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Review Article

Pediatric AIDS: An Overview

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Pediatric AIDS is an immune system disease in infants or children caused by virus. Since the first cases of human immunodeficiency Virus (HIV) infection were identified the number of children infected with HIV has risen dramatically in developing countries, the result of an increase number of HIV-infected woman of child bearing age in these areas. HIV is retrovirus can be transmitted vertically, sexually or via contaminated blood products or IV drug abuse. Vertically HIV infection occurs before birth, delivery or after birth. Nevirapine (200mg) given to the mother at onset of labour and 2mg/kg single dose to the infant within 1 week. The woman must receive maternal NVP dosing more than 2 hours before delivery.

Keywords: - Human immunodeficiency virus(HIV), Nevirapine, Retrovirus.

INTRODUCTION

Pediatric AIDS, (Acquired Immune Deficiency Syndrome) is caused by the human immunodeficiency virus (HIV). The term pediatric AIDS applies to the most advanced stages of HIV infection[1]. Most (91%) of pediatric patients with AIDS acquired their infection through perinatal transmission, whereas 7% acquired HIV infection through receipt. Since the first cases of human immunodeficiency virus (HIV) infection were identified, the number of children infected with HIV has risen dramatically in developing countries, the result of an increased number of HIV-infected women of childbearing age in these areas. HIV is a retrovirus and can be transmitted vertically, sexually, or via contaminated blood products or IV drug abuse. Vertical HIV infection occurs before birth, during delivery.

Physical examination

Symptoms of pediatric HIV infection found during physical examination include the following:

- Candidiasis: Most common oral and mucocutaneous presentation of HIV infection
- Thrush in the oral cavity and posterior pharynx: Observed in approximately 30% of HIV-infected children
- Linear gingival erythema and median rhomboid glossitis
- Oral hairy leukoplakia
- Parotid enlargement and recurrent aphthous ulcers

The genome layouts of HIV-1 and HIV type 2 (HIV-2) are shown in the image below[2]

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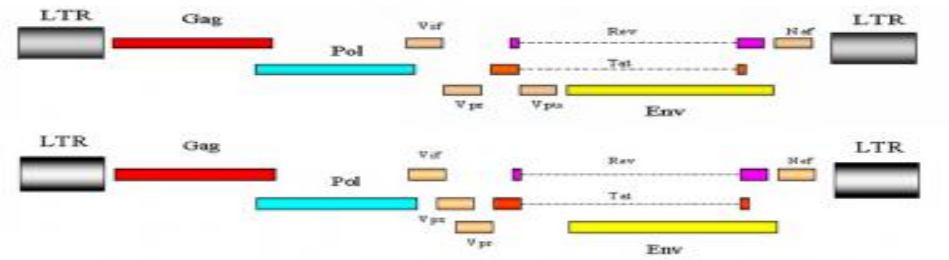

Genome layouts of HIV-1 (upper) and HIV-2 (lower)

- Herpetic infection with herpes simplex virus (HSV): May manifest as herpes labialis, gingivostomatitis, esophagitis, or chronic erosive, vesicular, and vegetating skin lesions; the involved areas of the lips, mouth, tongue, and esophagus are ulcerated
- HIV dermatitis: An erythematous, papular rash; observed in about 25% of children with HIV infection
- Dermatophytosis: Manifesting as an aggressive tinea capitis, corporis, versicolor, or onychomycosis
- *Pneumocystis jiroveci* (formerly *P carinii*) pneumonia (PCP): Most commonly manifests as cough, dyspnea, tachypnea, and fever
- Lipodystrophy: Presentations include peripheral lipoatrophy, truncal lipohypertrophy, and combined versions of these presentations; a more severe presentation occurs at puberty
- Digital clubbing: As a result of chronic lung disease
- Pitting or nonpitting edema in the extremities
- Generalized cervical, axillary, or inguinal lymphadenopathy

SYMPTOMS

Symptoms of pediatric HIV infection include the following:

