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Case Review

Management Strategies for HIV Infection in Paediatric Patients: A Comprehensive Review

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Abstract

HIV is a very dangerous infection brought on by a virus whose genome is made up of two identical single-stranded RNA molecules that are encased inside the core of the virus particle. The HIV virus is the cause of paediatric AIDS. It works by suppressing the immune system, which is clinically shown as a drop in CD4 cells. Rapid CD4 cell loss and accelerated disease progression are linked to high plasma viremia in HIV-1 infection [1]. The need to begin a successful ART in children with HIV infection is all the more important given that these children have high viral loads.

Especially in early childhood. The treatment of HIV in a result of advancements in antiretroviral therapy (ART). The goal of this review paper is to give a thorough summary of the current approach es and difficulties in managing HIV infection in paediatric patients. The treatment of HIV infection in paediatric patients has dramatically changed over time thanks to developments in antiretroviral therapy (ART). This review article seeks to give readers a thorough picture of the current approaches and difficulties in managing HIV infection in paediatric patients. We discuss various aspects, including diagnosis, treatment initiation, drug selection, monitoring, adherence support, prevention of opportunistic infections, and psychosocial considerations. Additionally, we highlight the recent advancements in paediatric HIV research and the `potential future directions in managing this complex disease.

Keywords: HIV Infection; Paediatric Patients; Antiretroviral Therapy; Diagnosis; Drug Selection; Monitoring; Adherence Support; Opportunistic Infections; Psychosocial Considerations; Recent Advances; Future Directions

Introduction

HIV infection continues to be a problem for the world's health, especially for young, vulnerable people. This section provides an overview of the epidemiology and etiopathogenesis of paediatric HIV infection and calls attention to the unique challenges in managing this population.

Etiopathogenesis

The immune system is the main area where the HIV virus affects the human body adversely. Immunesystem defects are mildly accompanied by HIV infection, which starts without any symptoms or indicators of sickness. From the time of infection to seroconversion, this phase can take up to threemonths. It is during this time that individuals who have recently been exposed to the virus can betested for the presence of HIV-specific antibodies. Although an infection's outcome and the amountof time it takes for a disease to manifest as clinical symptoms can greatly vary from person to person [2]. From initial infection to the onset of signs of advanced HIV illnesses and immunosuppression, a great number of years, often even years, pass.

Although people may appear to be in good condition during the primary infection, the virus is actively multiplying in the lymph nodes and blood of infected people. As a result, the surge in viral load in their bodies may gradually harm their immune systems [3].

During the symptomatic stage of the illness, which is the advanced stage of HIV disease (AIDS), a person may be susceptible to a number of opportunistic infections (OIs), including infections with Mycobacterium avium, Mycobacterium tuberculosis, Pneumocystis carinii, CMV, toxoplasmosis, and candidiasis. It is widely believed that a person contracts AIDS when their CD4+ T count is below 200 mm^3 and their plasma HIV load is high. With the introduction of highly active antiretroviral therapy (HAART), it may be questioned whether or not everyone who seroconverts to HIV will get AIDS.

HIV can weaken the immune system by attacking CD4+ T cells, which leads to immunodeficiency later on in the course of the illness [5]. One of these is the surface-adhesive CD4+ protein, to which HIV binds and enters the body. But it turns out that only having CD4+ molecules does not allow viruses to enter other cell types like monocytes and dendritic cells. Therefore, for the virus to enter cells, there must be a second entry point. As a result, it was determined that chemokine receptors serve an important function as co-receptors for HIV-1. For different cell types that HIV variants can use to infect cells, these co-receptors are available in a variety of forms. The two primary chemokine receptors reported to be essential for HIV entry are CCR5 and CXCR4 (also known as fusin).

