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CURRENT TREATMENT OPTIONS FOR CHILDREN AND ADOLESCENTS LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Lidija Popović-Dragonjić[1,2], Aleksandar Ranković[1,2], Maja Cvetanović[1,2], Milica Ćosić-Petković[1,2], Jelena Spasić[2], Jovana Tomić[1,2], Dane Krtinić[3,4]

The goal of human immunodeficiency virus (HIV) infection treatment in both adults and children and adolescents is to achieve a stable virological response, i.e., undetectable viral load in the blood for more than six months and recovery of immunity. Antiretroviral treatment of children and adolescents living with HIV (C/ALHIV) is even more specific and more difficult due to poorer therapeutic adherence, longer duration of infection and consequent toxic effects as well as chronic microinflammation. Another complicating factor is the lack of adequate pediatric pharmaceutical co-formulations depending on the region. With progress and the emergence of innovative types of therapy and strict guidelines, C/ALHIV are improving their quality of life and immune status. The most used official guidelines are the recommendations of the European AIDS Clinical Society (EACS), the World Health Organization (WHO), and the Center for Disease Control and Prevention (CDC). According to them, along with local conditions and opportunities, national guidelines are formed at the level of individual countries.

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[1]University of Niš, Faculty of Medicine, Department of Infectious Diseases and Epidemiology, Niš, Serbia
[2]University Clinical Center Niš, Clinic of Infectology, Niš, Serbia
[3]University of Niš, Faculty of Medicine, Department of Pharmacology with Toxikology, Niš, Serbia
[4]University Clinical Center Niš, Clinic for Oncology, Niš, Serbia

Contact: Lidija Popović-Dragonjić
81 Dr. Zorana Djindjića Blvd., 18000 Niš, Serbia
E-mail: lidija.popovic.dragonjic@medfak.ni.ac.rs

Introduction

Human immunodeficiency virus (HIV) infection is one of the most serious infectious diseases in children. Approximately 3 million children and adolescents worldwide are infected with HIV. The principle of early and lifelong antiretroviral therapy (ART) is crucial for sustained viral suppression, recovery, sustenance of immunity and prevention of acquired immune deficiency syndrome (AIDS). This principle significantly reduces morbidity and mortality from HIV-related diseases and improves quality of life. However, there are many more difficulties in treating HIV-related diseases in pediatric patients than in adults. Access to therapy, especially in the youngest children (neonates and infants), remains a major challenge due to the limited number of formulations suitable for use (1–3).

Despite great efforts to prevent mother-to-child transmission of HIV, children continue to be infected. Mortality from AIDS-defining conditions in children and adolescents is significantly associated with failure of viral suppression, severe immune suppression underlying severe opportunistic infections (4). During growing up, children and adolescents living with HIV (C/ALHIV) can develop various organic damages as a consequence of the toxicity of the therapy, such as cardiovascular, renal, metabolic and neurological (5–7).

There is a legitimate concern about the consequences of lifelong HIV persistence in children with perinatally acquired HIV. Due to the longer duration of persistent HIV infection and the underlying microinflammation, adolescents and young adults who were infected with HIV in childhood are at an even greater risk of developing diseases associated with immunosenescence. Chronic inflammation and immune activation lead to non-AIDS-defining comorbidities, including impairments of neurocognitive functions and cardiovascular system and metabolic alterations. Although the therapy decreases immune activation in children, levels remain higher than in their uninfected peers. The long survival capacity of early infected cells through clonal expansion is a major obstacle to a cure. The effects of lifelong

HIV persistence and lifelong ART are complex, such that children living with HIV have a higher risk of developing non-AIDS comorbidities (8).

This review presents the basics of ART for C/ALHIV, currently available therapeutic options, dosing, and safety analyzes of therapy by drug class for all pediatric groups (newborns, children, adolescents).

Current Recommendations

The subject of current research is the development of new, safe, more effective drugs that are also easier to use in the pediatric population. At the same time, the topic is the right time to start ART, the consideration of therapeutic options after the failure of first-line therapy, as well as the prevention of opportunistic infections (9−11).

The well-known guidelines for the treatment of the disease caused by HIV in the pediatric population are the guidelines of the European AIDS Clinical Society (EACS), Center for Disease Control and Prevention (CDC), as well as the World Health Organization (WHO). Most of the countries of the European Union, as well as our country, mainly adhere to the EACS guidelines. At the end of 2024, under the auspices of the Ministry of Health of the Republic of Serbia, the National Guide for the treatment of people living with HIV was officially published (12, 13). What all the guides have in common is the standpoint that postponing therapy is no longer recommended. Prompt therapy initiation is recommended in all C/ALHIV. WHO recommends testing newborns at 4–6 weeks of age and prompt ART in all infected children (14).

European AIDS Clinical Society Recommendations

The European AIDS Clinical Society (EACS) guideline covers a large and diverse geographic territory that includes varying levels of therapy availability. For this reason, a wide range of recommendations is included in the aforementioned guide, which is the opposite of uniform national guides. EACS Guidelines version 11.1. October 2022 (15, 16).

1. Starting ART in children and adolescents

•It is recommended to start ART in all C/ALHIV infections, regardless of age, clinical stage, level of CD4 cells, or Viral Load (VL), i.e., the concentration of virus in the blood.