- Unusually frequent and severe occurrences of common childhood bacterial infections, such as otitis media, sinusitis, and pneumonia
- Recurrent fungal infections, such as candidiasis (thrush), that do not respond to standard antifungal agents: Suggests lymphocytic dysfunction
- Recurrent or unusually severe viral infections, such as recurrent or disseminated herpes simplex or zoster infection or cytomegalovirus (CMV) retinitis; seen with moderate to severe cellular immune deficiency
- Growth failure
- Failure to thrive
- Wasting

- Failure to attain typical milestones: Suggests a developmental delay; such delays, particularly impairment in the development of expressive language, may indicate HIV encephalopathy
- Behavioral abnormalities (in older children), such as loss of concentration and memory, may also indicate HIV encephalopathy
- Extreme fatigue
- Rash
- Flu-symptoms
- Chills
- Weakness
- Weakened immune system
- Low CD4 +count
- Persistently swollen lymph nodes
- Persistently tender lymph nodes
- Rapid weight loss
- Persistent diarrhea
- Shortness of breath
- Dry cough
- Headache
- Stiff muscles
- Sore muscles [1]

Pediatric AIDS: Causes and Types

1. Viral diseases
2. Conditions involving a pathogen
3. Sexually transmitted diseases
4. Immune system conditions
5. Child health conditions
6. Infant health conditions
7. Teen health conditions

1. Viral diseases

A viral infection is any type of illness or disease caused by a virus, a type of microbe. Microbes are tiny organisms that cannot be seen without a microscope and include bacteria, fungi, and some parasites, as well as viruses[1]. Common symptoms of a viral infection include fatigue, flu-like symptoms and fever. For more information on symptoms, refer to symptoms of viral infection.

2. Conditions involving a pathogen

Medical conditions involving some type of pathogen, such as a virus or bacteria.

3. Sexually transmitted diseases

STDs, or sexually transmitted diseases, are caused by a bacterial infection, viral infection, or parasite infection that is passed from one person another during sexual contact. This sexual contact can involve vaginal, oral, or anal sex[1]. Some STDs can also be passed to another person through other means, such as through blood transfusions or from an infected mother to her baby during pregnancy or childbirth.

There are many STDs, including chlamydia, HIV/AIDS, syphilis, chancroid, pubic

lice, HPV, trichomoniasis,genital warts,gonorrhea and genital herpes.

4. Immune system conditions

The immune system helps the body defend against various microbes and pollutants. However, the immune system itself can have various failings. An impaired immune system is called immunocompromise and can leave the body vulnerable to various viral, bacterial, or fungal opportunistic infections. Causes of immune deficiency can include various illnesses such as viruses, chronic illness, or immune system illnesses (especially AIDS) [1]

5. Child health conditions

➢ **Causes of Types of Child health conditions:**

Review the cause informationfor the various types of Child health conditions:

- Food Additive Allergy
- Animal allergy
- Pet allergy
- Bird allergy
- Cat allergy
- Dog allergy

6. Infant health conditions

Infants may exhibit a variety of symptoms due to medical conditions. Such as Very common is a crying infant, which may be due to various simple reasons (e.g. hungry, thirsty, tired, lonely, etc.), or can indicate various medical conditions[1] For delayed or poor growth see growth symptoms and poor growth; loss of weight or delayed growth in an infant or child may be termed failure to thrive. Feeding problems may also indicate various conditions; see poor feeding.

7. Teen health conditions

Teen health conditions: Medical conditions typically afflicting teenagers, the various types of Teen health conditions:

- Marijuana overdose
- Myelogenous leukemia
- Non-Hodgkin's Lymphoma
- Hodgkin's Disease
- Osteosarcoma
- Ewing's sarcoma
- Rhabdomyosarcoma, embryonal

