many countries.

The following situations warrant resistance testing where available:

- Prior to initiating therapy in a patient exposed to possibly resistant virus
- In patients who fail to adequately respond to therapy
- In patients who experience viral "rebound" or a return of HIV RNA towards baseline provided adherence is assured.

Adherence to ART

Medication adherence is a central feature in the success or failure of ARV therapy. Poor adherence may lead to suboptimal levels of ARVs, which may facilitate the development of drug resistance to one or more drugs in the regimen. Long-term poor adherence may lead to cross-resistance to other drugs in the same class. Medication adherence of 95% (corresponding to missing not more than 3 doses per month of a twice-daily therapy) or higher is associated with the best chance of maximizing success of ART.

Adherence refers to a partnership between the patient, family and health care team to ensure that medication is taken exactly as prescribed. This entails two-way discussions with the patient and family to determine how they plan to incorporate medication dosing with their current lifestyle.

Efforts to support and maximize adherence should begin before the initiation of treatment. The development of an adherence plan and the education of children and their caregivers are important first steps.

The employment of additional methods may be necessary especially for young children, including the tasting of medications, practising the measurement of liquids, and training in pill swallowing.

Adherence, however, goes beyond initial education. It must be assessed at EACH

visit, and strategies to improve it should be discussed. Adherence in children is a special challenge because of a number of potential barriers. These barriers need to be addressed prior to starting therapy. Some of these include lack of disclosure to the patient or other family members, complex medication regimens, difficulty in measuring or administering medications, and dietary requirements and restrictions. Others are high pill/liquid burden, poor palatability, medication refusal and medication burn-out.

Assessing adherence is not simply asking if all medications are taken. It includes a self-report/report from parents/caregivers on timing of the medications, who gives the dugs, common problems encountered, pharmacy refill counts and pill counts.

Some strategies to improve adherence include having treatment partners, home visit by HBC or outreach teams, sunset/sunrise and use of fixed dose combinations.

Common Opportunistic and Co-Infections

Opportunistic infections (OIs) are caused by organisms, which in the immune competent host would not cause significant disease. The causative organisms of OIs in HIV-infected children include viruses, bacteria, fungi, protozoa and other parasites, which often co-exist.

ORAL THRUSH: Caused by Candida albicans and presents as white painless plaques on the buccal mucosa and/or pharyngeal mucosa or surface of the tongue that is not easily scrapped off. Treatment is the use of nystatin 100,000 – 200,000 iu delivered to the cheeks 4 -5 times in a day for 14 days or oral fluconazole 6mg/kg stat day 1 then 3mg/kg/dayfor 14 days.

PNEUMOCYSTIS PNEUMONIA: This is caused by pneumocystis jirovicii (carinii), presents as an acute/subacute non-productive cough, and difficulty in breathing. Diagnosis is usually clinical but it is confirmed by the isolation of the organism from bronchoalveolar lavage specimen. Chest radiograph shows focal interstitial infiltrates and mediastinal lymphadenopathy.

Treatment is trimethoprine 20mg/kg/day PO or IV for 21 days in 3-4 divided doses. Other drugs that could be used include dapsone, pentamidine, and clindamycin.

LYMPHOID INTERSTITIAL PNEUMONITIS (LIP): The cause is unknown but it is associated with co-infection with HIV and Epstein Barr virus, presents as recurrent cough, respiratory distress, parotid enlargement, generalised lymphadenopathy, hepatosplenomegaly, digital clubbing and poor response to TB therapy. Chest radiograph shows reticulo-nodular infiltrates, bilateral hilar/mediastinal lymphadenopathy, treatment is with the steroids-prednisolone.

TUBERCULOSIS

HIV infection increases a child's susceptibility to infection with *Mycobacterium tuberculosis*. The presence of TB may allow HIV to multiply quickly resulting in rapid progression of HIV and AIDS. Increasing levels of co-infection with TB and HIV in children have been reported from resource-limited countries[41] and the prevalence of HIV in TB infected children ranges from 10-60%[42, 43,44,45,46].

A high index of suspicion is required for the diagnosis of TB in HIV infected children.

History include unexplained weight loss or failure to thrive, unexplained fever >21 days, cough >21 days failure to respond to appropriate antibiotic treatment of presumed bacteria pneumonia or meningitis and exposure to an adult with probable or definite open TB.

Laboratory investigations include radiographs of chest, spine and any other relevant area as indicated, tuberculin skin test e.g. Mantoux (>/= 5mm is positive), Ziehl-Nielson stain of sputum or early morning aspirates for AFB, culture of sputum, gastric aspirates, pleural/ascitic fluid, CSF as indicated, lymph node biopsy, complete blood count and ESR.