Epidemiology

Globally, an estimated 38 million people are HIV-positive as of 2018 [4] the HIV pandemic is worst in Southern Africa. More than 10% of all HIV/AIDS patients reside in the region. Six other countries report adult HIV prevalence rates of at least 10%, while Eswatini, Botswana, and Lesotho all have rates exceeding 15%. Outside of Africa, The Bahamas has the highest prevalence rate (3.3%) [5].

The country with the highest absolute number of HIV/AIDS cases by the end of 2022 was South Africa (7.5 million cases), followed by Mozambique (2.2 million), India (2.1 million), and Nigeria (1.8 million). With a prevalence incidence of 1.3%, Nigeria has a lower rate than India, which is 0.2% lower [6]. The large number of HIV-positive individuals in South Africa is a result of the country's high disease prevalence (17.3%, one of the highest in the world). However, India's prevalence is substantially lower than that of the US and is roughly similar to that of Spain. UNAIDS identifies countries like Nigeria who have high HIV prevalence rates surpassing 1% as having generalised HIV epidemics (GHEs).

Diagnosis

Accurate and timely diagnosis of HIV infection in paediatric patients is crucial for initiating appropriate treatment. This section discusses the various diagnostic methods available, including virologic and serologic tests, and highlights considerations specific to paediatric populations.

Children vary from adults in that they have a faster rate of disease progression, high rates of viral mutation, a very high HIV-1 viral load, high rates of CD4+ cell death, and an excellent immunologic response to ART [7]. Infants, kids, and teenagers all have different clinical symptoms, and the majority of them are asymptomatic at birth and don't have any aberrant results. Since the global rollout of ART, there has been a shift in the range of opportunistic infections (OIs) from the time before ART. The spectrum of infections also varies in those on ART but non- adherent to therapy. WHO clinical criteria for presumptive diagnosis of severe HIV disease in infants and children less than 18 months of age is given below [8].

Clinical criteria for presumptive diagnosis of severe HIV disease in infants and children less than 18 months of age requiring ART in situations where virological testing is not available.

A presumptive diagnosis of severe HIV disease should be made if: The infant is confirmed HIV antibody positive; and Diagnosis of any AIDS-indicator condition(s) can be made: or The infant is symptomatic with two or more of the following: Oral thrush, Severe pneumonia Severe sepsis, Other factors that support the diagnosis of severe HIV disease in an HIV seropositive infant include: Recent HIV-related matemal death: or advanced HIV disease in the mother; CD4+ <20%, Confirmation of the diagnosis of HIV infection should be sought as soon as possible.

An integrated system of clinical, programmatic, and laboratory services that are continually evaluated for quality and outcome is needed to diagnose HIV infection in a baby or child. Children under the age of two should be treated as soon as possible after being identified as having been exposed to HIV since they can quickly decline and pass away.

The presence of maternal antibodies is all that common screening tests like the quick test and ELISA can detect, making it challenging to diagnose HIV infection in exposed infants. These tests

are therefore appropriate for children older than 18 months, and for children younger than 18 months, DNA-PCR testing utilising dried blood spots (DBS), which identifies viral DNA, is required. All paediatric diagnostic HIV testing must be done in a private setting with parental or guardian agreement after receiving counselling. Repeat DNA-PCR testing is required in breastfed infants at least 6 weeks following the end of breastfeeding in order to confirm the HIV negative result.

Major barrier to efficient management of paediatric AIDS is late detection of the HIV infection in the infants.

Minor portion of population refused to get their infant screened for HIV infection by giving reasons such as "the infant is too young to have a blood sample," "he looks healthy," "he is not ill," "this is not useful as parents are healthy," "they do not want to know if he is HIV-infected," and "it is useless to know as there is no means to take care of HIV-infected children." Different perceptions were reported: Mothers felt guilty and responsible for their infants' health, or felt the father should be the one to decide about HIV testing [9].

Antiretroviral therapy (ART) Initiation

The advent of ART has revolutionized the management of HIV infection in children.

The following significant institutions and sources frequently offer recommendations for HIV therapy in children.

