Chapter

Immune Dysfunction and Antiretroviral Therapy Challenges in Children and Adolescents Living with Human Immunodeficiency Virus

Mirvat Said and Adam W. Bartlett

Abstract

Human immunodeficiency virus (HIV) infection results in progressive decline in immune function ultimately leading to acquired immunodeficiency syndrome (AIDS) characterised by increased susceptibility to opportunistic infections and malignancies. In addition, it causes immune dysfunction, which manifests as a persistent inflammatory state due to dysregulation of cytokine production. Antiretroviral therapy (ART) not only improves immune function but also mitigates systemic immune activation associated with disease progression. Early initiation of ART in children living with HIV has led to a growing cohort surviving into adolescence and beyond. As such, they will experience lifelong exposure to an array of physiologic processes associated with systemic infection, immune dysfunction and antiretroviral medications. This leaves them not only susceptible to a range of morbidities associated with chronic inflammation, immune dysregulation, and drug toxicity but also vulnerable to treatment fatigue leading to issues with treatment adherence and engagement in care. Children experience additional barriers to maintaining suppressive ART due to limited paediatric-friendly formulations that are palatable and contribute to regimen complexity. Tolerability and durability of long-term ART are integral in optimising outcomes for children and adolescents living with HIV and maximising viability of future ART regimens throughout adulthood.

Keywords: HIV, antiretroviral therapy, children, adolescents, paediatric formulations, adherence, HIV drug resistance, morbidity, immune dysfunction

1. Introduction

In 2018, an estimated 2.8 million children and adolescents aged between 0 and 19 years were living with human immunodeficiency virus (HIV) globally [1]. There were approximately 1.6 million adolescents between the ages 10 and 19 years, including an estimated 190,000 with newly infected HIV in 2018, majority of whom reside in sub-Saharan Africa [1, 2]. Although the number of new HIV infections among children less than 10 years of age has declined by 41% from an

estimated 280,000 in 2010 to an estimated 160,000 in 2018, mostly due to successful strategies for prevention of mother to child transmission (pMTCT), we are far from meeting the global target goals of less than 20,000 new paediatric infections by 2020 [1, 3].

HIV targets CD4 T cells that play an important role in both humoral and cell-mediated immune responses to pathogens [4]. HIV infection causes immunodeficiency through depletion of CD4 T cells, defective function of CD4 T cells and macrophages, and dysregulation of cytokine production. This results in immune dysfunction, which manifests as increased susceptibility to opportunistic infections and a heightened immune activation state [5]. HIV disease progression in children not on ART is rapid compared to adults, and is associated with a mortality of up to 52% by the age of 2 years in sub-Saharan Africa [6].

The Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the 90–90-90 targets in 2014 with the aim to diagnose 90% of all people with HIV, provide ART to 90% for those diagnosed, and attain viral suppression in 90% of those treated by 2020 to end the AIDS epidemic by 2030 [7, 8]. In support of the targets, the World Health Organisation (WHO) implemented the "treat all" policy in 2015 that recommends initiating anti-retroviral therapy (ART) as soon as practical to all people with HIV infection regardless of age or disease stage with the aim to improve quality of life, maximise immune preservation and potential for immune reconstitution, and reduce risk of transmission [9]. Despite this, only 56% of children under the age of 15 years were accessing treatment in 2018 with considerable geographic variation in ART coverage (**Table 1**) [10]. Coordinated efforts to speed up access and availability of HIV treatment for children by stakeholders and development of optimal paediatric formulations still lags behind that of adults.

Early initiation of ART in children living with HIV has led to a growing cohort surviving into adolescence and beyond, transforming the paradigm of HIV infection from a terminal disease into a chronic condition [11, 12]. This has created additional management challenges related to long-term ART-associated morbidity and treatment fatigue. Of growing concern, despite treatment scale up, HIV mortality is increasing among older adolescents (15–19 years) whilst mortality in other age groups is declining [13]. This reflects gaps in adolescent HIV care to address complex management challenges faced by this vulnerable group including lack of engagement in care and poor treatment adherence [13].

To achieve the global targets, HIV programs need to address management challenges in children and adolescents including scaling up access to paediatric-friendly

Region	Living with HIV N	Receiving antiretroviral therapy N (%)
Asia and the Pacific	110,000	87,908 (80)
Caribbean	11,000	4982 (45)
East and Southern Africa	1,100,000	679,921 (62)
Latin America	31,000	15,861 (51)
Middle east and North Africa	9900	3666 (37)
West and Central Africa	450,000	132,216 (29)
Global	1,700,000	947,243 (56)

Complete data not reported for Eastern Europe, Central Asia, Western and Central Europe, and North America.

Table 1.
Estimates of children (0–14 years of age) living with HIV and receiving antiretroviral therapy in 2018 (UNAIDS) [10].

ART formulations, developing strategies to maximise engagement in care and ART adherence, and improve capacity to recognise and manage treatment failure to optimise ART durability and tolerability [8].

This chapter gives an overview of HIV-related immune dysfunction and discusses management challenges for children and adolescents living with HIV. It further outlines the multifaceted approaches to address these challenges to optimise outcomes for this vulnerable population.

2. Immune dysfunction in children and adolescents with human immunodeficiency virus

HIV binds to receptors on CD4 T cells, internalises into the cell and replicates itself [14]. Through this process, the virus progressively destroys the infected CD4 T cells resulting in depletion of the cells and immunodeficiency, thereby increasing susceptibility to opportunistic infections (**Figure 1**). Destruction of CD4 T cells can be countered by the generation of new CD4 T cells in the setting of immune activation, however this process may not restore all functionally important CD4 T cells and is not sustainable in the long-term [15]. Furthermore, HIV-related immune system activation and chronic inflammation has been associated with neurodevelopmental impairment, cardiovascular disease, and clinical HIV disease progression regardless of the CD4 count [16, 17].

ART arrests the HIV life cycle at various stages, thereby inhibiting replication of the virus. This restores cellular immunity resulting in a decline in incidence of opportunistic infections and improves survival. Following ART initiation, the incidence of the majority of opportunistic infections decreases to less than 2.5% [19]. ART has also been shown to reduce systemic immune activation that reduces inflammatory-mediated disease progression [5].

