Current Infectious Disease Reports (2019) 21: 7
https://doi.org/10.1007/s11908-019-0663-z

PEDIATRIC INFECTIOUS DISEASES (I. BROOK, SECTION EDITOR)

Antiretroviral Resistance Patterns in Children with HIV Infection

J. Nuttall[1] · V. Pillay[1]

Published online: 28 February 2019

Abstract

Purpose of Review To provide an update on the patterns of HIV drug resistance in children, including pretreatment drug resistance (PDR) and acquired drug resistance (ADR), focusing on children in low- and middle-income countries (LMICs) for whom empiric first-line (FL) and second-line (SL) antiretroviral regimens are usually recommended.

Recent Findings High levels of PDR, particularly to non-nucleoside reverse transcriptase inhibitors (NNRTIs), and poor treatment outcomes on NNRTI-based FL antiretroviral therapy (ART) have been widely reported among infants and young children. There is a paucity of recent data on the use of protease inhibitor (PI)-based FL and SL regimens in children, but studies have reported poor tolerability, adherence problems and the development of PI resistance. Limited access to virological monitoring and HIV drug resistance testing contributes to delays in identifying treatment failure due to ADR and delays in switching to SL regimens in children.

Summary Implementation of FL ART regimens that have a higher barrier to developing resistance and are safe and well tolerated is required in order to attain global treatment targets. Although PI-based regimens may be effective as FL or SL treatment in children, lack of appropriate formulations leading to poor tolerability, drug-drug interactions, and cost considerations have negatively impacted their use among children in LMICs. There is hope that dolutegravir-based regimens recommended for children by the World Health Organization will be widely implemented once child-friendly formulations are available, and dosing and safety studies currently underway are completed, and that this will significantly improve treatment outcomes.

Keywords Antiretroviral · HIV · Resistance · Children

Introduction

Antimicrobial resistance (AMR) is an inevitable consequence of the exposure of microorganisms to antimicrobials. In the context of HIV infection, resistance to antiretroviral (ARV) drugs impacts individual patients by reducing the available number of effective treatment options and threatens the success of both prevention and treatment programmes. Minimising HIV drug resistance by achieving high rates of viral suppression among people on treatment is critical to reaching UNAIDS 90-90-90 global treatment targets which aim to diagnose at least 90% of all people with HIV infection, provide antiretroviral therapy (ART) to at least 90% of those diagnosed and ensure that at least 90% of people on ART achieve virological suppression [1].

HIV drug resistance incorporates three main categories of resistance. Acquired HIV drug resistance (ADR) develops when HIV mutations emerge due to viral replication in individuals receiving ARV drugs. Transmitted HIV drug resistance (TDR) is detected in ARV drug-naïve individuals with no history of ARV drug exposure and occurs when previously uninfected individuals become infected with virus that has drug resistance mutations (DRMs). Pretreatment HIV drug resistance (PDR) is detected in ARV drug-naïve individuals initiating ART or individuals with prior ARV drug exposure who are initiating or reinitiating first-line ART. PDR may be either transmitted or acquired drug resistance or both [2••].

The purpose of this review is to provide an update on the patterns of HIV drug resistance in children, focusing on children in developing countries for whom empiric FL and SL

This article is part of the Topical Collection on *Pediatric Infectious Diseases*

✉ J. Nuttall
james.nuttall@uct.ac.za

[1] Paediatric Infectious Diseases Unit, Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, Rondebosch, Cape Town 7700, South Africa

ART regimens are usually recommended in the context of large-scale treatment programmes. The review focuses mainly on research studies published within the past 5 years.

HIV Drug Resistance and Children

UNAIDS estimates that in 2016 there were 2.1 million children < 15 years of age living with HIV infection globally and 160,000 new HIV infections in this age group, almost all as a result of mother to child transmission (MTCT). The estimated coverage of ARV drugs provided to pregnant women to prevent MTCT was 76% in 2016, and since 2010 the estimated numbers of new paediatric HIV infections have decreased by 47% and children dying from AIDS-related illnesses have decreased by 42% [3].