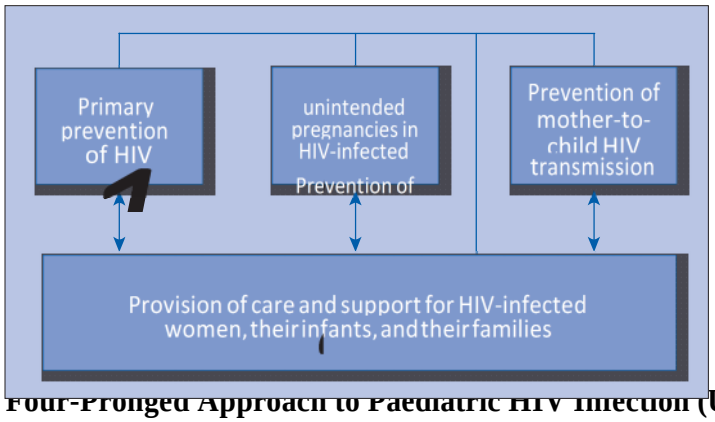

Fig. 1: Four-Pronged Approach to Paediatric HIV Infection (UN/WHO)

Preventing Paediatric HIV Infection

A four-pronged approach has been suggested for PMTCT of HIV.

Prong 1: Primary Prevention of HIV Infection

Primary prevention of HIV infection in men and women reduces the risk of heterosexual transmission and so directly affects MTCT [3]. Targeting pregnaand lactating women is a particularly pertinent strategy for preventing paediatric HIV infection.

Prong G: Preventing Unintended Pregnancy Among HIV-Infected Women

Adolescent females in Africa have a six-fold increased risk of HIV compared to males of the same age. This high risk of HIV acquisition stems from the young women's social, biological, and emotional vulnerabilities. Measures that may reduce HIV infection in adolescents include training in life skills and communication as a strategy to empower them to delay sexual debut and engage in less risky sexual behaviours. The establishment of youth-friendly sexual, reproductive, and VCT services is also an important way to increase access to services[3].

PMTCT efforts to date have focused almost exclusively on preventing transmission after an HIV-positive woman is already pregnant. PMTCT programmes could be made more effective by increasing contraceptive use among non-pregnant, non-contracepting HIV-positive women who do not want to get pregnant (including those identified during pregnancy and followed up post-pregnancy) through integrating family planning and PMTCT services.

Integrating family planning into PMTCT programmes and vice versa will require reorienting toward protection against the dual risks of unintended pregnancies and of HIV infection. Service providers and HIV-infected clients both need to promote dual protection, (especially by the use of condoms), to guard against unintended pregnancies as well as STIs

Prong 3: Preventing Mother-to-Child HIV Transmission

Specific interventions used to prevent HIV transmission from an infected mother to her child include use of ARV drugs, safer delivery practices, infant feeding, counselling, and support[3]. These interventions present real opportunities to improve services for all women and children, and healthcare providers should provide them as part of routine pregnancy, maternity, and post-pregnancy care for mothers and their infants.

Prong 4: Providing Care and Support to HIV-Infected Women, Their Infants, and Their Families Synergy Between Prevention and Care

Prevention and care are mutually reinforcing elements of an effective strategy for dealing with the paediatric HIV epidemic. Access to care will enhance community support for PMTCT programmes and increase the uptake of important interventions, such as HIV test- ing. Psychosocial and nutritional support, treating OIs, and ART are important in both preventing and treating paediatric HIV infection.

A comprehensive approach to the paediatric epidemic involves treat- ing the parents and other siblings to preserve the family unit, ensure a stable environment in which to nurture the children's growth and development, and reduce the prevalence of orphans [3].

Creating links between PMTCT programmes and those for the care and support of HIV-infected women, their infants, and their families will help to ensure that women themselves have access to the services they need. Furthermore, access to care and support services also en- hances PMTCT services within communities [3]. Such services include:

- Prevention and treatment of OIs
- Psychosocial and nutritional support
- Reproductive healthcare
- Control of STIs
- Family planning
- Antiretroviral therapy
- Young child care:
- Diagnosis of HIV
- Immunisations
- Growth and development monitoring
- Treatment of acute infections
- Routine de-worming
- Multivitamin supplementation
- Improved economic independence of women (poverty alleviation)

Diagnosis of Pediatric HIV infection

Children differ from adults in that they have high rates of viral replication, very high HIV-1 viral load, high rates of CD4+ cell destruction, viral mutation, faster rate of disease progression and good immunologic response to ART. Accurate diagnosis of pediatric HIV infection depends on laboratory tests, which can be divided into two categories:

1. **Antibody tests:** HIV ELISA, rapid tests, and Western Blot
2. **Virologic tests:** HIV DNA PCR assays, RNA assays including viral load, HIV immune comple dissociated p24 antigen assays, and HIV peripheral blood mononuclear viral culture

1. Antibody Tests

Antibody tests are the most widely used HIV diagnostic test and provide reliable evidence of HIV infection in adults and children who are older than 18 months. The HIV antibody test is less reliable in infants aged less than 18 months because they may still be carrying HIV-specific antibodies acquired from the mother in utero. The time it takes for an HIV-positive mother's maternal antibodies to be elimi- nated from an infant's system (seroreversion) varies[3]. The majority of uninfected non-breast-fed children will serorevert by age 15 months, but a smaller percentage (ranging from a low of 1% to a high of 18% in various studies) will not revert until age 18 months. Despite these limitations, HIV ELISA and rapid tests are the most widely available tests, and do provide (or exclude) evidence of exposure.

2. **Virologic Tests**

HIV Immune Complex Dissociated pG4 Antigen Assays

The p24 protein (antigen) is from the core proteins of the HIV virus .Detection of p24 antigen is definitive evidence of HIV infection. The p24 antigen assays use techniques that can be performed in most routine laboratories. In addition, they can be used for diagnosis in children less than 18 months of age [3]. Although the first-generation tests were highly specific, the sensitivity was lower than that of DNA PCR and RNA assays. The newer, ultra-sensitive p24 assays are more reliable, but require further evaluation for their use in infants.

HIV DNA PCR

The sensitivity of HIV DNA PCR is low during the first 1 to 2 weeks of life because this test is not able to detect very low levels of HIV DNA in babies infected a few minutes/hours/days earlier, during delivery and early breast-feeding. After 4 to 6 weeks of life, the sensitivity and specificity of HIV DNA PCR tests approach 100%, except in babies who have continuing exposure to HIV through breast-feeding.

New technologies, such as real-time PCR technologies, could provide a good alternative because they are rapid, simple, cheap, and adapt- able to the different clades of HIV. Their usefulness is still being evaluated.

HIV RNA Assays

HIV RNA assays detect viral RNA in plasma and other body fluids using a variety of methods (reverse transcriptase PCR, in vitro signal amplification nucleic acid probes [branched chain DNA], and nucleic acid sequence-based amplification [NASBA]).

RNA assays are more widely available than HIV DNA PCR tests, have a faster turnaround time, and require smaller blood volumes. RNA