- **World Health Organization (WHO):** The WHO changes its recommendations for HIV diagnosis, care, and therapy on a regular basis. This includes pediatric patients. Their guidelines are available on the WHO website in the HIV/AIDS section.
- **Centers for Disease Control and Prevention (CDC):** The US CDC offers recommendations to medical practitioners regarding several facets of HIV treatment, including the management of young patients. On their website, you can find information about recommendations, guidelines, and updates pertaining to HIV therapy for children.
- **National Institutes of Health (NIH):** The NIH publishes research and guidelines on pediatric HIV treatment through its various institutes, including the National Institute of Child Health and Human Development (NICHD) and the National Institute of Allergy and Infectious Diseases (NIAID).
- **International Antiviral Society-USA (IAS-USA):** This group provides professional advice and guidelines regarding the use of antiretroviral therapy and HIV treatment, taking into account the needs of younger patients.
- **The Pediatric Infectious Diseases Society (PIDS):** May offer recommendations or guidelines for treating infectious diseases in children, including HIV treatment.

Antiretroviral therapy (ART) is a group of drugs that block the virus's ability to replicate in different ways. It is used to treat HIV infection. In order to effectively control the virus and slow the progression of HIV, these medications are used in combination. The following are the primary categories of antiretroviral medications used in HIV treatment.

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs):

These are frequently the mainstay of many HIV treatment plans. They inhibit the reverse transcriptase enzyme, which prevents the virus from replicating. Tenofovir, emtricitabine, lamivudine, abacavir, and zidovudine are examples of common NRTIs.

Zidovudine

Considerations

Twice daily dosing (BD) is acceptable and preferred.

Dosing at the upper end of the range is recommended for CNS HIV disease, Dosing at lower end maybe preferred in settings where anaemia is prevalent.

Dose

180-240mg/m^2 per dose Twice daily [10].

Lamivudine

Considerations

Clearance in children <3 years old is increased, and minimal observed toxicity allows for higherdosing in younger children (up to 5mg/kg BD).

PK data on once daily dosing suggests acceptable troughs and overall troughs similar to BD dosing. Once daily dosing not recommended for children under 3 years.

Dose

4 mg/kg per dose Twice daily.

Abacavir

Considerations

Clearance in children <3 years old is increased, and it should therefore be used twice daily in thisage-group; once daily dosing not recommended for initiation of ART or in children <3 years but canbe used in children >3 years.

Because of potential for hypersensitivity, a substitution option should be made available.

Dose:

8-10 mg/kg per dose - twice daily.

Didanosine

Considerations

Enteric coated dosing forms are recommended rather than the buffered form. Needs to be given 1hour before or 2 hours after food.

Once daily dosing accepted over 6 years

Dose

- < 3 months 50 mg/m^2 per dose
- 3 months 120 mg/m^2 per dose twice daily.

Stavudine

Considerations

Needed as a priority product despite well recognized longer term toxicities (lipodystrophy in children and adults), as it is initially well tolerated, is safer to use in anaemia than AZT, and has lower laboratory monitoring requirements.

Avoid over-dosing wherever possible (noting recent revision to adult dosing recommendations to reduce), and especially for extended periods to minimize toxicity.

Dose

1 mg/kg per dose twice daily

Emtricitabine

Considerations

Safety and efficacy established for use in infants and children, using once daily dosing.

Dose

3mg/kg 0-3 months of age 6mg/kg for liquid forms 4.8-6 mg/kg for solid forms Once daily

Tenofovir

Considerations

Limited safety and toxicity data are available, and the dosing and safety continue to be studied in children and adolescents.

Dose

8 mg/kg which approximates, 300 mg once daily in adults Once daily.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Reverse transcriptase is inhibited by NNRTIs as well, although in a different way than by NRTIs.Nevirapine, rilpivirine, and efavirenz are examples of common NNRTIs.

Nevirapine

Considerations

A BSA based dose range of 150- 200 mg/m^2 for nevirapine is used to generate weight band dosing. Products and dosing schedules were sought that avoid dosing below minimum of 150 mg/m^2 wherever possible due to low barrier to development of HIV drug resistance.