•Rapid diagnosis of HIV infection for infants born to HIV-infected women and rapid initiation of therapy for HIV-infected infants are necessary

•The "U=U" campaign (undetectable = untransmissible) regarding the sexual transmission of HIV is approved, which is of particular importance for sexually active adolescents. "Untransmissible" means VL < 200 copies/mL for more than 6 months.

2. Initial combination regimen for treatment—naïve C/ALHIV (children and adolescents who have not been on ART before).

•If accessible, baseline resistance testing should be performed.

•All regimens of the first-line regimens at present comprise 2 nucleoside reverse transcriptase inhibitors (NRTIs) along with a drug from another class (third agent)

•The combination of dolutegravir (DTG) plus 2NRTIs is the preferred option for all children older than 4 weeks and 3 kg.

•While “preferred options” are recommended, “alternative options” are permissible and persist as an important choice in settings where ART availability is restricted or in individuals at certain risk of specific toxicities or drug–drug interactions (DDIs).

•Whenever possible, “third agent of the first-line” with a high barrier to resistance is chosen, given the potential challenges with adherence in children and adolescents.

•Always consider the resistance transmission possibility, including exposure of both mother and infant to ART after failure to prevent vertical transmission.

•In infants younger than 4 weeks and/or under 3 kg, when nevirapine (NVP) was administered in pregnancy or there is a threat of passed NVP resistance, other than non-nucleoside reverse transcriptase inhibitors (NNRTI)-based ART is preferred, including raltegravir (RAL) from birth or ritonavir-boosted lopinavir (LPV/r) from the second week (16−18).

Preferred and alternative first-line options in C/ALHIV and antiretroviral formulations useful for dosing and administration in children and adolescents are listed in Table 1 and Table 2, respectively (16).

1. Due to long-term toxicity, any child on ZDV therapy should be switched to ABC (preferred for younger children) or TAF/TDF (alternative for younger children, with renal/bone toxicity monitored by TDF) when age and/or weight allow the use of licensed formulations. When ABC is contraindicated in young children, a choice between ZDV, TDF or TAF on an individual level is recommended

2. LPV/r should not be given to infants before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days, although it may be considered if there is a risk of transmitted resistance to NVP and suitable INSTI formulations are not available. In these circumstances, the infant should be closely monitored for LPV/r-related toxicity (e.g., metabolic, endocrine, cardiac)

3. It is acceptable to continue therapy started with a 3rd agent other than DTG in the neonatal period. However, once the age of over 4 weeks and 3 kg is reached, switching to DTG is recommended if and when a suitable formulation is available

4. ABC should NOT be prescribed to HLA-B*57:01 positive individuals (where screening is available). ABC is not licensed for children under 3 months of age, but there are WHO-recommended dosing data for younger children

5. TDF is only approved for use from 2 years of age. Given concerns about potential effects on bone development and renal toxicity, TAF is recommended over TDF in all ages in settings where this is licensed and available.

6. DTG is allowed for use from 4 weeks and 3 kg. DTG is associated with excessive weight gain in adults, especially in combination with TAF. This has not yet been demonstrated in pediatric and adolescent observational studies or trials, but the possibility should be considered when using DTG. Families and youth should be counseled about this, and weight monitored

7. XTC indicates circumstances where FTC or 3TC can be used interchangeably

8. TAF is approved in Europe for the treatment of HIV in combination with FTC from 12 years of age and 35 kg in TAF/FTC and from 6 years of age and 25 kg in TAF/FTC/EVG/c. Since TAF is approved for use in younger ages and lighter weights, it can be included as a preferred option. TAF is associated with excessive weight gain in adults, especially when combined with DTG. This has not yet been demonstrated in pediatric and adolescent observational studies or trials; however, the possibility should be considered when using TAF. Families and youth should be counseled about this, and weight monitored

9. BIC is the preferred first-line option in adults. It has not yet been registered for use in children under 18 years of age, but may be considered in those under 18 years of age after professional consideration

10. Due to potential poor therapeutic adherence in adolescence, if preferred 3rd line agents (BIC or DTG) are not available/appropriate to possible alternative 3rd line agents, DRV/b resistance barrier should be preferred compared to EFV, RAL or RPV.

Table 1. Preferred and alternative first-line options in children and adolescents

	"Backbone'' therapy		**3rd agent (alphabetically)**	
Age	**Preferred**	**Alternative**	**Preferred**	**Alternative**
0–4 weeks	ZDV[(i)] + 3TC	-	LPV/r[(ii, iii)] NVP[(iii)] RAL[(iii)]	-
4 weeks–3 years	ABC[(iv)] + 3TC[(v)]	ZDV[(i)] + 3TC[(vi)] TDF[(vii)] + 3TC	DTG[(viii)]	LPV/r NVP RAL
3–6 years	ABC[(iv)] + 3TC[(v)]	TDF[(vii)] + XTC[(ix)] ZDV + XTC[(ix)]	DTG[(viii)]	DRV/r EFV LPV/r NVP RAL
6–12 years	ABC[(iv)] + 3TC[(v)] TAF[(x)] + XTC[(ix)]	TDF[(vii)] + XTC[(ix)]	DTG[(viii)]	DRV/r EFV EVG/c RAL
> 12 years	ABC[(iv)] + 3TC[(v)] TAF[(x)] + XTC[(ix)]	TDF[(vii)] + XTC[(ix)]	BIC[(xi)] DTG[(viii)]	DRV/b EFV[(xii)] RAL[(xii)] RPV[(xii)]

