

Children living with HIV: a narrative review of recent advances in pediatric HIV research and their implications for clinical practice

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Abstract: Despite the great strides that have been made in prevention of mother to child transmission (PMTCT), children continue to acquire HIV. The reduction in transmission is variable, for example in Africa, great gains have been made in Eastern and Southern Africa, but critical gaps remain in West and Central Africa. These gaps are also observed in the treatment of children living with HIV. Although there is increased access to lifesaving antiretroviral therapy (ART), management of pediatric HIV infection continues to be a challenge to clinicians in low-income countries where the disease burden is disproportionately high. On the contrary, recent advances in ART drug types and formulations provide great hope. In this narrative review, we present key updates in HIV care and promising ART research among children and adolescents living with HIV. We particularly highlight the dolutegravir (DTG) research which informed the change of the World Health Organization (WHO) ART guidelines in this age group. Significant gaps remain around management of children presenting with advanced disease to minimize mortality and in the long-term care and treatment of adolescents living with HIV. Research to address these sensitive areas is crucial for the realization of global, regional, and national pediatric HIV targets.

Keywords: antiretroviral therapy, HIV infection in children, PMTCT

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Introduction

Globally, an estimated 38 million people were living with HIV in 2020; of these, 1.8 million were children under 15 years.¹ In 2019, an estimated 1.7 million new infections were reported globally, with children accounting for 9% of these. Eighty-four percent of these new infections in children occurred in sub-Saharan Africa.¹ While Eastern and Southern African countries have made tremendous progress over the last 10 years with 38% reduction in new infections and 49% reduction in AIDS-related deaths; the reductions are suboptimal in West and Central African countries, registered at only 25% and 37%, respectively.¹ Eastern and Southern African countries like Uganda, Rwanda, Botswana, Zambia, and Zimbabwe among others have reached the fast track 90-90-90 HIV testing and treatment targets with

counterparts like Kenya, Malawi, and Tanzania following closely. However, Western and Central African countries are still far from achieving the targets. This has been attributed to less domestic and international focus on HIV in the Western and Central African regions.¹ AIDS-related death in children and adolescents is significantly associated with unsuppressed viral load, severe immune suppression which predisposes children to severe opportunistic infections, and under nutrition.^{2,3}

Great strides have been made in pediatric HIV research over the years, particularly in the area of antiretroviral therapy (ART) resulting in a rapid evolution of treatment guidelines. HIV treatment priorities have shifted from treatment of opportunistic infections/HIV-related illnesses, end-of-life care, psychosocial support, legal aid,

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community/family support for orphans, and HIV diagnosis in the 1990s to early diagnosis, early initiation of ART, viral suppression, quality of life, drug toxicities, adolescent care, psychosocial support, and transition to adult clinics in the recent years. The approaches to optimization of treatment outcomes among HIV-infected children include early diagnosis and ART initiation, treatment and prevention of infections, optimal monitoring, and optimal adherence to ART.

Current research continues to focus on development of safer, more efficacious, and more user-friendly drug formulations for children of all age groups; timing of initiation of ART; treatment options after first-line failure; and prevention of new opportunistic infections. Significant gaps remain in the care for children with advanced disease, second-line treatment failure, and the management of adolescent patients. This review highlights the recent advances in antiretroviral drug development for children, new strategies for improvement of treatment outcomes, and discusses the gaps that remain for future research.

ODYSSEY and P1093 trials

Dolutegravir (DTG) is a highly effective integrase inhibitor with a low propensity for developing resistance. It has been recommended and rolled out for use as a first-line drug among adults and children in combination with two nucleoside reverse transcriptase inhibitors.⁴ However, the tablets with the recommended doses for children were initially not readily available in resource-limited settings. The ODYSSEY trial in Uganda, Zimbabwe, and South Africa investigated the pharmacokinetics related to using the 50-mg film-coated adult tablet in children weighing 20 kg and above compared with the recommended lower dose film-coated and dispersible tablets. The study found that the 50 mg once daily film-coated tablets when used in children above 20 kg resulted in C_{trough} (Coefficient of variation) closer to that of fasted adults taking the same dose, compared with the then recommended lower dose formulations for children. The 50-mg film-coated tablet given once daily was also safe in these children.⁵ This allows for harmonization of adult and pediatric DTG dosing and improves children's access to DTG. These findings informed the 2019 World Health Organization (WHO) pediatric dosing guidelines

and led to the US Food and Drug Administration approval of adult dosing down to 20 kg. In addition, DTG has been demonstrated to have a high genetic barrier for developing resistance in children without excessive increases in weight, height, or body mass index over time.⁶ The DTG dispersible tablet resulted in a significantly higher concentration (1.76 times) compared with the film-coated tablet given at the same dose.⁷