A reduced dose is recommended for the first two weeks when initiating nevirapine treatment regimens.

Due to developmental changes in nevirapine metabolism, young children require a higher nevirapine dose relative to the NRTI components than delivered in current adult FDC combinations.

Dose

150-200 mg/m^2 per dose Twice daily.

Efavirenz

Considerations

- Because of potential for severe toxicity, a substitution option should be available.
- Dosing has not been established for children under 3 years. Approved dosing is already provided based on weight bands, and the dosing provided approximates this.
- Syrup and solid forms are not bioequivalent, with the syrup being over 30% less bioavailable. Evening dosing is preferred.

Dose

15 -18.75/kg solid form or 19.5 mg/kg syrup Once daily.

Protease inhibitors

HIV protease activity is inhibited by protease inhibitors, and this is a necessary step in the maturation of new virus particles. Atazanavir, Darunavir, and Lopinavir/Ritonavir are a few examples of PIs.

Lopinavir

Considerations

Clearance in children <3 years old is increased.

Heat-stable paediatric formulation is recently approved.

Actual exposure depends on metabolism and inter patient variability, which is considerable. Pharmacokinetic data suggests higher clearance if given with NNRTI hence WHO recommended target dosing is above approved dose. Lopinavir/ritonavir is currently the preferred PI.

Ritonovir

Considerations

Needed to use as pharmacological booster in treatment of children with a PI and for children receiving rifampicin-based anti tuberculosis therapy.

Dose

As a booster for Lopinavir: Ritonavir target doses are: 7–15 kg: 3 mg/kg 15–40 kg: 2.5 mg/kg Twice daily

Ritonavir dose and dosing frequency (once or twice daily) varies with the PI which it is combined with.

Integrase strand transfer inhibitors (INSTIs)

A more recent class of antiretroviral medications known as INSTIs prevents the integration of viral genetic material into the DNA of the host cell. Dolutegravir, bictegravir, and raltegravir are examples of common INSTIs.

Dolutegravir

Considerations

Despite excellent efficacy, safety and tolerability in adults, the effects of DTG in children and adolescents are poorly documented. DTG is approved for patients ≥12 years of age (recently anticipated at 6 years) and the IMPAACT study showed that 70% of adolescents (12 to <18 years old) treated with DTG achieve a complete viral suppression [11].

Dose

3 kg to <6 kg (<6 months)- 5mg 3 kg to <6 kg (≥6 months)-10mg 6 kg to <10 kg - 15mg.

CCR5 antagonists

CCR5 antagonists, like maraviroc, act by blocking the CCR5 co-receptor on CD4 cells, preventing HIV from entering and infecting these cells.

Maraviroc

Dose

2 kg to <4 kg: 30 mg twice daily 4kg to <6kg: 40 mg twice daily 6kg to <10kg: 100 mg twice daily.

Fusion inhibitors

Fusion inhibitors, such as enfuvirtide, block HIV from fusing with the host cell membrane, preventing entry and infection.

Enfuvirtide

Dose

Adolescent and Pediatric Dose (Ages 6–16 Years) Kids Under 6 Years Old: Not recommended for use in younger than six-year-olds.

For children under six years old, inject 2 mg/kg (maximum dose 90 mg [1 mL]) subcutaneously (SQ) into the abdomen, anterior thigh, or upper arm twice a day.

Adult and Adolescent Dose: 90 mg (1 mL) injected subcutaneously (SQ) twice daily into the abdomen, anterior thigh, or upper arm.

Antiretroviral drug selection

An overview of the various drug regimens is given in this section, along with an emphasis on the factors to be taken into account when tailoring treatment plans for pediatric patients.

Regardless of clinical or immunological stage, ART should be initiated for all children under 24 months of age who have been diagnosed with HIV infection.