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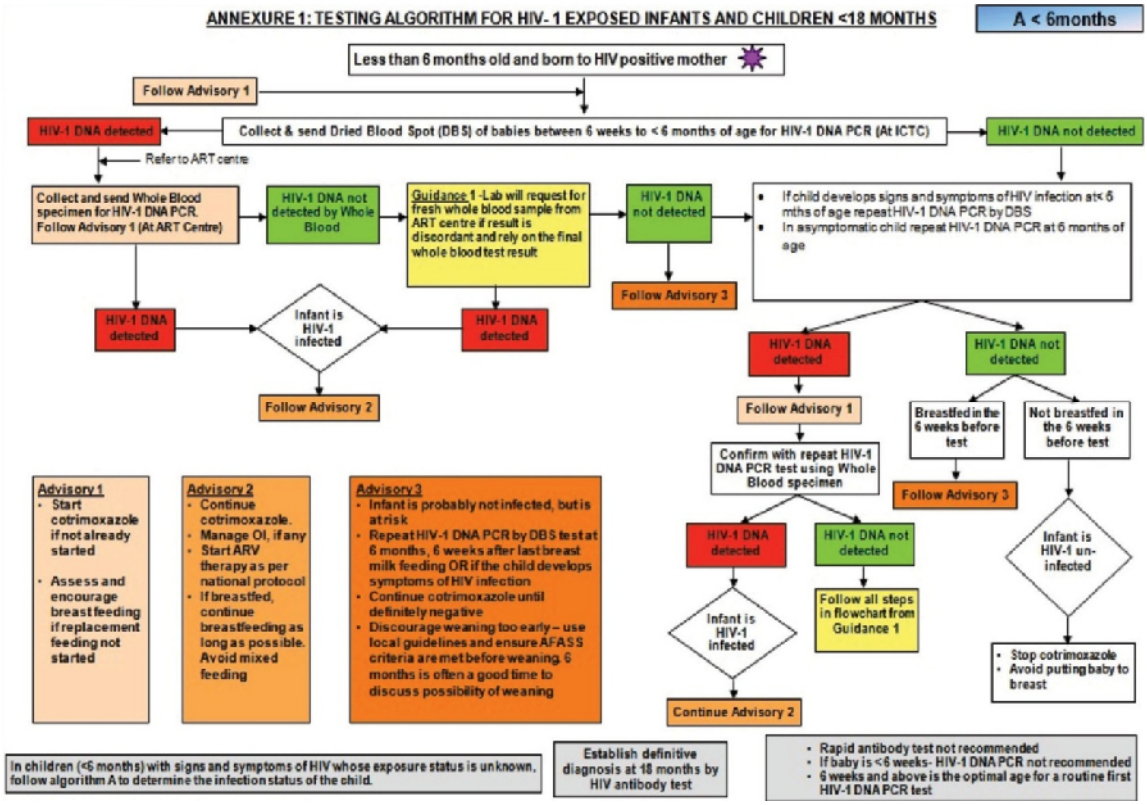
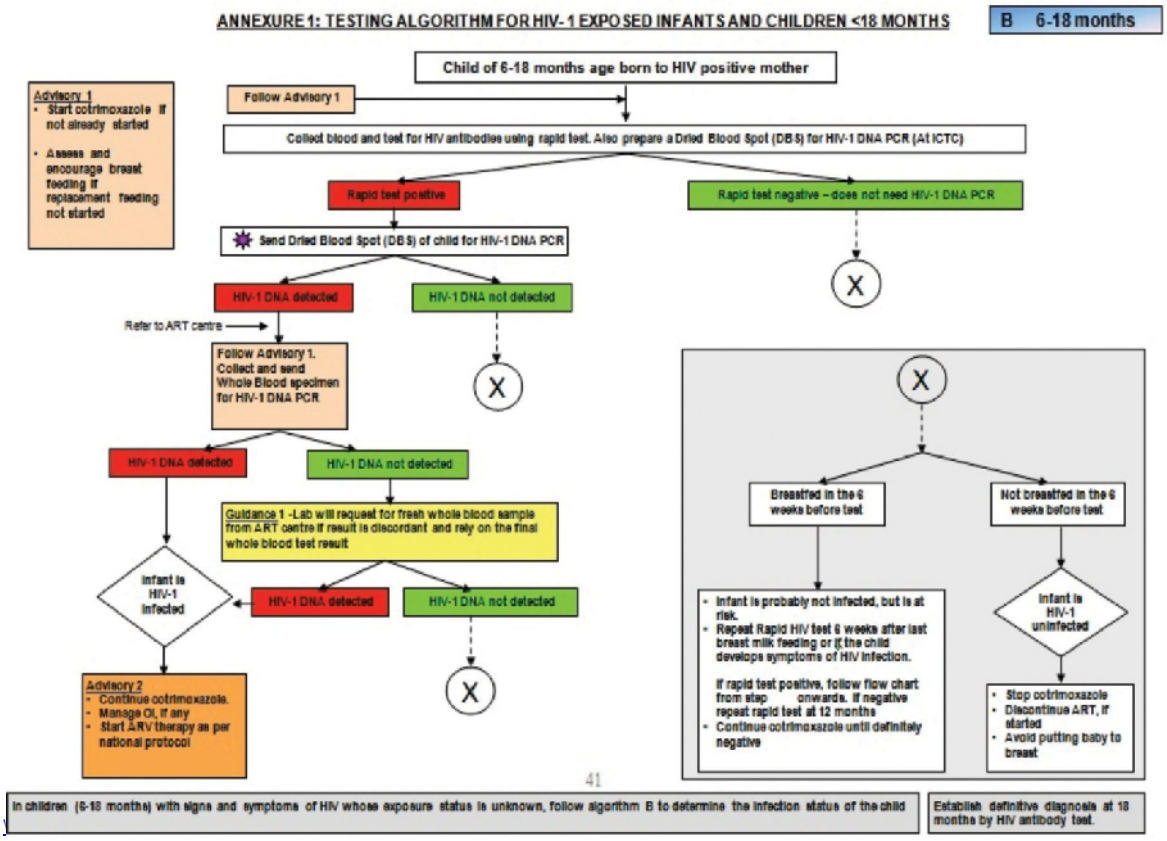