Although widespread implementation of prevention of mother to child transmission (PMTCT) interventions and ART for HIV-infected children has significantly reduced MTCT rates and paediatric HIV-associated mortality rates, increasing rates of PDR and ADR, particularly non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance and also acquired protease inhibitor (PI) resistance, have been reported in children during the last 5 years [4•, 5••, 6–8]. Children may develop ADR as a result of failure of viral suppression on ART, TDR as a result of transmission of resistant HIV from their mother or sexual partner in adolescents, and PDR as a result of TDR and/or prior ARV exposure through HIV transmission prevention interventions, particularly PMTCT programmes, or prior ART. Increasing rates of NNRTI resistance among HIV-infected adults, including pregnant women, contribute to the TDR component of PDR among newly diagnosed HIV-infected infants and children. A recently published systematic review and meta-regression analysis representing 56,044 adults in 63 low- and middle-income countries (LMICs) found prevalence estimates of NNRTI PDR during 2016 to be 11.0% (95% confidence interval (CI) 7.5–15.9) in Southern Africa, 10.1% (95% CI 5.1–19.4) in Eastern Africa, 7.2% (95% CI 2.9–16.5) in Western and Central Africa, and 9.4% (95% CI 6.6–13.2) in Latin America and the Caribbean. The highest annual increases in NNRTI PDR were in Southern Africa (23%, 95% CI 16–29%) [9]. Increasing rates of HIV drug resistance in both adults and children have important implications for selection of effective infant ARV prophylaxis for HIV-exposed infants in PMTCT programmes and selection of effective ART regimens for HIV-infected infants and children.

Table 1 indicates the position and amino acid substitution or insertions of mutations conferring resistance to commonly used PIs, NNRTIs, and nucleoside/nucleotide reverse transcriptase inhibitors (Ns/tRTIs) in children highlighting which substitutions confer high-level resistance to specific ARV drugs [10]. Whereas commonly occurring NNRTI DRMs typically confer intermediate-high-level resistance to multiple drugs in the NNRTI class, intermediate-high-level Ns/tRTI and PI resistance commonly occurs as a result of the cumulative acquisition of multiple DRMs including non-polymorphic accessory resistance mutations which individually are unlikely to cause significant resistance. The purpose of identifying DRMs at an individual or surveillance level is to ascertain which ARV drugs the predominant viral subtypes present are likely to be susceptible to and which ARV drugs should be avoided in ART regimens.

First-Line Antiretroviral Therapy

Pretreatment HIV Drug Resistance

In well-resourced settings, HIV drug resistance testing of individual patients prior to starting ART may be feasible and allow for individually tailored ART regimens. However, in resource-limited settings with large-scale treatment programmes, standardised empiric ART regimens (with the possibility of substitution of a few specific drugs for specific contraindications) are generally recommended for both adults and children. Surveillance of the prevalence and extent of PDR is critically important in determining whether changes to empiric first-line ART regimens are required. The World Health Organization (WHO) considers a national PDR prevalence of > 10% to an ARV drug or drug class as an indication to transition to a different empiric first-line ART regimen. This is based on modelling which predicts that ongoing use of a such a drug or drug class beyond this threshold will prevent attainment of global targets to end AIDS as a public health threat by 2030 [11]. The presence of PDR has been shown to be a strong predictor of treatment failure on first-line ART in children [12].

Single-site studies, national surveys and multi-country systematic reviews of PDR prevalence in children newly diagnosed with HIV infection have been reported during the last 5 years [4•, 5••, 12–15, 16••, 17, 18]. Standardised methodology for nationally representative annual surveys of the prevalence of HIV drug resistance among children < 18 months of age using remnant dried blood spot (DBS) specimens collected as part of routine early infant diagnosis (EID) testing in PMTCT programmes has been developed by the WHO [19]. This methodology is relevant to settings where large numbers of infants are exposed to or acquire HIV infection. Before 2014, the Democratic Republic of Congo, Mozambique, Swaziland, Togo, Uganda and Zimbabwe completed surveys in young children, and Nigeria, South Africa, Ethiopia, Kenya and Malawi have subsequently implemented surveillance [2••].