Early initiation of ART in children is critical for immune reconstitution and long-term immune preservation. Mathematical modelling using data from large

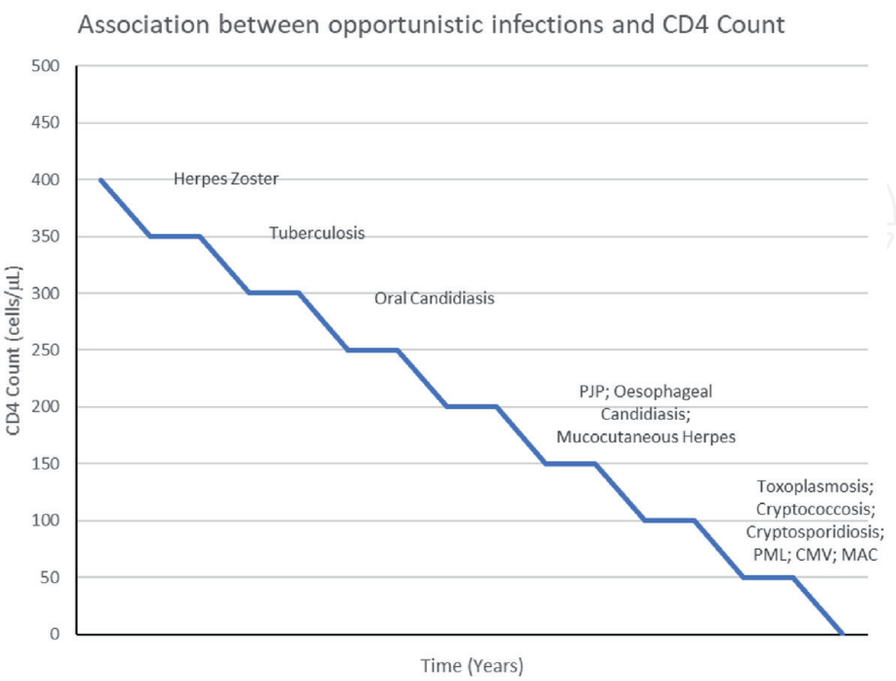

Figure 1.
Association between opportunistic infections and CD4 count [18]. CMV: Cytomegalovirus; MAC: Mycobacterium avium *complex; PJP:* Pneumocystis jirovecii *pneumonia; PML: Progressive multifocal leukoencephalopathy.*

European and African cohorts indicate that both age and CD4 count at ART initiation are important determinants of CD4 cell recovery [20, 21]. Children initiating ART under the age of 5 years have better potential for CD4 count recovery, with the potential for long-term CD4 count recovery diminishing every year after the age of 5 years that ART is initiated.

3. Antiretroviral therapy challenges in children and adolescents

There are limitations to paediatric-friendly ART formulations that pose important obstacles to maintaining good adherence in children. Most available paediatric ART formulations have poor palatability and constitute complex regimens [9]. Children often have to take a combination of pills and liquid formulations with short dosing intervals making it challenging for caregivers to administer. Fixed dose combinations (FDCs), which combine two or three antiretroviral medications have been shown to improve adherence [9]. Nonetheless, there are few available FDCs in non-pill form, limiting administration to older children who can swallow large pills. Complex storage and transportation is another challenge particularly with the liquid formulations that require cold chain storage [9].

ART drug development for children still lags behind that of adults despite major achievements in improving access to ART worldwide. There are a number of barriers slowing drug development for children. These include, lack of economic incentives for manufacturers contributed by the small paediatric market, with children making up less than 10% of people living with HIV and declining numbers of new paediatric HIV infections. The technical and pharmacokinetic complexities related to development of formulations that are safe, palatable and allow dosing across various ages and weight is challenging, requiring extensive research. Furthermore, outdated procurement practices and gaps in supply chains, delay in regulatory approvals at an individual country level, and stagnant government policies can result in further delay in uptake of new ART into treatment programs [11, 12].

The WHO ART recommendations for children are evolving with development of new antiretroviral medications. Most recently in 2018, WHO updated its treatment guidelines and now recommends the new integrase strand transfer inhibitor (INSTI)-based ART regimens including dolutegravir (DTG) for children older than 4 weeks of age and raltegravir (RAL) for neonates as a first line option (**Table 2**) [3]. INSTIs are comparatively efficacious, have a high barrier to resistance, and are better tolerated than protease inhibitors (PIs). However, the use of DTG is restricted by the only available DTG formulation (50 mg tablet) being approved for use in children who are at least 20 kg, with DTG dosing guidance for children less than

	Preferred	**Alternative**	**Special circumstances*****
Neonates	AZT + 3TC + RAL	AZT + 3TC + NVP	AZT + 3TC + LPV/r
Children	ABC + 3TC + DTG*	ABC + 3TC + LPV/r ABC + 3TC + RAL	ABC + 3TC + EFV** AZT + 3TC + EFV** AZT + 3TC + LPV/r AZT + 3TC + NVP AZT + 3TC + RAL ABC + 3TC + RAL

**DTG approved in children > = 20 kg.*
***From 3 years of age.*
****Where no alternatives are available.*

Table 2.
WHO 2018 recommendations for first line paediatric antiretroviral regimens [23].

20 kg still under development [3]. This along with the limited manufacturing capacity and cost limit accessibility of these regimens limit the use of INSTIs in children.

In the interim, lopinavir/ritonavir (LPV/r)-based regimens remain the only available first line ART for infants and young children as recommended by WHO. They are superior and more effective than the non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine (NVP) and efavirenz (EFV) [11]. There is also comparatively high resistance to NNRTIs, particularly in children whose mothers received NNRTIs to prevent mother to child transmission, which further limits the use of this drug class as first line [22]. **Table 2** illustrates the WHO recommended first line paediatric ART regimens for neonates and children.

LPV/r is available as an oral solution, heat stable tablets, oral pellets and oral granules. The LPV/r liquid formulation was developed for ease of administration in younger children and infants. However, the liquid formulations have issues with palatability and require caregivers to measure out the precise amount of liquid. Additionally, liquid formulations need cold chain storage, which can be an obstacle in resource limited settings [9]. In 2015, the USA food and drug formulation tentatively approved LPV/r oral pellets, and subsequently approved LPV/r oral granules in August 2018 [24]. The pellet and granule formulations offer advantages over the liquid form as they are easy to administer across dosing ranges, easy to store and transport, and palatable. However, there has been a slow uptake of these formulations in low and middle-income countries due to limited manufacturing capacity, making policy makers reluctant to transition to LPV/r based ART regimens [24].