Infants under 18 months old who have a clinical diagnosis of presumptive severe HIV should begin antiretroviral therapy (ART) if viral testing is not available, it is important to get HIV infection confirmed as soon as possible [12].

Antiretroviral therapy during pregnancy and delivery

ART can be used during pregnancy for maternal therapy or to stop the transmission of disease from mother to child. Antiretroviral therapy (ART) is used for both maternal therapeutic and neonatal prophylactic purposes when the HIV-positive woman satisfies the standard treatment initiation criteria for her condition [13]. ART in pregnancy will be used only for PMTCT (prevention of mother to child transmission) if there are no signs that treatment should be started. The goal of PMTCT is the only factor that influences the use of ART during delivery. ARV medications must adequately produce systemic drug levels in the fetus and cross the placenta in order to achieve a high level of PMTCT in utero. Pregnancy affects the disposition of ART through physiological changes affecting absorption, biotransformation and elimination of ARV drugs [14]. The standard of care for PMTCT is three drugs of ART throughout pregnancy, followed by intrapartum intravenous AZT in developed nations. Delaying the start of ART until the end of the first trimester of pregnancy is advised if a woman does not need it for her HIV disease, though an earlier start date may also be taken into consideration. A full schedule of prenatal PMTCT (prenatal ART beginning at the end of the first trimester plus intravenous AZT during delivery) is only available in developed countries due to cost and storage requirement concerns. For the PMTCT in resource-constrained settings, more pragmatic (e.g., oral drugs only), less intensive, and less costly shorter duration ART regimens have been developed.

These schemes include

- Beginning at 28–36 weeks gestation, mono or dual ART with AZT and lamivudine (3TC); beginning at 26–34 weeks gestation, triple ART with AZT/3TC plus abacavir (ABC), nevirapine (NVP), nelfinavir (NFV), or LPV/RTV.
- A single intrapartum dose of NVP (sdNVP) combined with an antepartum course of 3TC and AZT
- sdNVP plus oral AZT plus oral 3TC intrapartum
- sdNVP intrapartum without additional ART (no longer considered the most optimal approach for PMTCT)
- Neonatal antiretroviral prophylaxis.

In addition to complete elimination of breastfeeding, six weeks of neonatal AZT prophylaxis initiated promptly (within 6–12 hrs) postpartum is outlined for PMTCT by the perinatal ART guidelines in the US [6]. Concerns concerning the duration of AZT exposure have been raised due to the medication's capacity to cause temporary macrocytic anemia, which can develop into a clinically important condition, especially in premature infants [15]. These considerations, along with comparative pediatric studies, have led to the recommendation in Europe and the UK for a 4-week postpartum neonatal AZT prophylaxis with total elimination of breastfeeding for infants with a history of adequate prenatal and intrapartum ART [16,17]. Similar to maternal prophylaxis of MTCT, combination postpartum antiretroviral therapy (PMTCT) is thought to be more effective than monotherapy, especially in high- risk situations like non-use or irregular use of prenatal and/or intrapartum antiretroviral therapy (ART), an unsuppressed maternal viral load at delivery, and a history of HIV resistance in the mother. Few studies have prospectively assessed the use of combination antiretroviral therapy (ART) in neonates, despite the fact that in practice, the use of various combinations of ARV drugs in postpartum newborns is widely used for the scenarios described. The majority of studies that have been published to date have assessed the following combinations of ARV medications in neonates [15,18].

- AZT plus 3TC
- AZT plus NVP
- AZT plus 3TC plus NVP AZT plus 3TC plus NFV.