Abbreviations: ZDV—zidovudine, 3TC—lamivudin; LPV/r—lopinavir/ritonavir; NVP—nevirapine; RAL—raltegravir; ABC—abacavir; TDF—tenofovir disoproxil fumarate, DTG—dolutegravir; EFV—efavirenz; XTC—3TC or FTC; FTC—emtricitabine; EVG—elvitegravir; BIC—biktegravir; DRV/r—darunavir/ritonavir; TAF—tenofovir alafenamide

Table 2. Antiretroviral formulations useful for dosing and administration in children and adolescents

NRTI	
ABC	tablet (300 mg), solution (20 mg/mL)
FTC	capsule (200 mg), solution (10 mg/mL)
3TC	tablet (300, 150 mg), solution (10 mg/mL)
TDF	tablet (245, 204, 163, 123 mg), granules (33 mg/g)
ZDV	capsule (250 mg, 100 mg), solution (10 mg/mL) IV infusion: 10 mg/mL (20 mL/vial)
TAF/FTC	tablet (25/200 mg and 10/200 mg)
TDF/FTC	tablet (300/200 mg)
ABC/3TC	tablet (600/300 mg)
ZDV/3TC	tablet (300/150 mg)
NNRTI	
EFV	tablet (600 mg), capsule (200, 100, 50 mg)
NVP	tablet (200 mg), extended release tablet (400, 100 mg), suspension (10 mg/mL)
RPV	tablet (25 mg)
TDF/FTC/EFV	tablet (300/200/600 mg)
TAF/FTC/RPV	tablet (25/200/25 mg)
TDF/FTC/RPV	tablet (25/200/25 mg)
PI	
DRV	tablet (800, 600, 400, 150, 75 mg), solution (100 mg/mL)
DRV/c	tablet (800/150 mg)
LPV/r	tablet (200/50 mg and 100/25 mg), solution (80/20 mg/mL)
RTV	tablet (100 mg), powder for oral suspension (100 mg sachet)
TAF/FTC/DRV/c	tablet (10/200/800/150 mg)
INSTI	
DTG	tablet (50, 25, 10 mg), dispersible tablets (5 mg)
RAL	tablet (600 mg, 400 mg), chewable tablets (100, 25 mg,) granules for oral suspension (100 mg)
ABC/3TC/DTG	tablet (600/300/50 mg)
TAF/FTC/BIC	tablet (25/200/50 mg)
TAF/FTC/EVG/c	tablet (10/200/150/150 mg)
TDF/FTC/EVG/c	tablet (300/200/150/150 mg)

Abbreviations: ZDV—zidovudine; 3TC—lamivudin; LPV/r—lopinavir/ritonavir; NVP—nevirapine; RAL—raltegravir; ABC—abacavir; TDF—tenofovir disoproxil fumarate, DTG—dolutegravir; EFV—efavirenz; FTC—emtricitabine, EVG—elvitegravir; BIC—biktegravir; DRV—darunavir, DRV/r—darunavir/ritonavir; TAF—tenofovir alafenamide, RPV—rilpivirine, RTV—ritonavir, NRTI—nucleoside reverse transcriptase inhibitor, NNRTI—non-nucleoside reverse transcriptase inhibitor; PI—protease inhibitor; INSTI—integrase strand transfer inhibitor

World Health Organization Recommendations

The World Health Organization (WHO) has published updated *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach.* This publication brings together important clinical and programmatic additions by WHO since 2016, offering clear recommendations based on evidence and good clinical practice in relation to public health, with an individual-oriented approach and respect for human rights. This guide introduces the most recent recommendations on HIV testing strategies for entry points in HIV prevention and treatment and is composed of clear and comprehensive guidelines for diagnosis in children (19).

The diagnostic and therapeutic principles of caring for adults and C/ALHIV in Serbia are based on the EACS recommendations, taking into account the available diagnostic and therapeutic resources. WHO recommendations are also followed in circumstances of medication shortage (meaning that recommended drugs are in the process of registration or not yet). Preferred and

alternative first-line therapeutic regimens and preferred and alternative second-line therapeutic regimens are presented in Table 3 and Table 4, respectively. Considerations for switching to optimal treatment regimens for C/ALHIV regarded as steady on ART based on national guidelines are listed in Table 5 (19–31).