Alternative PIs such as darunavir/ritonavir (DRV/r) may be an option for children above 3 years of age who have failed first line LPV/r-based treatment. Studies have shown darunavir is not only effective in ART paediatric-experienced patients but also has low rates of resistance among children with prolonged PI exposure [25]. However, DRV/r is not recommended for children under the age of 3 years due to its toxicity profile. Although DRV/r is available as an oral solution, there is a paucity of data regarding its tolerability in young children.

With evolving optimal, new antiretroviral treatment options, children continue to be exposed to several classes of ART throughout their lives. Appropriate sequencing of age- and weight-based ART regimens, along with long-term treatment-related morbidities remains unclear and needs ongoing evaluation.

The innovations for paediatric-friendly formulations should strive towards safe, effective and palatable ART for children [9]. Several strategies have been put in place to improve development and access to paediatric-friendly formulations including:

- The Global Accelerator for Paediatric Formulations (GAP-f), a new mechanism working to support and formalise collaboration across sectors, and accelerate both upstream (strict drug regulatory authority filing and approvals, formulation development by innovators and generics, and generic manufacturing) and downstream processes (national treatment policy, management of supply chains and market uptake) to ensure that children are able to access the new optimal paediatric antiretroviral medications [26].

- Improving incentives for paediatric formulation development. Pharmaceutical companies Cipla and Mylan that developed LPV/r pellets and granules respectively, have committed to increase supply to meet the growing demand of these formulations until DTG generic formulation and dosing for children less than 20 kg becomes available. It will be essential for the Antiretroviral Procurement-Working Group (APWG) to regularly keep track of demands to ensure supply is not stripped [3].

- Investment in development of palatable, safe and effective antiretroviral medications and simplified regimens for ease of administration. FDC, ideally once a day, formulations would be beneficial in particular LPV/r-based regimens for children who cannot swallow tablets and potentially serve as an alternative for children who do not tolerate DTG (**Table 3**) [3]. Development of a FDC in the pipeline is ABC/3TC/DTG, a WHO recommended regimen, in a single formulation which will simplify treatment. However, there remains uncertainty as to the timing of its availability on the market and dosing guidance for children under 20 kg [3].

- Accelerating availability of DTG dosing for infants and young children through provision of incentives. Recently Unitaid provided financial incentives to the pharmaceutical companies Mylan and Macleods working to develop a generic DTG 10 mg dispersible tablet, which would be suitable for children <20 kg [3]. ViiV also committed to filing their 5 mg dispersible DTG with the US Food and Drug Administration (FDA) (**Table 3**).

- National programs should rapidly take up new formulations as they become available and timely provide necessary training to health care workers responsible for prescribing these medications.

Although there has been some progress with development of paediatric-friendly formulations discussed above, accelerating these processes remains a priority in order to achieve treatment success. Ongoing research and regular surveillance on access and uptake of the new ART formulations at national and global level is vital to recognise and address challenges that may arise. Additionally, longitudinal studies are needed to examine the long-term effects of exposure to several classes of ART in the paediatric population and optimal sequencing strategies of ART to limit treatment failure.

3.1 Non-adherence to antiretroviral treatment among children and adolescents

ART leads to improved survival and reduced HIV transmission rates, however high levels of adherence are required for sustained effects. Adherence to antiretroviral therapy is critical to achieve virological suppression, immune reconstitution and ultimately improved clinical outcomes among children and adolescents living with HIV [27]. Sub-optimal adherence includes missed doses, treatment interruptions or discontinuation, and sub-therapeutic dosing [28]. Non-adherence to ART is not only a barrier to achieve treatment success but is also a driver of resistance limiting future treatment options, and potentially increasing the risk of secondary transmission of drug resistant virus.

Adherence is a complex, dynamic process that can vary throughout the course of treatment and needs to be assessed continuously [29]. Adherence behaviour is influenced by multiple factors that can interplay with each other at different stages. These include patient factors, family and carer factors, patient-provider relationship, socio-cultural and medication related factors [28, 29]. It is therefore important to work closely with family, caregivers, and children and adolescents to best understand the barriers to adherence specific to the individual in order to provide tailored support.

Assessment of adherence should be routine with every clinic visit. A systematic review on ART adherence in adolescents with HIV found almost 40% are non-adherent to treatment [30]. In resource-limited settings, the range of ART adherence has been reported from 49–100% [29]. A contributing factor to this wide

Formulation	Q3 2019	Q4 2019	Q1 2020	Q2 2020	Q3 2020	Q4 2020
LPV/r			Cipla pellet and Mylan granule capacity expansion			
ABC/3TC/ LPV/r	Cipla FDA filing		Mylan FDA filing	Cipla FDA approved (t)	Mylan FDA approved (t)	
DTG		ViiV DTG 5 mg DT FDA filing	Mylan and Macleods DTG 10 mg DT scored FDA filing		ViiV DTG 5 mg DT FDA approval	Mylan and Macleods DTG 10 mg scored DT FDA approval (t)

3TC: Lamivudine; ABC: Abacavir; DT: Dispersible tablet; FDA: Food drug administration; LPV: Lopinavir; Q: Quarter; r: Ritonavir; (t): tentative.

Table 3.
Estimated timeline for development of key paediatric antiretroviral therapies [3].

variation is the lack of standardised methods for measuring adherence. In most instances, adherence is measured subjectively by self or caregiver reporting, and hence is subject to self-enhancement and recall bias. Objective measures of adherence are costly and include HIV viral load, pill counting, electronic dose monitoring and drug detection in biological samples [13, 28, 29]. Discrepancies between pill count and viral load results of 40% have been reported [29].

3.1.1 Barriers to antiretroviral therapy among adolescents living with HIV

Adolescence is a period of dramatic neurocognitive and physiological change and often includes experimentation with sexual behaviour, alcohol and recreational drug use. Furthermore, there is a decrease in the engagement of health care services that may influence adherence [12, 30]. The rising mortality for older adolescents (15–19 years) living with HIV has been attributed to complex challenges with ART adherence and poor retention in care [30].