The IMPAACT P1093 study reported about the safety and efficacy of a DTG-based ART regimen among 23 treatment-experienced adolescents through a median 153 weeks of follow-up. DTG was well tolerated and safe, with no discontinuation due to adverse events. The adolescents who reported over 95% adherence on 3-day recall had virological success (<50 copies/ml) during follow-up.⁸ These findings suggest that not only is DTG safe for ART experienced adolescents in the long term, but also highly efficacious. Coupled with adherence monitoring and counseling, DTG can be effectively used in the adolescent population.

The LOLIPOP study

The WHO recommends the use of lopinavir/ritonavir as part of first-line treatment regimens in situations where children are intolerant to DTG, it is contra-indicated, or appropriate formulations are not available.⁴ The formulations of lopinavir/ritonavir that are currently in use include syrups, pellets, and tablets. Lopinavir/ritonavir has a bitter taste which affects adherence in children. Syrups require refrigeration and tablets are difficult to administer in younger children. There is ongoing research into more acceptable and tolerable formulations of lopinavir/ritonavir for children including fixed-dose combination granules of abacavir, lamivudine, and Lopinavir/ritonavir (4 in 1 formulation called quadrimune). The LOLIPOP study is a phase I/II, open-label, randomized cross over pharmacokinetic, safety, and acceptability study in Uganda. Preliminary findings showed the 4-in-1 was safe and effective in achieving or maintaining viral suppression. Furthermore, the 4-in-1 provided comparable drug exposures with the abacavir/lamivudine (60/30 mg) dispersible tablets plus lopinavir/ritonavir 40 10 mg pellets in majority of the participating children abacavir/lamivudine 60/30 mg.⁹ A qualitative study nested within the LOLIPOP study assessed caregivers' acceptability of the 4 in

1 formulation in comparison to lopinavir/ritonavir (40/10 mg) pellets plus dual. The study found that caregivers found the 4 in 1 formulation more acceptable than lopinavir/ritonavir pellets or other previous formulations, partly due to their palatability (strawberry flavored), easy storage and administration, and packaging.¹⁰ This is an important finding in as far as improving adherence to ART and treatment outcomes among younger children.

Gilead studies; GS-US-292-0106 and GS-9883/F/TAF studies

While adults have access to fixed-dose combinations, which improve treatment adherence, no single dose, once daily tablets are approved for use in children under 12 years. The GS-US-292-0106 is an open-label single-arm study being done in Uganda, the United States, and Thailand. Part A of this study, which assessed pharmacokinetics of a once daily single-tablet coformulation of 150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine, and 10 mg tenofovir alafenamide among 23 virologically suppressed children aged 6–11 years is complete. During the 24-week follow-up, participants reported only mild and moderate adverse events and maintained viral suppression (HIV-1 RNA <50 copies/ml). The tablet caused modest increases in the area under the curve (AUC) for the different tablet components compared to adult data; tenofovir alafenamide (71%), tenofovir (52%), elvitegravir (34%), cobicistat (58%), and emtricitabine (75%).¹¹ A lower dose of this combination is being tested in children ≥ 2 years and interim analyses show high acceptability and sustained virological suppression.¹² The bicitegravir, emtricitabine, and tenofovir alafenamide 50/200/25 mg single-tablet fixed-dose combination was also safe and efficacious with no clinically relevant exposures in 100 adolescents and children aged 6–18 years compared with adults.¹³

The GS-9883/F/TAF study explored the long-term safety, tolerability, efficacy, and treatment outcomes of bicitegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) 50/200/25 mg among children and adolescents aged 6–18 years (≥ 25 kg) from South Africa, Uganda, the United States, and Thailand who were virologically suppressed (HIV-1 RNA <50 cells/ml) and had CD4 ≥ 200 cells/ μ l. The study also explored the use of B/F/TAF low-dose tablet (LDT, 30/120/15 mg)

among younger children aged ≥ 2 years (14 to <25 kg) and assessed acceptability, palatability, safety, and efficacy.