When compared to AZT monotherapy, recent data from a sizable international trial indicate higher rates of neutropenia and anemia associated with dual (AZT plus 3TC) and triple (AZT plus 3TC plus NFV) ART [19]. This study has led to the US to discontinue the recommendation of NFV and 3TC during the neonatal period. Instead, cases of high risk for MTCT should be considered for dual ART prophylaxis, which includes three doses of NVP (birth-48 hours, 48 hours, and 96 hours postpartum) in the first week of life [15]. Mono therapy with NVP remains an equitable alternative to AZT neonatal prophylaxis in WHO guidelines. Postnatal ARV prophylaxis is stopped in children who are exclusively fed formula after 4-6

weeks, as previously mentioned. For the duration of breastfeeding, breastfed infants—who make up the majority of newborns in HIV epidemic areas worldwide— remain at risk for MTCT. Completely stopping breastfeeding and substituting exclusively with formula feeding has not shown to be a safe or practical alternative in resource-constrained settings due to a number of financial and logistical challenges, chief among them the scarcity of clean water and the high infant morbidity and mortality linked to formula feeding [20].

In locations with limited resources The World Health Organisation advises daily NVP for newborns up to one week following the discontinuation of breastfeeding. Under the same option, 4–6 weeks of daily NVP is recommended for infants without breastfeeding or those breastfed by women on ART(20). As another option, daily AZT or NVP therapy for 4–6 weeks is recommended for neonates independent of infant feeding (breastfed or formula fed), while triple maternal ART is recommended until 1 week after cessation of all breastfeeding. The most common ART regimens for breastfeeding mothers are those with two NRTIs (ZDV, 3TC, TDF) in combination with one NNRTI (EFV, NVP) or co-formulated boosted PI (LPV/RTV), depending on availability and cost considerations [20].

Paediatric antiretroviral drugs

Throughout childhood, there are notable changes in the PK and pharmacodynamics (PD) of ART due to the development and maturation of organ systems involved in the absorption, metabolism, and elimination of ARV drugs. In order to achieve similar systemic ARV exposures, younger children need a much higher dose of ARV drugs per weight or body surface area than adults do due to their faster clearance of ARV drugs. The PK and PD of ART in children can be influenced by a number of factors, including co-morbidities and nutritional status, in addition to the developmental changes in the PK of ARV drugs. Significant anemia, decreased weight, and delayed growth in HIV-positive children are common obstacles to antiretroviral therapy (ART) in settings with limited resources [21,22]. The absorption of ARV medications may be impacted by concurrent conditions like hepatitis, malabsorption, and diarrhea. Malnutrition-related metabolic and endocrine disorders may affect how lipohilic ARV medications, like PIs, are distributed and cleared from the body as a whole [23]. The selection of ART for children is further complicated by therapeutic interventions for co-morbidities like tuberculosis that carry a high risk of drug-drug interactions. Although the development of pediatric ART dosing guidelines has been largely successful, there is still a shortage of information regarding the developmental changes in ARV PK/PD in children. When pediatric patients experience drug-drug interactions and ART failure, therapeutic drug monitoring (TDM) of ARV medications should be taken into consideration, especially in cases where adherence failure has not been proven [24].

Monitoring and adherence support

Regular monitoring of viral load, CD4 count, and drug toxicity is essential for optimising treatment outcomes in paediatric patients. This section discusses the recommended monitoring parameters and strategies for promoting adherence to ART in children, including the involvement of caregivers and the role of multidisciplinary healthcare teams.

Routine viral load monitoring of infants and children diagnosed with HIV should be prioritized for several reasons. Data from systematic reviews and meta-analyses from LMIC, along with data from national viral load (VL) monitoring programs, show that infants and children have lower rates of viral suppression than adults do. There aren't many kid-friendly antiretroviral medications or tasty formulations available. Furthermore, children's unique emotional and developmental problems can complicate the daily administration of medications, make adherence difficult, and make it difficult to achieve sustained viral suppression [25]. The efficacy of early ART for achieving viral suppression, promoting immune reconstitution, and reducing morbidity and mortality in children is well- established [26,27]. Nevertheless, information on the prevalence of VL suppression in kids receiving routine monitoring in LMICs, as opposed to more focused VL testing of kids suspected of treatment failure, was not available until recently. Early findings from large representative samples and age- disaggregated reporting from national routine VL monitoring programs in Kenya and Uganda show that rates of viral suppression are lower in infants, children, and adolescents than in adults [28,29]. Using nationally representative data from routine viral load monitoring, the overall rate of viral suppression among children in five eastern-southern African countries was 62% [30]. Former research from one or more LMIC facilities has reported similarly low rates of viral suppression [31,32]. Using data from nine studies conducted in resource-constrained settings between 1997 and 2008, Ciaranello., *et al*. [10]