Several factors contribute to adherence behaviour in this age group. These include [27]:

- Lifestyle barriers such as forgetting to take medications, worrying about disclosure of HIV status, and varied schedules (e.g., schooling)

- Physical factors such as feeling well that may result in complacency and neglecting to take antiretroviral medications.

- Medication related barriers including: (i) treatment fatigue, an important factor particularly in adolescents with perinatal HIV infection who have experienced multiple ART regimens over a prolonged period; (ii) complexity of ART regimens (e.g., pill burden and frequent dosing); (iii) toxicities and adverse effects associated with ART that lead to a reluctance in taking medications.

- Lack of health literacy, poor treatment knowledge and/or understanding of the importance of treatment adherence.

- Disclosure status, including non-disclosure of HIV status to adolescents with perinatal HIV infection by caregivers.

- Structural factors such as lack of transport to travel to the clinics to obtain medications [27].

3.1.2 Barriers to antiretroviral therapy among children with HIV

The obstacles to adherence in children include limited paediatric-friendly formulations (as previously discussed), barriers associated with caregivers that includes forgetting doses, incorrectly measuring liquid formulations, and changes in routine resulting in delays in administration. Some caregivers place responsibility for managing medications to older children before they are developmentally prepared to undertake such a task. Socio-cultural factors that influence adherence across the age groups include poverty, violence, substance abuse, poor mental health and lack of social supports.

3.1.3 Interventions to improve adherence to antiretroviral therapy in children and adolescents

Interventions to improve adherence should be tailored to the individual's needs. Strategies to improve adherence can be grouped as medication-related, patient/family-related, and health care provider-related strategies.

3.1.3.1 Medication-related strategies

- Efforts should be made to simplify regimens with regards to the number of pills or volume of liquid required to be administered and reduce dosing frequency. When feasible, once daily FDC antiretroviral regimens should be prescribed to lessen pill burden and hence improve adherence particularly for older children and adolescents [28].

- Pill swallowing training [28, 31].

- Adherence support through medication education, blister packs and refill reminders.

- Wider access to paediatric-friendly formulations that are palatable.

- Minimising drug toxicities through regular monitoring for adverse effects and potential drug–drug interactions, and a proactive approach in trialling different dosing strategies or switches in ART regimens as required (if feasible).

3.1.3.2 Patient/family-related strategies

Health care providers should evaluate potential barriers to adherence, discuss goals of therapy, importance of optimising adherence, and strategies to support adherence prior initiating ART [28]. Demonstration of drug administration equipment such as use of syringes and medication cups, and ensuring supply of these is important. Provision of information and adherence tools such as written and visual aids may be useful, however this should take into consideration literacy levels of the caregiver.

The use of behaviour modification techniques such as positive reinforcements and provision of incentives to encourage medication compliance can be effective. Trained community outreach workers can provide directly observed therapy and closer adherence support to children with poor adherence particularly those living in regional or remote settings [28]. This can be resource intensive, and therefore not a sustainable long-term solution in low- and middle-income countries. Early recognition and treatment of mental health disorders such as depression, which may impact adherence, should be addressed. This will depend on availability of appropriate mental health services.

In instances where the child has not been informed of their HIV status, timing of HIV disclosure should be discussed with the caregivers. A systematic review evaluating ART adherence and disclosure demonstrated mixed results, with some studies showing improved adherence while other studies finding worse adherence [28, 32]. The decision to disclose HIV status should take into consideration the needs of the child and family, cognitive capacity of the child and psychosocial situation.

For adolescents living with HIV, it is paramount to engage them in management decisions. Use of electronic devices to support adherence such as mobile applications that serve as reminders to take medications and sending text message reminders may be useful. A systematic review found the two most effective interventions were a phone-based counselling approach with adherence monitors and weekly individual and family counselling [13].

3.1.3.3 Health care provider related strategies

Health care providers can improve adherence by establishing a rapport with the patient and family, fostering a trusting relationship and encouraging open communication.

Creating child and adolescent centred multidisciplinary health care settings has been shown to improve treatment outcomes. Adolescent-friendly clinics providing peer counselling, peer navigators and psychosocial supports at clinics and school have demonstrated substantial improvement in retention of adolescents and young adults living with HIV [13]. Such a service also presents a supportive environment to discuss adherence barriers, provide reproductive health education, mental health and disclosure supports, and social activities to promote not only adherence but also retention.

Factors that influence adherence are complex and dynamic, and need to be continuously assessed [29]. A multidisciplinary approach to address adherence challenges is necessary. There remains a paucity of evidence supporting interventions that improve adherence particularly in adolescents. As such, there is a need for evidence-based innovative interventions that are feasible, sustainable and importantly tailored to the individual patient. Ultimately, this will improve treatment outcomes, reduce resistance to ART and be an important step forward towards achieving global targets [13].

3.2 Antiretroviral treatment-related morbidity

The benefits of early initiation and improved access to ART are well recognised, resulting in significant reduction in HIV related morbidity and mortality. Nonetheless, children and adolescents with early exposure to ART experience an array of multisystem morbidities including metabolic complications, increased risk of cardiovascular disease, and neuropsychological challenges. In this section, we discuss morbidities associated with ART faced by children and adolescents.

3.2.1 Metabolic complications

Lipodystrophy syndrome involves redistribution of body fat, which can manifest as lipoatrophy (decrease subcutaneous fat in the face and limbs) with or without central adiposity (lipohypertrophy) [33]. The prevalence of lipodystrophy among children living with HIV can range from 1–57% [34–36]. Studies from sub-Saharan Africa reported a lipodystrophy prevalence of 27–30% among children aged 1 to 18 years, with older children and use of stavudine (d4T) being major risk factors [33].

The pathogenesis of ART-related lipodystrophy is not well understood and felt to be multifactorial including direct effects on lipid metabolism, mitochondrial toxicity and genetic predisposition. Lipodystrophy is a complication of the NRTIs including d4T and zidovudine (AZT). PIs have also been implicated but to a lesser extent. Lipodystrophy has been described to most likely develop during puberty, and such body changes can result in stigmatisation potentially leading to poor adherence and treatment failure.