Table 3. Preferred and alternative first-line therapeutic regimens

Population	Preferred first-line regimen	Alternative first-line regimen	Special circumstances
Adolescents	TDF + 3TC (or FTC) + DTG[a]	TDF + 3TC + EFV 400 mg[b]	TDF + 3TC (or FTC) + EFV 600 mg[b] ZDV + 3TC + EFV 600 mg[b] TDF + 3TC (or FTC) + PI/r[b] TDF + 3TC (or FTC) + RAL TAF[c] + 3TC (or FTC) + DTG ABC + 3TC + DTG[a]
Children	ABC + 3TC + DTG[d]	ABC + 3TC + LPV/r ABC + 3TC + RAL[e] TAF + 3TC (or FTC) + DTG[f]	ABC + 3TC + EFV (or NVP) ZDV + 3TC + EFV[g] (or NVP) ZDV + 3TC + LPV/r (or RAL)
Neonates	ZDV + 3TC + RAL[h]	ZDV + 3TC + NVP	ZDV + 3TC + LPV/r[i]

Abbreviations: 3TC—lamivudine; ABC—abacavir; ZDV—zidovudine; DTG—dolutegravir; EFV—efavirenz; FTC—emtricitabine; LPV/r—lopinavir/ritonavir; NVP—nevirapine; PI/r—ritonavir-boosted protease inhibitor; RAL—raltegravir; TAF—tenofovir alafenamide; TDF—tenofovir disoproxil fumarate

a) Effective contraception should be offered to adolescent girls of reproductive age. DTG can be prescribed to adolescent girls of reproductive age or potentially pregnant or who are not using contraception if they are fully informed of the potential increased risk of neural tube defects (at conception and up to the end of the first trimester). If pregnancy is detected after the first trimester, DTG should be started or continued throughout the pregnancy

b) EFV-based ART should not be used in settings with national pre-treatment EFV resistance estimates of 10% or more. DTG-based ART is preferred, and if DTG is not available, a boosted PI-based regimen should be used. The choice of PI/r depends on the program characteristics;

c) TAF may be considered for people with established osteoporosis and/or impaired kidney function

d) For age and weight groups with an approved dosage of DTG

e) RAL should be used as an alternative regimen only if LPV/r solid formulations are not available

f) For age and weight groups with approved TAF dosing

g) EFV should not be used for children under the age of three

h) Infants initiated on ART with a RAL-based regimen should be switched to LPV/r solid formulation as soon as possible

i) LPV/r syrup or granules can be used if started after two weeks of age.

Table 4. Preferred and alternative second-line therapeutic regimens

Population	First-line regimen failure	Preferred second-line regimens	Alternative second-line regimens
Adolescents[a]	TDF[b] + 3TC (or FTC) + DTG[c] TDF + 3TC (or FTC) + EFV (or NVP) ZDV + 3TC + EFV (or NVP)	ZDV + 3TC + ATV/r (or LPV/r) ZDV + 3TC + DTG[c] TDF[b] + 3TC (or FTC) + DTG[c]	ZDV + 3TC + DRV/r[d] ZDV + 3TC + ATV/r (or LPV/r or DRV/r)[d] TDFb + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r)[d]
Children and infants	ABC + 3TC + DTG[e] ABC (or ZDV) + 3TC + LPV/r ABC (or ZDV) + 3TC + EFV ZDV + 3TC + NVP	ZDV + 3TC + LPV/r (or ATV/r[f]) ZDV + 3TC + LPV/r (or ATV/r[f]) ZDV (or ABC) + 3TC + DTG[e]ABC + 3TC + DTG[e]	ZDV + 3TC + DRV/r[g] ZDV (or ABC) + 3TC + RALZDV (or ABC) + 3TC + LPV/r (or ATV/r[f])ABC + 3TC + LPV/r (or ATV/r[f] or DRV/r[g]

Abbreviations: 3TC—lamivudine; ABC—abacavir; ATV/r—atazanavir/ritonavir; ZDV—zidovudine; DRV/r—darunavir/ritonavir; DTG—dolutegravir; EFV—efavirenz; FTC—emtricitabine; LPV/r—lopinavir/ritonavir; NVP—nevirapine; RAL—raltegravir; TDF—tenofovir disoproxil fumarate

a) Sequencing is necessary if PIs are used in first-line ART: ATV/r (or LPV/r or DRV/r, depending on programmatic considerations) +

TDF + 3TC (or FTC), then AZT + 3TC + DTG in second-line therapy lines.

b) Effective contraception should be offered to adolescent girls of reproductive age. DTG can be prescribed to adolescent girls of reproductive age who can potentially become pregnant or who are not using effective contraception if they are fully informed of the potential increased risk of

neural tube defects (at conception and through the end of the first trimester). If pregnancy is detected after the first trimester, DTG should be started or continued throughout the pregnancy.

c) TAF can be used as an alternative NRTI in special situations for adolescents.

d) RAL + LPV/r can be used as an alternative second-line therapeutic regimen for adolescents.

e) The European Medicines Agency currently only approves DTG for children weighing at least 15 kg and more broadly for children weighing over 20 kg who can take the 50 mg film-coated tablets intended for adults. Dosing studies for younger children are ongoing, with approval expected in early 2020, but the 2016 WHO recommendations for second-line ART still apply (based on PI for children failing NNRTIs and RAL for children LPV/r has failed). TAF (tenofovir alafenamide) can be used as an alternative NRTI in children weighing at least 25 kg.

f) ATV/r can be used as an alternative to LPV/r for children older than three months, but there is limited availability of appropriate formulations for children younger than six years, a lack of a fixed-dose formulation, and the need for separate drug administration. Ritonavir booster should be considered when choosing this regimen.

g) DRV should not be used in children under three years of age and should be combined with an appropriate dose of ritonavir.