Fig. 2. Early infant diagnosis (EID): Testing algorithm for HIV-1 exposed infants <6



age

assays are also more sensitive for early detection of infection (first 2 months of life) than HIV DNA PCR tests.

Quantitative RNA (viral load tests) tests are used to determine the risk of HIV disease progression and to guide decisions for initiating ART [3].

HIV Peripheral Blood Mononuclear Viral Culture

The HIV peripheral blood mononuclear viral culture assay was the gold standard of HIV detection in the past, before the development of simpler and less expensive tests based on detection of HIV nucleic acid sequences DNA PCR or RNA PCR assays. This assay has a lower sensitivity than the other tests described above, and must be per- formed in protected laboratories (also called *P2 labs*). Current use is limited to research laboratories.

Treatment of Pediatric AIDS

There is no cure but treatment is aimed at slowing the progression of the disease and managing any opportunistic infections or other AIDS-related conditions as they arise [3]. The mainstay of treatment is antiretroviral medications.

The goals of treatment with ARV drugs are to:

- Prolong the survival of HIV-infected children
- Promote optimal growth and development
- Preserve, enhance, or reconstitute the immune system and therefore reduce opportunistic infections
- Suppress HIV replication and therefore prevent disease progression
- Reduce the morbidity of children and improve their quality of life

This is best achieved with a combination of antiretroviral agents which include[1]:

Nucleoside reverse transcriptase (RT) inhibitors - also called nucleoside analogs

- Zidovudine (AZT) - also called ZDV
- Zalcitibine (ddC)
- Didanosine (ddI)
- Stavudine (d4T)
- 3TC (lamivudine)
- Abacavir
- Tenofovir

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) - usually in combination with other antiretroviral drugs

- Delvaridine (Rescriptor)
- Nevirapine (Viramune)
- Efravirenz (Sustiva)
- Protease inhibitors
- Ritonavir (Norvir)
- Saquinivir (Invirase)
- Indinavir (Crixivan)
- Amprenivir (Agenerase)
- Nelfinavir (Viracept)
- Lopinavir (Kaletra)

- Fusion inhibitors - Enfuvirtide
- Integrase inhibitors - Raltegravir
- Cellular chemokine receptor (CCR5)antagonists - Maraviroc

Table 4: Antiretroviral Drugs in Paediatric Practice

Drug	Formulation	Dosage	Adverse Events	Comments
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)				
Zidovudine *AZT, ZDV, or Retrovir*	Suspension 10 mg/ml Capsules 100 mg, 250 mg Tablets 300 mg	180 mg/m2 bd Or 180–240 mg/m2 tds Neonatal dose: 2 mg/kg qid	Neutropaenia, anaemia, headache; myopathy, lactic acidosis (rare)	Can be given with food Store at room temperature
Lamivudine *3TC*	Suspension 10 mg/ml Tablets 150 mg	4 mg/kg bd Neonatal dose: 2 mg/kg bd	Headache, abdominal pain, fatigue, pancreatitis, peripheral neuropathy; neutropaenia, ↑ LFTs, lactic acidosis (rare)	Can be given with food Store at room temperature
Stavudine *d4T, Zerit*	Suspension 1 mg /ml Capsules 20 mg, 30 mg, 40 mg	1 mg/kg bd	Headache, GI upset, rash; peripheral neuropathy, ↑ LFTs, pancreatitis, lactic acidosis	Can be given with food Keep suspension refrigerated
Didanosine *ddI, Videx*	Suspension 10 mg/ml Tablets 25 mg, 50 mg, 100 mg, 150 mg	90–120 mg/m2 bd	Diarrhoea, abdominal pain, nausea; peripheral neuropathy, pancreatitis, lactic acidosis, ↑ LFTs	Give on empty stomach Keep suspension refrigerated
Abacavir *ABC, Ziagen*	Suspension 20 mg/ml Tablets 300 mg	8 mg/kg bd	Hypersensitivity rash (5%), fever, malaise, mucositis, pancreatitis, lactic acidosis	Can be given with food Store at room temperature *Do not rechallenge after hyper- sensitivity*
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)				
Nevirapine *NVP, Viramune*	Suspension 10 mg/ml Tablets 200 mg	Start with 120 mg/m2 once daily for 14 days Increase to full dose (120–200 mg/m2) every 12 hrs (maximum 200mg every 12 hrs) if no rash or severe adverse events	Rashes, Stevens-Johnson Syndrome, ↑ LFTs; hypersensitivity and hepatitis	Can be given with food Store at room temperature *Watch for liver toxicity*