The diagnosis of lipodystrophy is usually clinical, particularly in resource-limited settings. Anthropometric measurements may be used, which are inexpensive but require experience and standardisation. The use of dual energy X-ray absorptiometry to assess fat distribution is restricted by cost in resource-limited settings [33]. Active clinical surveillance for fat maldistribution particularly in children receiving antiretroviral drugs associated with lipodystrophy and monitoring of lipid profile is necessary.

Insulin resistance and dyslipidemias are commonly linked to lipodystrophy, potentially increasing the lifetime risk of cardiovascular disease. PIs have been associated with elevated triglycerides, low-density lipoprotein cholesterol and total cholesterol. Children receiving LPV/r have been shown to have higher low-density lipoprotein cholesterol and triglyceride levels compared to children receiving NVP [37]. Although the long-term risk of cardiovascular disease in children on ART remains uncertain, the observed elevation in cholesterol levels at a young age is a predictor of long-term risk of premature atherosclerotic disease. Lipid profiles should be obtained from children and adolescents prior initiation of ART and ideally monitored every 6–12 months.

Insulin resistance is less common in children compared to adults. Impaired glucose homeostasis has been reported in 8–35% of children with HIV on ART, which includes impaired glucose tolerance, impaired fasting glucose and type 2 diabetes mellitus [33]. Prolonged exposure to high insulin levels may increase the risk of type 2 diabetes mellitus, a risk factor for cardiovascular disease. Management of insulin resistance includes lifestyle modifications (e.g., diet and exercise), as well as switching to a PI-sparing regimen.

3.2.2 Cardiovascular disease

Cardiovascular complications of HIV infection was recognised early in the epidemic particularly in adults. Evidence suggests children and adolescents with perinatal HIV infection may be at risk of cardiovascular disease due to long term viral effects and exposure to certain classes of ART, especially NRTIs and PIs [33].

Potential cardiovascular risk factors for children with perinatal HIV Infection include dyslipidaemia associated with PIs, as well as heightened vascular inflammation and endothelial dysfunction that may predispose to future atherosclerosis, however supporting data remains limited [33]. HIV related cardiomyopathy has been reported as a potential cardiovascular complication, with a suggested pathogenesis involving mitochondrial toxicity associated with NRTIs (e.g., zalcitabine,

didanosine (ddI), d4T and AZT), viral cytopathic effects on cardiac myocytes, and increased cytokine production within the myocardium [38].

Children with perinatal HIV infection remain at risk of long-term cardiovascular disease and thus warrant close surveillance [38]. This may be a challenge in resource-limited settings where diagnostic screening for cardiovascular disease may not be readily available. Therefore, an emphasis should be placed on prevention strategies such as lifestyle modifications, whilst more cost-effective cardiovascular monitoring needs to be evaluated [33].

3.2.3 Lactic acidosis

Hyperlactatemia is a well-known complication of ART. It can vary in severity from asymptomatic to life threatening. In children, the estimated prevalence of mild to moderate hyperlactatemia is 35–50%, with severe forms being rare [33].

Lactic acidosis has been associated with NRTI-induced mitochondrial toxicity. D4T and ddI have the greatest effect, with AZT, 3TC, tenofovir disoproxil fumarate (TDF) and abacavir (ABC) having a lesser effect on the mitochondria. Most children with hyperlactatemia are asymptomatic [33]. The clinical presentation of lactic acidosis is non-specific and can include malaise, abdominal pain, vomiting, muscle weakness and dyspnoea. Supportive laboratory findings include elevated transaminases, lactate dehydrogenase deficiency, amylase, lipase, increased anion gap on venous blood gas and a raised lactate level. Diagnosis requires a high index of clinical suspicion and confirmed with raised venous lactate level [33].

Management of lactic acidosis involves ceasing the offending antiretroviral agent and switching to an agent that is less likely to cause mitochondrial toxicity. In severe forms, NRTI–sparing regimens are advisable [33].

3.2.4 Bone disease

Children and adolescents with perinatal HIV infection are considered at increased risk for lower bone mineral density (BMD) due to the effects of a chronic viral infection and exposure to ART (particularly TDF), though the evidence is mixed [38]. Some studies illustrate significant BMD loss among children treated with TDF-containing salvage regimens [39, 40], whilst other studies demonstrate no association [38]. Other risk factors associated with low BMD include advanced HIV stage and a high viral load [33]. Furthermore, HIV infection is an established cause of pubertal delay which may influence bone mass and subsequent risk of osteoporosis and fractures. Long-term use of certain contraceptives such as depot medroxyprogesterone acetate may contribute to loss of BMD in adolescent females [41].

Longitudinal data are required to further evaluate bone density changes through puberty while on ART to guide treatment regimens and identify bone disease among children and adolescents with perinatal HIV infection [38]. In addition, further exploration to identify interventions to minimise the long-term risk of osteoporosis are needed.

3.2.5 Psychological complications

Children and adolescents with perinatal HIV infection are at increased risk of mental and behavioural disorders. This is influenced by several factors including long-term chronic disease management, psychosocial stressors, stigma and the neurocognitive impact of HIV infection. The most common mental health disorders reported include anxiety, depression, behavioural disorders, learning difficulties

and attention deficit hyperactivity disorder [38]. HIV health care providers should be trained to integrate screening of mental health and behavioural disorders into routine care of these children and refer to appropriate services where available. This is an integral component of the holistic long-term management of HIV that will ultimately serve to improve ART adherence, engagement in care, neurocognitive development and social relationships [41].

3.2.6 Reproductive health complications

Clinicians managing adolescents of childbearing potential should assess their fertility intentions and review the potential drug–drug interactions between ART and contraception options to avoid adverse outcomes. There are potential interactions between NRTIs and some PIs with oral contraceptives that reduces their efficacy; whereas RAL does not interact with oestrogen-based contraceptives. There is preliminary data to suggest DTG may increase the risk of neural tube defects [41], and this should be a consideration when discussing ART regimen options during pregnancy. As part of comprehensive HIV care, reproductive health education should be provided to adolescents including risks of sexual transmission of HIV (and other infections) and perinatal HIV transmission, contraception, and access to family planning services.