Table 5. Considerations for switching to optimal treatment regimens for children considered stable on ART based on national guidelines

Current regimen	Weight	Optimal regimen to switch	Considerations
ZDV + 3TC + NVP ZDV + 3TC + EFV ABC + 3TC + NVP	< 20 kg	ABC + 3TC + LPV/r	If stable, children can switch to DTG when they reach 20 kg
	20–30 kg	ABC + 3TC + DTG	If stable, children can switch to TDF + 3TC + DTG when they reach 30 kg
	> 30 kg	TDF + 3TC + DTG	–
ABC + 3TC + EFV	< 20 kg	No switches until they reach 20 kg, unless there is therapeutic failure	Switching to optimal regimens for these children is beneficial when they reach 20 kg, and DTG can be used to maintain once-daily administration
	20–30 kg	ABC + 3TC + DTG	If stable, children can switch to TDF + 3TC + DTG when they reach 30 kg
	> 30 kg	TDF + 3TC + DTG	–
ABC + 3TC + LPV/r ZDV + 3TC + LPV/r	< 20 kg	No switch until they reach 20 kg, unless there is therapeutic failure	Ensure pill use as soon as possible to reduce pill burden. Switching from ZDV + 3TC + LPV/r to ABC + 3TC + LPV/r may also be considered to reduce pill burden and preserve the antiviral advantage of NRTI sequencing
	20–30 kg	ABC + 3TC + DTG	If stable, children can be switched to TDF + 3TC + DTG when they reach 30 kg
	> 30 kg	TDF + 3TC + DTG	–

Abbreviations: 3TC—lamivudine; ABC—abacavir; ZDV—zidovudine; DTG—dolutegravir; EFV—efavirenz; LPV/r—lopinavir/ritonavir; NVP—nevirapine; TDF—tenofovir disoproxil fumarate; NRTI—nucleoside reverse transcriptase inhibitor

Centers for Diseasy and preventien Recommendations

The fixed-dose combination of bictegravir (BIC)/emtricitabine (FTC)/tenofovir alafenamide (TAF) is the preferred regimen based on the initial regimen with integrase inhibitors (INSTI) in children at least 2 years of

age who weigh at least 14 kg (previously preferred in children older than 6 years or whose weight is equal to or greater than 25 kg). FTC/TAF is recommended as the preferred combination with two NRTIs in children and adolescents weighing at least 14 kg when used with an INSTI or NNRTI (previously recommended for children and adolescents weighing 25 kg and more). Doravirine (DOR) is the recommended alternative to NNRTI for children and adolescents weighing at least 35 kg, either in a fixed combination of DOR/FTC/tenofovir disoproxil fumarate (TDF) or in combination with any two NNRTIs. This recommendation is based on efficacy and tolerability in adult and pediatric pharmacokinetic studies. A Centers for Diseasy and preventien (CDC) panel recommends use of abacavir (ABC) as the preferred NRTI component from birth in full-term infants after a negative HLA-B5701 test as part of a dual ABC/lamivudine (3TC) or ABC/FTC combination (previously ABC/3TC or ABC/FTC was the preferred NRTI combination after 3 months of age) (32–37).

When to start treatment?

ART consisting of 3 drugs from at least 2 classes should be started in all treatment-naïve C/ALHIV. Postponed treatment of HIV infection is discouraged. Prompt initiation of treatment (within 1–2 weeks of diagnosis) is suggested in all HIV-infected children older than 6 weeks but younger than 12 weeks. This rapid start should be well thought out in order to achieve and maintain adherence in children. Some of these infants will already be on prophylactic treatment (initiated as soon as possible in high-risk infants), and a change in this regimen may be considered. If initiation of ART in a child is unfeasible for any cause, the child's virological and immunological condition (HIV viral load and CD4+ T cells) should be supervised until the treatment start (38).

Historically, some antecedent drugs have been much more toxic and have been connected with enhanced emergence of resistance. Therefore, maintenance therapy used to be commonly advised in different age cohorts and in the initial phase of HIV infection. Nowadays, it has ceased to be the situation, and all C/ALHIV should be treated as soon as possible to evade disease advancement, to avoid infections, to secure growth and sexual maturation, to escape the neurocognitive repercussions of HIV disease, to help in obtaining a normal life span and possibly prevent additional HIV infection spread (treatment as prevention). All children on treatment should be monitored regularly for treatment efficacy and any toxicity associated with therapy (38, 39).

There is sufficient data on the dosage of zidovudine (ZDV), 3TC and NVP for therapy in premature infants. For term infants, there is also enough information for FTC, ABC, and raltegravir (RAL). ABC is not Food and Drug Agency-approved from birth. However, ABC is recommended by a CDC panel based on pharmacokinetics and safety data to be used from birth with administration for HLA-B5701 testing only (must be negative for HLA-B5701 to tolerate the drug). For full-term infants older than 2 weeks (but not preterm infants), there is sufficient data on LPV/r dosing. Triple therapy should be started as soon as the diagnosis is confirmed (40).

Preferred initial therapy in treatment-naïve infants and children consists of a backbone combination of two NRTIs plus an INSTI or NNRTI (preferred) or a protease inhibitor (PI) (alternative and requires boosting). Backbone NRTI options include the following: ABC plus 3TC or FTC preferred after negative HLA-B5701 testing, ZDV substitutes for ABC before HLA testing or if tolerated, effective, and prefers family not to switch. Although ZDV is not the preferred drug for children aged 6 years or more, it might be extended instead of switching to another ART drug if it effectively suppresses the viral load. It is also a replacement option for therapy start in children. NNRTI options comprise the following: for children aged less than 14 days, NVP is the preferred NNRTI. An alternative is rilpivirine therapy for children older than 12 years. Efavirenz is not proposed for children under 3 years of age and is not the preferred therapy because it has multiple side effects that affect sleep and cause neuropsychiatric symptoms (41).