conducted a meta-analysis in 2009 and discovered that the pooled estimate for 12-month viral suppression(HIV RNA <400 copies/mL) in children under the age of 15 was 70%. (95% confidence interval [CI]: 67–73) [33].

CD4 count

When HIV first appeared in the 1980s, developments in flow cytometry and the manufacturing of monoclonal antibodies came together, making CD4+ T cell counting (also known as CD4 counts) the primary immune monitoring technique. The absolute CD4 count is more commonly used than the CD4 percentage (the percentage of lymphocytes expressing CD4) or the CD4:CD8 ratio because the former has been used in the majority of drug trials and natural history studies that have suggested thresholds for chemoprophylaxis. Additionally, physiological expansions of the CD8+ population, such as in response to HIV itself, may cause perturbations to the CD4:CD8 ratio. Cell populations can be counted using flow cytometers based on size (forward scatter), granularity (side scatter), and staining with up to four monoclonal antibodies, each of which is conjugated to a distinct color stain. In the days of outdated technology, the operator had to physically identify populations—or "gate" them—that contained CD4+ cells in order to determine their percentage. Using the so-called "two platform approach," this percentage was then correlated with the absolute lymphocyte count obtained from haematology counters to determine the absolute CD4 count. Each of these two procedures has the potential to produce an error.

Debris and non-lymphoid cells may contaminate manually generated lymphocyte gates. The technology available for flow cytometry will determine how this is resolved [34].

Double staining of CD3 with CD4 or CD8 allows the exclusion of CD3− CD4+ (monocytes) and CD3− CD8+ (natural killer cell) populations [35].

With two colour cytometry, gating on an initial sample for CD45+ (leucocyte common antigen) and excluding CD14+ (monocyte marker) cells improves the purity of the subsequently counted lymphocytes, [36] but requires extra processing.

With three colour cytometry, simultaneous gating on CD45 and side scatter allows determination of two markers of interest (for example, CD3 and either CD4 or CD8) [37]. The presence of anti-CD3 allows a consistency check for the total T cell count.

One of the main sources of error in separately derived lymphocyte counts has been found to be the requirement for up to two additional steps (the use of a haematology analyser and differential white cell count) [35], Certain flow cytometers can produce absolute counts directly, and these are now the preferred methods. Examples of these techniques include precision fluidics and the addition of a known number of fluorescent particles for each volume of blood [38]. A smooth transition requires audit and liaison to prevent unexpected changes in absolute CD4 values that could arise from switching from older technologies to these "single platform CD4 methods".

CD4 interpretation

CD4 counts are impacted by various factors. For instance, the CD4 count can fluctuate by up to 50% throughout the day [39]. It is important to remember that a few of the pathological conditions can resemble HIV infection clinically. These modifications have the following effects.

It is best to perform CD4 counts at regular intervals throughout the day and to avoid doing so when sick.

It is recommended to obtain three baseline values in the initial weeks following the diagnosis. Counts can then be performed every three months after the onset of symptoms or every six months in patients who are asymptomatic. When a patient's treatment is changing, more frequent testing makes sense. HIV infection cannot be diagnosed by CD4 counts. The author's observations and anecdotal data indicate that this does happen, but substituting CD4 counts for HIV serology is not clinically valid [38,40].