Table 5. Antiretroviral Drugs in Paediatric Practice

Drug	Formulation	Dosage	Adverse Events	Comments
Efavirenz *EFV, Stocrin*	Capsules 50 mg, 200 mg	Single daily dose 10–15 kg: 200 mg 15–20 kg: 250 mg 20–25 kg: 300 mg 25–32.5 kg: 350 mg 32.5–40 kg: 400 mg >40 kg: 600 mg	Rash (mild), somnolence, abnormal dreams, insomnia, confusion, hallucinations, euphoria, amnesia, agitation, abnormal thinking	Can be given with food Administer at night Store at room temperature No pharmacokinetic data <10 kg and <3 years of age
Protease inhibitors (PIs)				
Ritonavir *RTV, Norvir*	Suspension 80 mg/ml Capsules 100 mg	Initial dose of 250 mg/m^2 bd. Increase by 50 mg/m^2 bd at 2–3 day intervals to 400 mg/m^2 bd. If <2 yrs of age, maximum dose 450 mg/m^2 bd	GI intolerance, headache, anorexia, LFTs; Abnormal lipids (rare)	Give with food Palatability improved by mixing with milk, honey, ice cream, yogurt or chocolate milkshake Store in refrigerator or room temperature
Nelfinavir *NFV, Vira-cept*	Suspension 50 mg/1 gm spoon Tablets 250 mg	Paediatric: 55 mg/kg bd Adolescent: 750 mg tds or 1250 mg bd	Diarrhoea, vomiting, rash; Abnormal lipids, exacerba- tion of chronic liver disease (rare)	Administer with food. Suspen- sion may be mixed with water, milk, pudding, ice cream, formula
Lopinavir / ritonavir *LPV/RTV, Kaletra*	Suspension 80 mg LPV and 20 mg RTV per ml Capsules 133.3 mg LPV and 33.3 mg RTV	230 mg/m^2 LPV/57.5mg/m^2 RTV bd up to a maximum of 400 mg LPV/ 100 mg RTV bd Increase dose with NVP or EFV co-administration (refer package insert)	GI intolerance, rash, headache; Abnormal lipids, hyperglycaemia, pancreatitis (rare)	Give with food. A high fat meal increases absorption Refrigerate suspension or keep at room temperature for 2 months
Fixed drug combinations				
D4T/3TC/ NVP (Triomune)	Tablet 40mg/50mg/200 mg	1 tablet twice daily de- pending on child's weight		Tablet broken up as per weight of child. Attainment of accurate dosage difficult with breakage of tablet.

Other treatment approaches include: Highly active antiretroviral therapy (HAART) - a treatment strategy of aggressive use of medications. Often used in initial treatment of children

- Treatment and prevention of opportunistic infections
- Foscarnet - for CMV eye infections
- Ganciclovir - for CMV eye infections
- Fluconazole - for fungal infections
- Trimethoprim/sulfamethoxazole (TMP/SMX) - for PCP
- Pentamidine - for PCP