INSTI therapy choices:

- Infants under 14 days of age but ≥ 2 kg: RAL (oral suspension or powder for suspension) can be used for treatment as prophylaxis in high-risk infants. It is an alternative after 4 weeks of age when dolutegravir becomes the preferred therapy.
- Children aged at least 4 weeks and ≥ 3 kg: initial therapy with DTG is preferred
- Children 2 years of age or older (≥ 14 kg): BIC in combination with a fixed dose (FDC) preferred initial therapy
- Children 3 years of age or older (≥ 25 kg): EVG/c is an alternative to INSTI
- Children aged 3 years or older (≥ 25 kg): EVG/c/FTC/TAF is an alternative fixed-dose combination therapy. PI options include the following:
- Children older than 14 days: LPV/r preferred PI therapy
- Children older than 3 months: ATV/r is an alternative therapy
- Children older than 3 years: DRV/r-twice daily is an alternative therapy
- Cobicistat (PI booster) and ritonavir- or cobicistat-boosted regimens can be used as an alternative to ritonavir boosting in children. Additionally, cobicistat-boosted atazanavir and cobicistat-boosted darunavir are suitable alternatives for children (39, 41, 42).

Conclusion

Previous forms of antiretroviral therapy had numerous toxic effects and interactions. Therefore it was justified to delay therapy initiation in order to have less negative impact over time on the health status of C/ALHIV. The new guidelines

currently include therapy that is comfortable for daily use without toxicity. For this reason, it is suggested to start therapy as soon as possible. This not only restores the immune status of the C/ALHIV and prevents opportunistic infections and malignancies, but also affects to some extent the reduction of the level of microinflammation and consequent immunosenescence.

References

1. Dirajlal-Fargo S, Koay WLA, Rakhmanina N. Pediatric Antiretroviral Therapy. Handb Exp Pharmacol 2020;261:285-323. [CrossRef] [PubMed]
2. Amuge P, Lugemwa A, Wynne B, Mujuru HA, Violari A, Kityo CM, et al. Once-daily dolutegravir-based antiretroviral therapy in infants and children living with HIV from age 4 weeks: results from the below 14 kg cohort in the randomised ODYSSEY trial. Lancet HIV 2022 ;9(9):e638-48. [CrossRef] [PubMed]
3. Arage G, Assefa M, Worku T, Semahegn A. Survival rate of HIV-infected children after initiation of the antiretroviral therapy and its predictors in Ethiopia: A facility-based retrospective cohort. SAGE Open Med 2019;7:2050312119838957. [CrossRef] [PubMed]
4. Nalwanga D, Musiime V. Children living with HIV: a narrative review of recent advances in pediatric HIV research and their implications for clinical practice. Ther Adv Infect Dis 2022;9:20499361221077544. [CrossRef] [PubMed]
5. Fortuny C, Deyà-Martínez Á, Chiappini E, Galli L, de Martino M, Noguera-Julian A. Metabolic and renal adverse effects of antiretroviral therapy in HIV-infected children and adolescents. Pediatr Infect Dis J 2015;34(5 Suppl 1):S36-43. [CrossRef] [PubMed]
6. Morris SE, Strehlau R, Shiau S, Abrams EJ, Tiemessen CT, Kuhn L, et al. Healthy dynamics of CD4 T cells may drive HIV resurgence in perinatally-infected infants on antiretroviral therapy. PLoS Pathog 2022;18(8):e1010751. [CrossRef] [PubMed]
7. Jacobs TG, Schouwenburg S, Penazzato M, Archary M, Ruel TD, van den Anker J, et al. What babies need: accelerating access to current and novel antiretroviral drugs in neonates through pharmacokinetic studies. Lancet HIV 2022;9(9):e649-57. [CrossRef] [PubMed]
8. Katusiime MG, Van Zyl GU, Cotton MF, Kearney MF. HIV-1 Persistence in Children during Suppressive ART. Viruses. 2021; 13(6):1134. [CrossRef] [PubMed]
9. European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) study group in EuroCoord. Long-term trends in mortality and AIDS-defining events after combination ART initiation among children and adolescents with perinatal HIV infection in 17 middle- and high-income countries in Europe and Thailand: a cohort study. *PLoS Med* 2018; 15: e1002491. [CrossRef] [PubMed]
10. Turkova A, Waalewijn H, Chan MK, Bollen PDJ, Bwakura-Dangarembizi MF, Kekitiinwa AR, et al. Dolutegravir twice-daily dosing in children with HIV-associated tuberculosis: a pharmacokinetic and safety study within the open-label, multicentre, randomised, non-inferiority ODYSSEY trial. Lancet HIV 2022;9(9):e627-37. [CrossRef] [PubMed]
11. Ruggiero A, Pascucci GR, Cotugno N, Domínguez-Rodríguez S, Rinaldi S, Tagarro A, et al. Determinants of B-Cell Compartment Hyperactivation in European Adolescents Living With Perinatally Acquired HIV-1 After Over 10 Years of Suppressive Therapy. Front Immunol 2022;13:860418. [CrossRef] [PubMed]
12. Ranin J, Brkić S, Marić D, Vrbić M, Ranković A, Popović Dragonjić L, et al. Operating group for the development of the guide. National Guide to Good Clinical Practice. Treatment of people living with HIV infection. Belgrade, 2024. Academy of Medical Sciences of the Serbian Medical Association. Ministry of Health of the Republic of Serbia, Belgrade.
13. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection [Internet]. U.S. Department of Health and Human Services; 2022 Apr 11 [cited 2024 Dec 12]. Available from: https://aidsinfo.nih.gov/guidelines/html/2/pediatric-treatment-guidelines/0
14. Sheahan A, Feinstein L, Dube Q, Edmonds A, Chirambo CM, Smith E, et al. Early Antiretroviral Therapy Initiation and Mortality Among Infants Diagnosed With HIV in the First 12 Weeks of Life: Experiences From Kinshasa, DR Congo and Blantyre, Malawi. Pediatr Infect Dis J 2017;36(7):654-8. [CrossRef] [PubMed]
15. European AIDS Clinical Society. EACS Guidelines. Version 11.1 [Internet]. Brussels: EACS; 2022 [cited 2024 Dec 12]. Available from: https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf
16. European AIDS Clinical Society. EACS Guidelines. Version 12.0 [Internet]. Brussels: EACS; 2023 [cited 2024 Dec 12]. Available from: https://www.eacsociety.org/media/guidelines-12.0.pdf