The WHO completed a systematic review of studies published between 1 January 2014 and 30 April 2017 on PDR in children starting ART in LMICs [2••]. Seven studies were included providing data on 1128 HIV-infected children aged

Table 1 Position and amino acid substitutions or insertions of mutations conferring resistance to commonly used protease inhibitors (PIs), nucleoside/nucleotide reverse transcriptase inhibitors (Ns/tRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) in children

PI mutations													
	30	32	33	46	47	48	50	54	76	82	84	88	90
Consensus (wild-type)	D	V	L	M	I	G	I	I	L	V	I	N	L
ATV/r		I	F	IL	V	VM	L	VTALM		ATFS	V	S	M
DRV/r		I	F		VA		V	LM	V	F	V		
LPV/r		I	F	IL	VA	VM	V	VTALM	V	AFTS	V		M

Ns/tRTI mutations													
	Non-thymidine analogue mutations					Thymidine analogue mutations						Multidrug resistance mutations	
	184	65	70	74	115	41	67	70	210	215	219	61	151
Consensus (wild-type)	M	K	K	L	Y	M	D	K	L	T	K	T	Q
3TC	VI	R										Ins	M
FTC	VI	R										Ins	M
ABC	VI	R	E	VI	F	L			W	FY		Ins	M
TDF		R	E		F	L		R	W	FY		Ins	M
ZDV						L	N	R	W	FY	QE	Ins	M

NNRTI mutations									
	100	101	103	106	138	181	188	190	230
Consensus (wild-type)	L	K	K	V	E	Y	Y	G	M
EFV	I	EP	NS	AM		CIV	LCH	ASE	L
ETR	I	EP			AGKQ	CIV	L	ASE	L
NVP	I	EP	NS	AM		CIV	LCH	ASE	L
RPV	I	EP			AGKQ	CIV	L	ASE	L

Amino acids substitutions marked in red confer high-level resistance

Amino acids: A, alanine; C, cysteine; D, aspartic acid; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine; *Ins*, insertion

Antiretroviral drugs: *ATV/r*, atazanavir/ritonavir; *DRV/r*, darunavir/ritonavir; *LPV/r*, lopinavir/ritonavir; *3TC*, lamivudine; *FTC*, emtricitabine; *ABC*, abacavir; *TDF*, tenofovir; *ZDV*, zidovudine; *EFV*, efavirenz; *ETR*, etravirine; *NVP*, nevirapine; *RPV*, rilpivirine

4–114 months (median 20 months). None of the studies included data on young adolescents aged 13–15 years. Of the 1128 children, 354 (31.3%) had detectable DRMs, the median prevalence of NNRTI resistance was 49.3% (range 7.5–100%) and 4/7 studies found > 50% of PMTCT-exposed children had NNRTI DRMs. Heterogeneity of age, PMTCT exposure status and mutation reporting practices across studies precluded performing a more detailed analysis of pooled data [2••].

A study from South Africa, published in 2014 based on data collected in 2011, reported that in the era of more effective PMTCT regimens including combination ART (cART) for pregnant women and infant ARV prophylaxis with a minimum of 6 weeks of nevirapine (NVP), 122/230 (53%) children < 2 years of age who were newly diagnosed with HIV infection through EID had DRMs. Two-thirds of HIV-infected children had been exposed to maternal and/or infant PMTCT of whom 56.8%, 14.8% and 1.3% had NNRTI, Ns/tRTI and PI mutations respectively. NNRTI mutations occurred more commonly among younger children. Alarmingly, among the children with no reported or recorded PMTCT exposure, resistance to NNRTIs, Ns/tRTIs and PIs was present in 24%, 10.7% and 1.3% respectively. An important conclusion

reached by the authors was that a lack of reported or recorded PMTCT exposure does not exclude PDR [13].