After 96 weeks of follow-up, 99% of children aged 6–18 years were virologically suppressed. None of the participants were reported to develop treatment-emergent resistance. Very few drug-related adverse effects were reported and only one child had the treatment discontinued following neuropsychological complaints. All the participants reported that the treatment was palatable and acceptable. In the ≥ 2 year's age group, 91% remained virologically suppressed by week 24 on treatment with no reports of treatment emergent resistance. Over 84% of participants' caregivers reported acceptability while over 91% reported the treatment was palatable.¹⁴ The study will also investigate the use of the fixed-dose combination of bicitegravir 3.75 mg/emtricitabine 15 mg/tenofovir alafenamide 1.88 mg (B/F/TAF 3.75/15/1.88 mg) tablet for oral suspension among children aged less than 2 years.

These findings suggest that there is hope for a safe efficacious once daily single-dose tablet for children. When rolled out for clinical use, this tablet will significantly improve treatment adherence not only in older children (6–11 years) and adolescents but also in younger children.

Ongoing challenges in care for children living with HIV

Management of advanced HIV

Despite the widespread availability of effective ART, more than 690,000 people died from AIDS-related deaths worldwide in 2019. Of these, 95,000 were children less than 15 years.¹ Management of advanced disease in children is still very challenging. Patients at high risk of mortality are often either newly diagnosed with HIV or failing on their ART regimens at presentation. They present with severe immunosuppression evidenced by severe opportunistic infections and features of malnutrition.

The REALITY trial

'The Reduction of EARly mortalITy in HIV-infected Adults and Children Starting Antiretroviral Therapy (REALITY)' trial tried to address this problem. It was an open-label,

randomized controlled trial, among adults and children at least 5 years of age. The REALITY trial randomized participants to standard of care (co-trimoxazole) according to national guidelines or an enhanced prophylaxis package (12 weeks of fluconazole 100 mg daily, 12 weeks of fixed-dose combination of co-trimoxazole, isoniazid, and pyridoxine as a once daily tablet, 5 days of azithromycin and a single dose of albendazole). All the drugs were started simultaneously on the same day as ART. The enhanced prophylaxis package was reported to reduce mortality by 27% over 24 weeks.¹⁵ The study also investigated the effect of ready-to-use supplementary food on mortality among these patients. The control group received nutritional supplementation when recommended by the current guidelines. This ready-to-use supplementary food did not reduce early mortality in this population.¹⁶

The WHO defines advanced disease as all children younger than 5 years with HIV, and those older than 5 years with CD4 cell count <200 cells/mm³ or WHO stage 3 or 4 event. WHO, taking the REALITY trial results into consideration, recommends that a package of interventions including screening for tuberculosis and cryptococcal antigen (in adolescents), treatment and prophylaxis with co-trimoxazole, TB preventive treatment, fluconazole (among cryptococcal antigen-positive adolescents with no evidence of meningitis), rapid initiation of ART (same day) unless clinical symptoms suggest TB or cryptococcal meningitis, and intensified adherence support interventions be offered to everyone with advanced HIV disease.¹⁷

Findings from key studies are summarized in Table 1.

The EMPIRICAL trial

An ongoing trial, the Empirical trial (NCT03915366), is aiming at reducing mortality among HIV-infected infants. It is a randomized factorial clinical trial, which is being conducted in Uganda, Zimbabwe, Zambia, Mozambique, Ivory Coast, and Malawi. The objective of the study is to evaluate the safety and efficacy of empirical treatment against cytomegalovirus and tuberculosis in HIV-infected infants hospitalized for severe pneumonia. This study will provide insights into whether additional interventions are

warranted for HIV-infected infants with advanced disease.