17.Waalewijn H, Chan MK, Bollen PDJ, Mujuru HA, Makumbi S, Kekitiinwa AR, et al. Dolutegravir dosing for children with HIV weighing less than 20 kg: pharmacokinetic and safety substudies nested in the open-label, multicentre, randomised, non-inferiority ODYSSEY trial. Lancet HIV 2022;9(5):e341-52. [CrossRef] [PubMed]
18.Turkova A, White E, Mujuru HA, Kekitiinwa AR, Kityo CM, Violari A, et al. Dolutegravir as First- or Second-Line Treatment for HIV-1 Infection in Children. N Engl J Med 2021;385(27):2531-2543. [CrossRef] [PubMed]
19.World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach [Internet]. Geneva: WHO; 2021 Jul 16 [cited 2024 Dec12]. Available from: https://www.who.int/news/item/16-07-2021-who-publishes-new-consolidated-hiv-guidelines-for-prevention-testing-treatment-service-delivery-monitoring
20. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. N Engl J Med 2018;378:979–81. [CrossRef] [PubMed]
21.Wang X, Cerrone M, Ferretti F, Castrillo N, Maartens G, McClure M et al. Pharmacokinetics of dolutegravir 100 mg once daily with rifampicin. Int J Antimicrob Agents 2019;54(2):202-6. [CrossRef] [PubMed]
22.World Health Organization. Update of recommendations on first- and second-line antiretroviral regimens [Internet]. Geneva: WHO; 2019 [cited 2024 Dec12]. Available from: https://www.who.int/publications/i/item/WHO-CDS-HIV-19.15
23.World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach [Internet]. Geneva: WHO; 2021 Jul 16 [cited 2024 Dec12]. Available from: https://www.who.int/publications/i/item/9789240031593
24.Lamorde M, Wang X, Neary M, Bisdomini E, Nakalema S, Byakika-Kibwika P et al. Pharmacokinetics, pharmacodynamics, and pharmacogenetics of efavirenz 400 mg once daily during pregnancy and post-partum. Clin Infect Dis 2018;67:785–90. [CrossRef] [PubMed]
25.Cottrell ML, Hadzic T, Kashuba AD. Clinical pharmacokinetic, pharmacodynamic and drug-interaction profile of the integrase inhibitor dolutegravir. Clin Pharmacokinet 2013;52:981–94. [CrossRef] [PubMed]
26.Llibre JM, Pulido F, García F, Garcia Deltoro M, Blanco JL, Delgado R. Genetic barrier to resistance for dolutegravir. AIDS Rev 2015;17(1):56–64. [PubMed]
27.World Health Organization. Guidelines on the public health response to pretreatment HIV drug resistance: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection [Internet]. Geneva: WHO; 2017 [cited 2024 Dec12]. Available from: https://www.who.int/hiv/pub/guidelines/hivdr-guidelines-2017/en
28.Smith RA, Raugi DN, Pan C, Sow PS, Seydi M, Mullins JI et al. In vitro activity of dolutegravir against wild-type and integrase inhibitor-resistant HIV-2. Retrovirology 2015;12:10. [CrossRef] [PubMed]
29.Treviño A, Cabezas T, Lozano AB, García-Delgado R, Force L, Fernández-Montero JM et al. Dolutegravir for the treatment of HIV-2 infection. J Clin Virol 2015;64:12–5. [CrossRef] [PubMed]
30. Vitoria M, Hill A, Ford N, Doherty M, Clayden P, Venter F et al. The transition to dolutegravir and other new antiretrovirals in low- and middle-income countries – what are the issues? AIDS. 2018;32:1551–61. [CrossRef] [PubMed]
31.Cerrone M, Wang X, Neary M, Weaver C, Fedele S, DayWeber I et al. Pharmacokinetics of efavirenz 400 mg once daily coadministered with isoniazid and rifampicin in human immunodeficiency virus–infected individuals. Clin Infect Dis 2018;68(3):446–52. [CrossRef] [PubMed]
32.Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? J Virus Erad 2019;5(1):e45–7. [CrossRef] [PubMed]
33. Dugdale CM, Ciaranello AL, Bekker L-G, Stern ME, Myer L, Wood R et al. Risks and benefits of dolutegravir-and efavirenz-based strategies for South African women with HIV of child-bearing potential: a modeling study. Ann Intern Med 2019;170(9):614–25. [CrossRef] [PubMed]
34.Phillips AN, Venter F, Havlir D, Pozniak A, Kuritzkes D, Wensing A et al. Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study. Lancet HIV 2019;6(2):e116–27. [CrossRef] [PubMed]
35.Atta CA, Fiest KM, Frolkis AD, Jette N, Pringsheim T, St Germaine-Smith C et al. Global birth prevalence of spina bifida by folic acid fortification status: a systematic review and metaanalysis. Am J Public Health 2016;106(1):e24–34. [CrossRef] [PubMed]
36.Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr 2013;62(1):21–7. [CrossRef] [PubMed]
37.Dooley KE, Kaplan R, Mwelase N, Grinsztejn B, Ticona E, Lacerda M et al. Dolutegravir-based antiretroviral therapy for patients co-infected with tuberculosis and HIV: a multicenter, noncomparative, open-label, randomized trial. Clin Infect Dis 2020;70(4):549–56. [CrossRef] [PubMed]
38.Lee C, Sapasap J, LaRochelle J, Smith RO, Badowski ME. Antiretroviral Therapy in Children and Adolescents: A Look Into Modern Single Tablet Regimens. J Pediatr Pharmacol Ther 2021;26(8):783-94. [CrossRef] [PubMed]
39.Centers for Disease Control and Prevention. Revised classification system for human immunodeficiency virus infection in children less than 13 years of age [Internet]. MMWR. 1994;43(No. RR-12). Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00032890.htm
40.Abbas M, Bakhthyar A, Bazzi R. Neonatal HIV [Internet]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022 Sep 20 [cited 2024 Jan]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK55879
41.Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection [Internet]. U.S. Department of