Similar findings were reported in a Ugandan study in children < 12 years of age prior to starting ART which found HIV DRMs in 10% of all the children, 15.2% of children < 3 years of age, 35% of children exposed to PMTCT, 15.6% of children with unknown PMTCT exposure and 7.7% in ARV-naïve children [15]. A recently published Nigerian study assessed the national PDR prevalence in HIV-infected children < 18 months of age using the WHO surveillance protocol and EID remnant DBS methodology. DRMs were detected in 205/430 (48%) infants conferring resistance to NNRTIs in 45%, Ns/tRTIs in 22% and dual class Ns/tRTIs/NNRTIs in 20%. Resistance to PIs was 2%. As in other similar studies, NNRTI and dual class Ns/tRTI/NNRTI DRMs were detected in 54% and 29% respectively of 204 PMTCT-exposed children but DRMs were also detected in 34% of 132 PMTCT-unexposed children [16••].

The findings of these national studies concur with a recently published systematic literature review with meta-analysis of PDR in children in sub-Saharan African (SSA) countries [4•]. Boerma et al. pooled data on 2617 children with a median age of ≤ 12 years in 19 studies from 13 countries and found a statistically significant difference in PDR prevalence of 42.7% (95% CI 26.2–59.1%) in PMTCT-exposed children compared to 12.7% (95% CI 6.7–18.7%) in PMTCT-unexposed children. NNRTI DRMs were detected in 32.4% (95% CI 18.7–46.1%) of PMTCT-exposed and in 9.7% (95% CI 4.6–14.8%) of PMTCT-unexposed children [4•]. The observed increase in PDR prevalence in PMTCT-unexposed children from 0% in 2004 to 26.8% in 2013 is likely to be a reflection of increasing rates of NNRTI TDR from HIV-infected pregnant and/or breastfeeding women to their children although difficulties with verification of PMTCT exposure may be a contributory factor [9, 13, 16••].

An analysis of HIV drug resistance in infants and young children < 18 months of age from Mozambique, Swaziland, South Africa, Uganda and Zimbabwe who were newly diagnosed with HIV infection between 2011 and 2014 provided data on different levels of resistance and the various mutations to different ARV drugs across the different countries [5••]. Overall, the commonest NNRTI DRMs were at positions 181 (29.7%) and 103 (19.2%). In South Africa, the K103N mutation occurred more frequently than mutations at position 181. This is likely to be a reflection of the more prevalent use of efavirenz (EFV)-based ART regimens (as opposed to NVP-based ART) in adults including pregnant and breastfeeding women and earlier adoption of WHO Option B+ in the PMTCT programme with lifelong cART initiation for all pregnant and breastfeeding women regardless of HIV clinical stage and CD4 cell count criteria. Cross-resistance rates of 20–60% to one or both of the second-generation NNRTIs, etravirine and rilpivirine, which are not yet approved for use in young children preclude their usefulness as potential future treatment options either in first-line or subsequent ART regimens among children with NNRTI PDR. Ns/tRTI resistance, the prevalence of which was considerably lower than NNRTI resistance (8.9% compared to 53.0%), was driven mostly by stavudine (D4T) and lamivudine (3TC)/emtricitabine (FTC) resistance reflecting the D4T/3TC NRTI backbone most commonly used in these countries at the time. Overall, the prevalence of Ns/tRTI mutations at position 65, associated with resistance to tenofovir (TDF), was low (< 5%), and in South Africa and Zimbabwe, position 65 mutations were more common than in other countries which may be a reflection of greater TDF use in maternal regimens in these two countries at the time of the study. Although TDF is not commonly used in first-line ART regimens for young children as a result of a lack of availability of paediatric formulations and toxicity concerns, TDF is a potentially important component of second- and third-line ART regimens in older children and adults [5••].