3.3 Resistance to antiretroviral therapy

Development of HIV drug resistance resulting in treatment failure is a growing concern. Resistance to ART limits alternative treatment options, fuels progression of HIV disease and threatens the success of treatment programs [42]. There are three classes of HIV drug resistance. Acquired drug resistance (ADR) develops when HIV mutations emerge while on antiretroviral medications. Transmitted drug resistance (TDR) occurs through the transmission of resistant HIV. Pre-treatment drug resistance (PDR) is detected in anti-retroviral naïve patients as a result of TDR or following exposure to ART through pMTCT strategies [42]. PDR is a strong predictor of treatment failure and should inform recommended first line ART regimens. The WHO advises a national PDR prevalence of greater than 10% to an antiretroviral drug or drug class as an indication to switch to a different empiric first line ART regimen [42].

Studies across sub-Saharan Africa have shown virological failure ranging between 13 and 64% [43–47], with the proportion of antiretroviral drug resistance around 90% among those with virological failure [45, 46]. National surveys on HIV drug resistance in newly diagnosed HIV infection in infants and children less than 18 months of age across sub-Saharan African countries found an overall prevalence of HIV drug resistance to one or more antiretroviral drugs of 54.1% [22]. NNRTI resistance was present in 53%, predominantly in pMTCT-exposed children; and NRTI resistance present in 8.9%, which was largely driven by d4T and lamivudine (3TC)/emtricitabine (FTC) resistance reflecting the d4T/3TC backbone used at the time in these countries. A systematic literature review on PDR from 13 sub-Saharan African countries found a PDR prevalence of 42.7% in pMTCT-exposed children compared to 12.7% in pMTCT-unexposed children [48]. This study also demonstrated an increase in PDR in pMTCT–unexposed children from 0% in 2004 to 26.8% in 2013, which likely reflects NNRTI TDR from pregnant and/or breastfeeding women to their children. These findings are supported by a systematic literature review on PDR in children starting ART in low-and middle-income countries, which found a median prevalence of NNRTI resistance of 49.3% and more than 50% of pMTCT-exposed children with NNRTI resistance [49].

The high prevalence of PDR to NNRTIs in children supports recommendations to commence children on PI- or DTG-based regimens as the preferred first line due to lower levels of PDR and higher barriers to resistance. Longitudinal observational data from an Asian cohort of children and adolescents receiving second line PI-based regimens showed acquired PI resistance of less than 10% [50]. PI PDR prevalence rates in infants and young children in sub-Saharan African countries are reported as less than 3% [42]. This is likely due to the low rate of maternal PI-based regimens and the higher barrier to resistance for boosted PI regimens. However, widespread use of PI-based regimens in resource-limited settings has been hindered by the lack of access to appropriate paediatric-friendly formulations, prohibitive costs and procurement issues [42].

It is paramount to sustain high levels of viral suppression among children and adolescents with HIV in order to minimise development of HIV drug resistance [42]. To help achieve this, scaling up of viral load monitoring and HIV genotyping at initiation of treatment and throughout treatment is necessary to better understand the prevalence of antiretroviral drug resistance in children and adolescents. This will allow early recognition of treatment failure and guide treatment adjustments to subsequent suppressive ART regimens. Continued efforts to improve treatment adherence, prioritising first line therapies with high genetic barriers to resistance and ensuring availability of third line therapy is critical to reaching the UNAIDS 90-90-90 target goals [46].

4. Conclusion

Successful efforts of pMTCT programs has resulted in declining numbers of HIV infection in children worldwide. However, a considerable number of children and adolescents are living with HIV who require lifelong ART. HIV causes progressive CD4 T cell-related immunodeficiency and chronic immune system activation that results in an array of infectious and non-infectious morbidities and mortality. Early ART initiation is integral in achieving the treatment goals of maximising sustained viral suppression, optimising immunologic status, reducing HIV-related morbidity, and increasing survival. The global scale-up of ART has transformed HIV into a manageable chronic disease, however children and adolescents living with HIV continue to face unique management challenges with respect to ART and supportive care.

ART adherence and engagement in care are key to achieving the goals of therapy. Current challenges to ART adherence include the limited availability of paediatric-friendly formulations, lack of simplified regimens, and psychosocial complexities of managing children and adolescents through periods of marked biopsychosocial development. To improve ART adherence in children there is a need to accelerate development of paediatric-friendly formulations that are palatable and safe for children, with simplified regimens that are easy to administer and able to be transported and stored with minimal resources. Investment and collaboration across public and private sectors are integral to promote access to such paediatric-friendly ART globally. A holistic, multidisciplinary approach to managing children and adolescents living with HIV through the provision of comprehensive child and adolescent HIV health services that provide psychosocial support, surveillance and management of disease- and treatment-related morbidity, mental health screening, and reproductive health counselling is necessary to optimise engagement in care and treatment outcomes. Ongoing efforts to implement effective strategies to identify and manage treatment failure, through upscaling of HIV viral load testing, enhanced adherence support, and access to alternate effective ART regimens are

required to maximise ART durability, minimise the development of antiretroviral resistance, and preserve future ART options.

Children and adolescents living with HIV have been and will continue to be exposed to various ART regimens throughout their lives as new antiretroviral agents become available and novel ART regimens introduced. The long-term impact of lifelong exposure to multiple antiretroviral agents with regards to treatment response and morbidity is uncertain and needs ongoing evaluation. Longitudinal studies are essential to provide data on long-term treatment outcomes and antiretroviral drug toxicities to inform optimal sequencing of ART regimens.

A coordinated approach incorporating all stakeholders involved in addressing HIV in children and adolescents throughout their life course is necessary to navigate the challenges in reaching the successive targets set for children and adolescents in overcoming the epidemic. This will require sustained financial, research, and political commitment to best inform HIV models of care for this vulnerable group.

Conflict of interest

The authors have no conflicts of interests to declare.