Health and Human Services; 2022 Apr 11 [cited 2024 Dec 12]. Available from: https://aidsinfo.nih.gov/guidelines/html/2/pediatric-treatment-guidelines/0

42. Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014 [Internet]. MMWR. 2014;63(No. RR-3):11-10. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6303a1.htm

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SAVREMENE OPCIJE LEČENJA DECE I ADOLESCENATA KOJI ŽIVE SA HIV INFEKCIJOM

Lidija Popović Dragonjić[1,2], Aleksandar Ranković[1,2], Maja Cvetanović[1,2], Milica Ćosić Petković[1,2], Jelena Spasić[2], Jovana Tomić[1,2], Dane Krtinić[3,4]

[1]Univerzitet u Nišu, Medicinski fakultet, Katedra Infektologija i epidemiologija, Niš, Srbija
[2]Univerzitetski klinički centar Niš, Klinika za infektologiju, Niš, Srbija
[3]Univerzitet u Nišu, Medicinski fakultet, Katedra Farmakologija sa toksikologijom, Niš, Srbija
[4]Univerzitetski klinički centar Niš, Klinika za onkologiju, Niš, Srbija

Kontakt: Lidija Popović Dragonjić
Bulevar dr Zorana Đinđića 81, 18000 Niš, Srbija
E-mail: lidija.popovic.dragonjic@medfak.ni.ac.rs

Cilj lečenja infekcije virusom humane imunodeficijencije (engl. *human immunodeficiency virus* – HIV) i kod odraslih i kod dece i adolescenata jeste postizanje stabilnog odgovora imunosistema na infekciju virusom, koji podrazumeva činjenicu da virus nije detektovan u krvi duže od šest meseci i oporavak imuniteta. Lečenje dece i adolescenata koji žive sa HIV-om (engl. *children and adolescents living with* HIV – C/ALHIV) specifičnije je i teže zbog slabijeg pridržavanja terapije, dužeg trajanja infekcije i posledičnih toksičnih efekata, kao i zbog hronične mikroinflamacije. Još jedan otežavajući faktor predstavlja nedostatak adekvatnih pedijatrijskih farmaceutskih koformulacija u zavisnosti od regiona. Napredak i pojava inovativnih vidova terapije i jasnih smernica doveli su do poboljšanja kvaliteta života i imunološkog statusa dece i adolescenata koji žive sa HIV-om. Kao najčešće korišćene zvanične smernice izdvajaju se preporuke Evropskog kliničkog udruženja za AIDS (engl. *European AIDS Clinical Society* – EACS), Svetske zdravstvene organizacije (SZO) i Centra za kontrolu i prevenciju bolesti (engl. *Center for Disease Control and Prevention* – CDC). Na osnovu pomenutih smernica i lokalnih uslova i mogućnosti formiraju se i nacionalni vodiči na nivou pojedinih država.

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***Ključne reči**: virus humane imunodeficijencije, deca, adolescenti, antiretroviralna terapija, smernice*