The most important aspect of TB-HIV co-infection is the timing of commencement of ARVs in a child on anti-Tb medications.

For WHO paediatric clinical stage 3 and 4, the recommendation is that ARVs should be started soon after commencement of TB treatment (between 2 and 8 weeks following start of TB treatment). In the recommended regimen, for children above 3 years of age or above 10kg, Nelfinavir is used to replace Nevirapine, for those not in this category triple NNRTI regimen is used.

For WHO paediatric clinical stage 1 and 2, TB treatment is commenced first, and the patient is closely monitored for the need to start ARVs. In some instances, ARVs is started after the intensive phase of TB treatment or after completion of the treatment.

SUPPORTIVE CARE IN HIV AND AIDS

Nutrition

Malnutrition is a common condition in HIV infected children and is a major contributor to morbidity and mortality[47].

HIV infection can result in nutritional deficiencies and growth failure, thus nutrition plays a critical role in the care and support of HIV infected children. It is important to maintain adequate nutritional status in HIV-infected children through nutritional management, monitoring of growth parameters and early dietary consultation.

Goals of nutrition management in paediatric HIV and AIDS are:

1. Prevention or mitigation of factors associated with risk of malnutrition
2. Appropriate infant feeding practices
3. Nutritional supplementation and rehabilitation.

The discovery that HIV can be transmitted through breastfeeding and the fact that breastfeeding is one of the most important child survival strategies have made safe infant feeding one of the most complex, challenging and emotional aspects of PMTCT programme. Among HIV infected mothers, the estimated additional risk of transmission from breast milk, over and above the risk during pregnancy and delivery, is about 15% for HIV-exposed babies who are breast-fed for up to 6 months and about 20% for babies who breastfeed into the second year of life.

Consequently, infant feeding counselling, long recognised as important for all mothers, has become even more important with the emergence of HIV. Therefore, mothers should be counselled and allowed to make an informed choice of the method of feeding to be adopted for their children. The mother and her family should be supported in her choice of feeding option by the health worker and the community.

Feeding options in the context of HIV infection include replacement feeding (breast milk substitutes) plus multivitamins when AFASS criteria are met (commercial infant formula; home prepared milk such as modified fresh animal milk and full cream milk); exclusive breastfeeding for 6 months with abrupt cessation and introduction of complementary feeds including animal milk; modified breastfeeding: exclusive breastfeeding with early cessation as soon as AFASS criteria are met or expressing and heat-treating breast milk; wet nursing by HIV negative surrogate mothers.

Mixed feeding, i.e. concomitant feeding with breast milk and any other fluid or foods including breast milk substitutes and water should be discouraged as it increases the risk of HIV transmission to the infant.

Complementary feeding

After 6 months of age, milk feeds alone become inadequate to sustain growth. Complementary feeds should therefore be introduced at the age of 6 months. The food should be sourced locally and prepared appropriately. Multivitamins and micronutrient supplements should be given.

Psychosocial support

A diagnosis of HIV infection in a child has the potential to disrupt the family stability by placing uncertainty over the family's future. Many families affected by AIDS are already burdened with poverty and now they need to spend more on the child. Psychosocial stress also affects adherence to treatment.

The care of the HIV infected child should be comprehensive using a multidisciplinary approach. This should be family-centred to strengthen the family's ability to cope with the child's illness and its psychological consequences. Counselling and psychosocial support are integral components of the holistic approach to caring for an HIV-infected child.

Psychosocial Assessment for anticipated family adaptation should include the following:

- Child and family's knowledge and reactions to the disease
- Beliefs, attitudes and expectations regarding treatment and outcome
- Coping ability during previous crises
- History of depression and/or non-prescribed drug and alcohol use
- Nature and stability of residential and occupational arrangements
- Quality of relationships between members of both nuclear and extended family
- Level of disclosure
- Socio-economic status of the family
- Socio-cultural factors or religious beliefs that might affect treatment decisions and adaptation
- Sources of emotional and financial support
- Health status of other family members

CONTROL OF THE PAEDIATRIC AIDS

The control of the paediatric AIDS can be achieved if all hands will be on deck to cub the common modes of transmission of this condition. Thus screening of all pregnant women after voluntary confidential counselling, prompt institution of prophylactic antiretroviral therapy after delivery of exposed children, proper screening of blood before transfusion, avoidance of use of potential contaminated objects, proper treatment and follow up of

infected children and intensive education on general prevention of acquiring this disease will all help in putting this disease under control.

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