Management of adolescents

Thanks to increasing availability of ART worldwide, more children are surviving infancy. As such, the adolescent population is growing. Management of adolescents presents unique challenges. One of the main challenges highlighted is mental health disorders. Recent studies in Uganda and South Africa document a high prevalence of psychiatric and behavioral disorders in adolescents, particularly attention-deficit hyperactivity disorder (ADHD).^{18,19} These disorders, unless specifically screened for, could be missed during routine HIV care. This calls for closer attention to adolescents' mental health and specialist care in order to improve their quality of life. Other challenges of adolescents include chronic lung disease, particularly obliterative bronchiolitis following recurrent severe respiratory tract infections and tuberculosis, bronchiectasis, cardiovascular and renal complications,²⁰ stunting, and pubertal delay.²¹ According to Kranzer *et al.*, adolescents aged 15–19 also have a significantly higher rate of loss to follow-up compared with other children.²² Adolescents who are lost to follow-up are likely to miss their ART and develop severe life-threatening opportunistic infections. Management of HIV-infected adolescents therefore calls for extensive screening for comorbid conditions with specialist care for identified conditions. Preventive measures include early initiation of ART, routine vaccination, prophylaxis against opportunistic infections, as well as improving nutrition.

Resistance

Emerging resistance to antiretroviral drugs presents a growing challenge to treatment of HIV. HIV drug resistance is usually a result of exposing the virus to suboptimal levels of a drug, incompletely suppressing the virus, and applying drug selective pressure. This largely occurs in following poor treatment adherence. In children, HIV resistance can also be acquired from their ART-exposed mothers. Resistance is less likely to develop when fixed-dose combinations of antiretroviral drugs with similar half-lives are used as selective drug pressure on the virus is less likely even with inadequate adherence.²³ Routine viral

Table 1. Table summarizing key findings from recent studies.

Study	Key findings
ODYSSEY	The Dolutegravir 50 mg film-coated tablet is safe and efficacious with similar bioavailability to adults when used in children above 20 kg than lower dose formulations.
IMPAACT P1093	Dolutegravir was well tolerated and safe among adolescents through 153 weeks of follow-up.
LOLIPOP	Fixed-dose combination granules of abacavir, lamivudine, and Lopinavir/ritonavir (4 in 1 formulation called quadrimune) is safe and effective in achieving or maintaining viral suppression, produces good drug exposure, and is more acceptable than Lopinavir/ritonavir pellets or other previous formulations.
GS-US-292-0106	Once daily single-tablet coformulation of 150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine, and 10 mg tenofovir alafenamide maintained viral suppression and was safe in 24 weeks of follow-up among children 6–11 years.
GS-9883/F/TAF	Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) 50/200/25 mg was safe, acceptable, and maintained viral suppression through 96 weeks of follow-up among children and adolescents aged 6–18 years (≥ 25 kg).
REALITY	An enhanced prophylaxis package (12 weeks of fluconazole 100 mg daily), 12 weeks of fixed-dose combination of co-trimoxazole, isoniazid, and pyridoxine as a once daily tablet, 5 days of azithromycin and a single dose of albendazole enhanced prophylaxis package reduced mortality by 27% over 24 weeks compared to standard of care (co-trimoxazole) according to national guidelines. Ready-to-use supplementary food did not reduce early mortality.
SMILE	Once daily integrase inhibitors plus darunavir/ritonavir was noninferior to standard of care triple ART and was equally safe among virologically children aged 6–18 years.

ART, antiretroviral therapy.

load monitoring can also help to reduce development of resistance. It results in early detection of virological failure, allowing adequate interventions including adherence counseling and treatment modification to be instigated in a timely manner.^{20,24,25}

New models of care and antiretroviral drugs in the pipeline

Even in the face of many challenges, a lot can be done to consolidate the progress made in pediatric HIV. Current advances include the following:

1. *Differentiated Service Delivery (DSD) Model*
The DSD model is a client-centered approach where care is tailored to the patients' specific needs. This method simplifies HIV services for both the clients and the health system. The DSD model is especially beneficial in the face of the current

'treat all' approach to HIV management.²⁶ The decentralized care allows clients in underserved populations to access care and improve their quality of life while reducing expenses that would have otherwise have been incurred by the health system. DSDs should go beyond providing care to stable patients to providing care across all aspects of HIV care from prevention to management of advanced disease in order to effectively improve pediatric HIV treatment outcomes.