Complications list of Pediatric AIDS

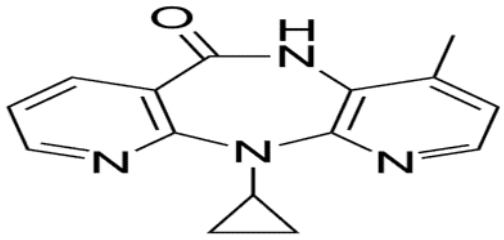
The list of complications that have been mentioned in various sources for Pediatric AIDS includes[1]:

- Wasting syndrome
- AIDS dementia complex
- Peripheral neuropathy
- Progressive multifocal leukoencephalopathy
- Death - usually due to opportunistic infections
- Malabsorption
- Depression
- Thrombocytopenia

NEVIRAPINE DRUG

Nevirapine (**NVP**), marketed under the trade name **Viramune** among others, is a medication used to treat and prevent HIV/AIDS, specifically HIV-1. It is generally recommended for use with other antiretroviral medication. It may be used to prevent mother to child spread during birth but is not recommended following other exposures [5]. It is taken by mouth. It appears to be safe for use during pregnancy. It is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and works by blocking the function of reverse transcriptase[5].

Structure of Nevirapine



This drug is usually in combination with one or more PIs as well as nucleotide reverse transcriptase inhibitor (NRTIs), especially in those who have not previously taken an NNRTI. This drug is generally only to be considered for used in HIV-1 infected population once CD4 cell counts are very low.

Mechanism of action

Nevirapine falls in the non-nucleoside reverse transcriptase inhibitor (NNRTI) class of antiretrovirals. Both nucleoside and non-nucleoside RTIs inhibit the same target, the reverse transcriptase enzyme, an essential viral enzyme which transcribes viral RNA into DNA. Unlike nucleoside RTIs, which bind at the polymerase active site, NNRTIs bind to a

hydrophobic pocket in the subdomain of p66 which is about 10 angstrom away from the active site (known as the NNRTI pocket) [5]. Therefore, this NNRTI-binding pocket will inhibit reverse transcription in a way that is distinct to the NRTIs. Nevirapine is not effective against HIV-2, as the pocket of the HIV-2 reverse transcriptase has a different structure, which confers intrinsic resistance to the NNRTI class.

Resistance to nevirapine develops rapidly if viral replication is not completely suppressed. The most common mutations observed after nevirapine treatment are Y181C and K103N, which are also observed with other NNRTIs[5].

As all NNRTIs bind within the same pocket, viral strains which are resistant to nevirapine are usually also resistant to the other NNRTIs, efavirenz and delavirdine. However, second generation NNRTIs like rilpivirine and etravirine are effective in treatment for HIV strains resistant to nevirapine and other first generation drugs in that same class.

Adverse effects

The most common adverse effect of nevirapine is the development of mild or moderate rash (13%). Severe or life-threatening skin reactions have been observed in 1.5% of patients, including- Stevens–Johnson syndrome, toxic epidermal necrolysis and hypersensitivity[5].

- Common side effects include: rash, headache, nausea, feeling tired, and liver problems.

Medicinal uses:

Nevirapine is used in adults and in children 6 years of age infected with HIV-1 as part of combination antiretroviral treatment (ART or cART). This drug is generally only to be considered for used in HIV-1 infected population once CD4 cell counts are very low. Nevirapine may also form a useful component of salvage regimens after virological failure, usually in combination with one or more PIs as well as nucleotide reverse transcriptase inhibitor (NRTIs), especially in those who have not previously taken an NNRTI[5].

Preventing mother-to-child transmission

A single dose of nevirapine given to both mother and child reduced the rate of HIV transmission by almost 50% compared with a very short course of zidovudine (AZT) prophylaxis, in a clinical trial in Uganda.[5] A subsequent study in Thailand showed that prophylaxis with single-dose nevirapine in addition to zidovudine is more effective than zidovudine alone. These and other trials have led the World Health Organization to endorse the use of single-dose nevirapine prophylaxis in many developing world settings as a cost-effective way of reducing mother-to-child transmission.A major concern with this approach is that NNRTI resistance mutations are commonly observed in both mothers and infants

after single-dose nevirapine, and may compromise the response to future NNRTI-containing regimens. A short course of maternal zidovudine/lamivudine is recommended by the U.S. Public Health Service Task Force to reduce this risk[5].

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