Author details

Mirvat Said[1] and Adam W. Bartlett[2,3]*

1 Department of Paediatrics and Child Health, Sydney Children's Hospital, Sydney, Australia

2 Department of Immunology and Infectious Diseases, Sydney Children's Hospital, Sydney, Australia

3 School of Women's and Children's Health, UNSW Sydney, Australia

*Address all correspondence to: adam.bartlett@health.nsw.gov.au

References

[1] United Nations International Children's Emergency Fund. HIV and AIDS. 2019. Available from: https://www.unicef.org/hiv

[2] United Nations International Children's Emergency Plan. Adolescent HIV prevention. 2019. Available from: https://data.unicef.org/topic/hivaids/adolescents-young-people/

[3] Initiative CHA. HiV market report - the state of HiV treatment, testing, and prevention in low-and middle-income countries; 2019

[4] Akase IE, Musa BOP, Obiako RO, Ahmad Elfulatiy A, Mohammed AA. Immune dysfunction in HIV: A possible role for pro- and anti-inflammatory cytokines in HIV staging. Journal of Immunology Research. 2017;**2017**:4128398

[5] Alvarez P, Mwamzuka M, Marshed F, Kravietz A, Ilmet T, Ahmed A, et al. Immune activation despite preserved CD4 T cells in perinatally HIV-infected children and adolescents. PLoS One. 2017;**12**(12):e0190332

[6] Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: A pooled analysis. Lancet. 2004;**364**(9441):1236-1243

[7] Kisesa A, Chamla D. Getting to 90-90-90 targets for children and adolescents HIV in low and concentrated epidemics: Bottlenecks, opportunities, and solutions. Current Opinion in HIV and AIDS. 2016;**11**(Suppl 1):S1-S5

[8] Bain LE, Nkoke C, Noubiap JJN. UNAIDS 90-90-90 targets to end the AIDS epidemic by 2020 are not realistic: Comment on "can the UNAIDS 90-90-90 target be achieved? A systematic analysis of national HIV treatment cascades". BMJ Global Health. 2017;**2**(2):e000227

[9] Schlatter AF, Deathe AR, Vreeman RC. The need for pediatric formulations to treat children with HIV. AIDS Research and Treatment. 2016;**2016**:1654938

[10] HIV/AIDS JUNPo. Joint United Nations Programme on HIV/AIDS. 2018. Available from: https://aidsinfo.unaids.org

[11] Nebot Giralt A, Nostlinger C, Lee J, Salami O, Lallemant M, Ouma O, et al. Understanding the acceptability and adherence to paediatric antiretroviral treatment in the new formulation of pellets (LPV/r): The protocol of a realist evaluation. BMJ Open. 2017;**7**(3):e014528

[12] Bartlett AW, Truong KH, Songtaweesin WN, Chokephaibulkit K, Hansudewechakul R, Ly PS, et al. Characteristics, mortality and outcomes at transition for adolescents with perinatal HIV infection in Asia. AIDS. 2018;**32**(12):1689-1697

[13] Enane LA, Vreeman RC, Foster C. Retention and adherence: Global challenges for the long-term care of adolescents and young adults living with HIV. Current Opinion in HIV and AIDS. 2018;**13**(3):212-219

[14] Abul K, Abbas AHL. Pillai Shiv. Basic Immunology Functions and Disorders of the Immune System. Canada: Elsevier; 2016

[15] Okoye AA, Picker LJ. CD4(+) T-cell depletion in HIV infection: Mechanisms of immunological failure. Immunological Reviews. 2013;**254**(1):54-64

[16] Warriner AH, Burkholder GA, Overton ET. HIV-related metabolic comorbidities in the current ART era.

Infectious Disease Clinics of North America. 2014;**28**(3):457-476

[17] Hearps AC, Martin GE, Rajasuriar R, Crowe SM. Inflammatory co-morbidities in HIV+ individuals: Learning lessons from healthy ageing. Current HIV/AIDS Reports. 2014;**11**(1):20-34

[18] Weisner AM, Johnson AP, Lamagni TL, Arnold E, Warner M, Heath PT, et al. Characterization of group B streptococci recovered from infants with invasive disease in England and Wales. Clinical Infectious Diseases. 2004;**38**(9):1203-1208

[19] MR, Drouin O, Bartlett G, Nguyen Q, Low A, Gavriilidis G, et al. Incidence and prevalence of opportunistic and other infections and the impact of antiretroviral therapy among HIV-infected children in Low- and middle-income countries: A systematic review and meta-analysis. Clinical Infectious Diseases. 2016;**62**(12):1586-1594

[20] Picat MQ, Lewis J, Musiime V, Prendergast A, Nathoo K, Kekitiinwa A, et al. Predicting patterns of long-term CD4 reconstitution in HIV-infected children starting antiretroviral therapy in sub-Saharan Africa: A cohort-based modelling study. PLoS Medicine. 2013;**10**(10):e1001542

[21] Lewis J, Walker AS, Castro H, De Rossi A, Gibb DM, Giaquinto C, et al. Age and CD4 count at initiation of antiretroviral therapy in HIV-infected children: Effects on long-term T-cell reconstitution. The Journal of Infectious Diseases. 2012;**205**(4):548-556

[22] Jordan MR, Penazzato M, Cournil A, Vubil A, Jani I, Hunt G, et al. Human immunodeficiency virus (HIV) drug resistance in African infants and young children newly diagnosed with HIV: A multicountry analysis. Clinical Infectious Diseases. 2017;**65**(12):2018-2025

[23] Organization WH. World Health Organization. Policy Brief. The 2018 Optimal formulary and limited-use list for Paediatric ARVS. WHO. 2018. Available from: https://apps.who.int/iris/bitstream/handle/10665/273153/WHO-CDS-HIV-18.15-eng.pdf?ua=1.