2. *New drugs*

Recent studies are looking into use of neutralizing antibodies such as 3BNC117 and VRC01 to prevent replication of HIV and clear affected cells. Crowell *et al.* investigated the ability of VRC01 to cause a sustained viral control in the absence of ART among 19 virologically suppressed adults in

Thailand. Although VRC01 was tolerated as monotherapy, it did not sustain viral suppression after 24 weeks of ART interruption.²⁷ VRC01 and other immunotherapies could be effective as combined regimens.

3. Use of long-acting injectable drugs
Although not yet widely available for clinical use, long-acting injectable drugs like cabotegravir, rilpivirine, leronlimab, islatravir, and albuviride among others show promise toward addressing the treatment adherence challenges among adolescents once readily available. Research into resistance associated with these drugs, as well as their effectiveness in various populations, is warranted.²⁸

4. Treatment simplification
Optimal adherence can be achieved by treatment simplification and provision of drug formulations appropriate for children. The ARROW trial team investigated the once daily versus twice daily abacavir + lamivudine in children aged 3–12 years and found that they were bioequivalent, and the once daily dose was preferred.²⁹ The once daily abacavir + lamivudine was also not inferior to the twice daily formulation in virological suppression, development of resistance, side effect profile, or clinical and immunological outcomes.³⁰ This meant that treatment could indeed be simplified to optimize treatment adherence and outcomes among HIV-infected children. Treatment simplification could also take the form of more user-friendly options including easier administration or storage, such as the more heat stable lopinavir/ritonavir pellets investigated in comparison to the syrup requiring refrigeration and tablets. The pellets were more acceptable than the syrup with similar lopinavir/ritonavir concentrations.^{31,32}

Studies have investigated whether simplification to fewer and safer drugs among virologically suppressed individuals will reduce drug exposure and hence long-term toxicities and improve treatment adherence. The BREATHER trial showed that short cycle efavirenz-based therapy (5 days on 2 days off) was noninferior to continuous therapy.³³ A follow-on study, the BREATHER Plus, will investigate whether similar results will be obtained with DTG-based treatment.

The SMILE trial (NCT02383108) investigated the safety and antiviral effect of once daily integrase inhibitors plus darunavir/ritonavir when compared with standard of care triple ART among 318 virologically suppressed children aged 6–18 years in Africa, Europe, Thailand, and Latin America. The study found that once daily integrase inhibitors plus darunavir/ritonavir was noninferior to standard of care triple ART and was equally safe.³⁴ The study's final results were released at IAS 2021 (<https://www.ias2021.org>).

Discussion

Recent research has explored and tried to address the unique challenges of managing opportunistic infections among patients with advanced HIV. These patients have limited or no immune reserves for fighting infections. ART reduces the viral load and allows the body to regain some immune function which instead often leads to immune reconstitution syndrome (IRIS). This presents with worsening or unmasking of opportunistic infections and significantly increases the risk of death among these children. Findings from the REALITY trial have provided guidance for active screening and treatment for opportunistic infections, timing of ART, and continuous follow-up and management of IRIS in patients with advanced ART. Findings from the EMPIRICAL study will provide guidance on the management of severe pneumonia from undiagnosed cytomegalovirus and tuberculosis in HIV-infected infants in order to reduce days of hospitalization and improve treatment outcomes in this age group. Whereas the studies summarized in the review present significant ART advances in children and adolescents, they also highlight specific challenges in the management of HIV-infected adolescents including mental health problems, chronic lung diseases, and pubertal delay among others. This calls for implementation of adolescent friendly HIV treatment and follow-up services in order to improve the treatment outcomes and quality of life of HIV-infected patients globally.

Conclusion

While the ultimate aim is to eliminate mother to child transmission of HIV, it is important that the children that acquire it grow up to adulthood free of the effects of the virus or of treatment

modalities against it. In the last 10 years or so, great strides have been made toward provision of efficacious and safe ART regimens to HIV-infected children. However, gaps remain particularly around managing advanced disease and care for adolescents. These need to be addressed if global, regional, and national pediatric HIV targets are to be met.

Author contributions

Damalie Nalwanga: Conceptualization; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Victor Musiime: Conceptualization; Methodology; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Conflict of interest statement

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