For epidemiological purposes, all HIV-positive patients with a CD4 count < 200×10^6/litre are now included in the USA's expanded definition of AIDS cases. In the UK, HIV staging is determined by clinical factors, and this practice is not advised. But when the CD4 count declines, the likelihood of contracting particular opportunist infections rises. Pneumocystis pneumonia, for instance, is uncommon unless the CD4 count is less than 200×10^6/litre [42]. Chemoprophylaxis was the main factor in the decline in HIV infection mortality before highly active antiretroviral regimens were

available. It can reduce the risk of pneumocystis pneumonia by up to 80% in patients with a CD4 count below this threshold. Similar recommendations have been made for additional preventative measures.

Compared to adults, newborns have higher CD4 counts, which peak at six months of age [37]. When trends over time are available, the CD4 count in children with HIV infection can be used to determine whether antiretroviral agents are indicated and is a good predictor of outcome [42,43]. There are no established CD4-based recommendations for the prevention of pneumocystis pneumonia in children, but it is obvious that adult values should not be applied. Regardless of CD4 counts, primary prophylaxis may be recommended because many children with HIV infection have never been exposed to certain pathogens [43]. Antiretroviral drug trials have frequently used changes in CD4 counts as end points to speed up outcomes and prevent irreversible harm. Nevertheless, it is possible that CD4+ lymphocytes are not important players at every stage of infection [45] and that CD4 counts do not accurately reflect T cell function, as there is sometimes a negative correlation between CD4 counts and clinical outcome. CD4 counts are generally improved and viral loads are decreased by highly active antiretroviral therapy, or HAART. However, once CD4 counts have increased above the thresholds, people on HAART may experience opportunist infections. For instance, even after the CD4 count rises above 100×10^6/litre, there is still a chance of cytomegalovirus (CMV), presumably because HIV permanently destroys certain T cell clones [46] [47]. These opportunist infections typically manifest abnormally and happen during the first three months of HAART therapy. Other options, like CMV polymerase chain reaction (PCR) monitoring, only provide partial details regarding when CMV prophylaxis should be administered [48]. Either new CD4 count thresholds for chemoprophylaxis on HAART or tests of susceptibility to particular pathogens are needed to overcome this kind of issue.

Other phenotypic changes have been investigated as surrogate markers in HIV infection. For example, the expression of CD38, a marker of cytotoxicity, is increased on CD8+ lymphocytes in HIV infection [49]. CD38 expression is associated with a poor prognosis, independent of CD4 count [50] especially when the number of CD38 molecules on each CD8 cell is estimated to be high [51]. CD38 expression returns towards normal during antiretroviral treatment [52], but the use of CD38 has not been widespread however.

Conclusion

In summary, the field of managing HIV in pediatric patients is dynamic and ever-evolving, necessitating a thorough and multidisciplinary approach. With the passage of time, considerable progress has been made in comprehending the particular difficulties posed by HIV in children, which has resulted in the creation of antiretroviral medications that work well for this patient population. The literature review highlights the significance of timely diagnosis, effective antiretroviral treatment initiation, and continuous surveillance of viral load and immune status.

Optimizing pediatric HIV management outcomes requires integrating nutritional interventions, adherence counseling, and psychosocial support. Furthermore, the investigation of new treatment approaches, like long-acting antiretroviral combinations and creative preventative techniques, demonstrates the scientific community's dedication to enhancing the lives of children living with HIV. Notwithstanding the advancements, certain obstacles still exist, such as the enduring stigma, restricted healthcare accessibility in specific areas, and the possibility of medication resistance. To solve these problems and keep improving pediatric HIV management techniques, ongoing research is crucial. In order to guarantee equitable access to care and realize the ultimate goal of an HIV-free generation, collaborative initiatives involving healthcare providers, researchers, policymakers, and communities are essential. In conclusion, despite notable advancements in the treatment of pediatric HIV, ongoing work to improve prevention, diagnosis, and treatment options is still necessary. Through a focus on comprehensive care, attention to social determinants, and international cooperation, we can work toward a day when children impacted by HIV not only survive, but also flourish and lead happy, healthy lives.

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