[24] Malati CY, Golin R, O'Brien L, Sugandhi N, Srivastava M, Larson C, et al. Pursuing use of optimal formulations for paediatric HIV epidemic control - a look at the use of LPV/r oral pellets and oral granules. Journal of the International AIDS Society. 2019;**22**(4):e25267

[25] Boerma RS, Boender TS, van Hensbroek MB, Rinke de Wit TF, Sigaloff KC. Sequencing paediatric antiretroviral therapy in the context of a public health approach. Journal of the International AIDS Society. 2015;**18**(Suppl 6):20265

[26] Penazzato M, Lewis L, Watkins M, Prabhu V, Pascual F, Auton M, et al. Shortening the decade-long gap between adult and paediatric drug formulations: A new framework based on the HIV experience in low- and middle-income countries. Journal of the International AIDS Society. 2018;**21**(Suppl 1):e25049

[27] Agwu AL, Fairlie L. Antiretroviral treatment, management challenges and outcomes in perinatally HIV-infected adolescents. Journal of the International AIDS Society. 2013;**16**:18579

[28] Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. 2019. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf

[29] Martelli G, Antonucci R, Mukurasi A, Zepherine H, Nostlinger C. Adherence to antiretroviral treatment among children and adolescents in

Tanzania: Comparison between pill count and viral load outcomes in a rural context of Mwanza region. PLoS One. 2019;**14**(3):e0214014

[30] Kim SH, Gerver SM, Fidler S, Ward H. Adherence to antiretroviral therapy in adolescents living with HIV: Systematic review and meta-analysis. AIDS. 2014;**28**(13):1945-1956

[31] Garvie PA, Lensing S, Rai SN. Efficacy of a pill-swallowing training intervention to improve antiretroviral medication adherence in pediatric patients with HIV/AIDS. Pediatrics. 2007;**119**(4):e893-e899

[32] Nichols J, Steinmetz A, Paintsil E. Impact of HIV-status disclosure on adherence to antiretroviral therapy among HIV-infected children in resource-limited settings: A systematic review. AIDS and Behavior. 2017;**21**(1):59-69

[33] Barlow-Mosha L, Eckard AR, McComsey GA, Musoke PM. Metabolic complications and treatment of perinatally HIV-infected children and adolescents. Journal of the International AIDS Society. 2013;**16**:18600

[34] European Paediatric Lipodystrophy Group. Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. AIDS. 2004;**18**(10):1443-1451

[35] Alam N, Cortina-Borja M, Goetghebuer T, Marczynska M, Vigano A, Thorne C. Body fat abnormality in HIV-infected children and adolescents living in Europe: Prevalence and risk factors. Journal of Acquired Immune Deficiency Syndromes. 2012;**59**(3):314-324

[36] Kinabo GD, Sprengers M, Msuya LJ, Shayo AM, van Asten H, Dolmans WM, et al. Prevalence of lipodystrophy in HIV-infected children in Tanzania on highly active antiretroviral therapy. The Pediatric Infectious Disease Journal. 2013;**32**(1):39-44

[37] Arpadi S, Shiau S, Strehlau R, Martens L, Patel F, Coovadia A, et al. Metabolic abnormalities and body composition of HIV-infected children on Lopinavir or Nevirapine-based antiretroviral therapy. Archives of Disease in Childhood. 2013;**98**(4):258-264

[38] Vreeman RC, Scanlon ML, McHenry MS, Nyandiko WM. The physical and psychological effects of HIV infection and its treatment on perinatally HIV-infected children. Journal of the International AIDS Society. 2015;**18**(Suppl 6):20258

[39] Gafni RI, Hazra R, Reynolds JC, Maldarelli F, Tullio AN, DeCarlo E, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: Impact on bone mineral density in HIV-infected children. Pediatrics. 2006;**118**(3):e711-e718

[40] Purdy JB, Gafni RI, Reynolds JC, Zeichner S, Hazra R. Decreased bone mineral density with off-label use of tenofovir in children and adolescents infected with human immunodeficiency virus. The Journal of Pediatrics. 2008;**152**(4):582-584

[41] Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Specific Issues in Antiretroviral Therapy for Adolescents Living with HIV Infection. 2019. Available from: https://aidsinfo.nih.gov/guidelines/html/2/pediatric-arv/78/specific-issues-in-antiretroviral-therapy-for-adolescents-living-with-hiv-infection

[42] Nuttall J, Pillay V. Antiretroviral resistance patterns in children with HIV infection. Current Infectious Disease Reports. 2019;**21**(2):7

[43] Kebe K, Thiam M, Diagne Gueye NR, Diop H, Dia A, Signate Sy H, et al. High rate of antiretroviral

drug resistance mutations in HIV type 1-infected Senegalese children in virological failure on first-line treatment according to the World Health Organization guidelines. AIDS Research and Human Retroviruses. 2013;**29**(2):242-249

[44] Salou M, Dagnra AY, Butel C, Vidal N, Serrano L, Takassi E, et al. High rates of virological failure and drug resistance in perinatally HIV-1-infected children and adolescents receiving lifelong antiretroviral therapy in routine clinics in Togo. Journal of the International AIDS Society. 2016;**19**(1):20683

[45] Muri L, Gamell A, Ntamatungiro AJ, Glass TR, Luwanda LB, Battegay M, et al. Development of HIV drug resistance and therapeutic failure in children and adolescents in rural Tanzania: An emerging public health concern. AIDS. 2017;**31**(1):61-70

[46] Cisse AM, Laborde-Balen G, Kebe-Fall K, Drame A, Diop H, Diop K, et al. High level of treatment failure and drug resistance to first-line antiretroviral therapies among HIV-infected children receiving decentralized care in Senegal. BMC Pediatrics. 2019;**19**(1):47

[47] Makadzange AT, Higgins-Biddle M, Chimukangara B, Birri R, Gordon M, Mahlanza T, et al. Clinical, Virologic, immunologic outcomes and emerging HIV drug resistance patterns in children and adolescents in public ART Care in Zimbabwe. PLoS One. 2015;**10**(12):e0144057

[48] Boerma RS, Sigaloff KC, Akanmu AS, Inzaule S. Boele van Hensbroek M, Rinke de Wit TF, et al. alarming increase in pretreatment HIV drug resistance in children living in sub-Saharan Africa: A systematic review and meta-analysis. The Journal of Antimicrobial Chemotherapy. 2017;**72**(2):365-371

[49] World Health Organization. HIV drug resistance report. Global perspective on all forms of HIV drug resistance in both adults and children focussing on systematic literature reviews of nationally representative surveys in LMICs; 2017

[50] Prasitsuebsai W, Teeraananchai S, Singtoroj T, Truong KH, Ananworanich J, Do VC, et al. Treatment outcomes and resistance patterns of children and adolescents on second-line antiretroviral therapy in Asia. Journal of Acquired Immune Deficiency Syndromes. 2016;**72**(4):380-386