Protease inhibitor PDR in infants and young children newly diagnosed with HIV infection in SSA countries has been found to be very uncommon with prevalence rates of < 3% reported [4•, 5••, 13, 16••, 18, 20]. This is most likely a reflection of low rates of maternal PI-based ART regimens, usually used as second-line treatment in adults, being used during pregnancy and/or breastfeeding at the time of data collection in these studies and the higher barrier of boosted PI regimens to the development of significant PI resistance.

The integrase strand transfer inhibitor (INSTI), raltegravir (RAL), was included as an alternative component of second-line ART regimens in children failing PI-based ART regimens and as a component of third-line ART regimens in adults including pregnant and breastfeeding women in a 2015 WHO guidelines policy brief [21]. Subsequently, dolutegravir (DTG) has been included initially as an alternative and then as the preferred component of first-line and second-line ART regimens in WHO 2016 and 2018 guidance respectively [22, 23••]. INSTI PDR in infants or young children newly diagnosed with HIV infection (as a result of TDR from the mother) or in children with previous INSTI exposure (ADR) may have occurred but has not been reported from LMICs. A study investigating the prevalence and patterns of major and accessory resistance mutations resulting in primary resistance to INSTIs in various HIV-1 subtypes sequenced from 425 INSTI-naive HIV-infected adults found these naturally occurring mutations to be rare and occurring at low-level detection thresholds. This suggests that INSTI-based ART regimens are likely to be effective across the different HIV-1 subtypes prevalent in SSA [24].

Acquired HIV Drug Resistance

The WHO recommendations on first-line ART regimens for children have evolved based on availability of

pharmacokinetic, safety and efficacy data in paediatric populations as well as of ARV formulations suitable for infants and young children. Regimens comprising an NNRTI (NVP in children < 3 years of age, and NVP or EFV in children ≥ 3 years of age) in combination with 2 Ns/tRTIs were initially recommended [25]. The development of PIs and subsequently boosted PIs, and the early recognition that the use of NVP for PMTCT could result in NNRTI-resistant virus in children who became HIV-infected despite PMTCT led to the incorporation of ritonavir (RTV) followed lopinavir/ritonavir (LPV/r) into first-line ART regimens for NVP-exposed infants and young children [26, 27]. In 2013, the WHO-recommended PI-based ART with LPV/r in all children < 3 years of age starting ART regardless of previous NNRTI exposure during PMTCT [28]. This recommendation was based on clinical trials showing superior efficacy of LPV/r-based compared to NVP-based first-line ART in children < 3 years of age together with data showing increasing rates of NNRTI PDR in infants and young children regardless of PMTCT exposure [13, 29, 30].

The WHO undertook a systematic literature review of ADR in children between 2014 and 2017 that included 10 published studies reflecting data collected between 2009 and 2013 in Central African Republic, Rwanda, South Africa, United Republic of Tanzania, Zimbabwe and Indonesia/Thailand/Vietnam [2••]. The studies included children on first-line NNRTI-based ART [31–36], first-line PI-based ART [6, 7, 32] and second-line PI-based ART [36, 37••]. Among 2579 children on ART (median age 8.84 years (range 1–12.2) and median 50.8% males), 988 (38%) had DRMs. In children with DRMs, NNRTI resistance was reported in a median 69.4% (range 12–95%), and K103N and M184V were the most commonly detected reverse transcriptase (RT) mutations, detected in 39.8% and 76.6% of children respectively [2••].

A study from the United Republic of Tanzania, published in 2017 and included in the WHO systematic literature review, illustrates the high rate of virological failure and extent of ARV drug resistance in children failing first-line NNRTI-based ART [31]. In this study, 25.4% of 213 children on ART for a median of 4.3 years (84% on NNRTI-based ART at the time of the study) had virological failure and 90% of children with virological failure had DRMs. Among children with DRMs, resistance to Ns/tRTIs and NNRTIs was found in 80.8% (95% CI 70.1–91.5) and 90.2% (95% CI 82.0–98.4), respectively, conferring major drug resistance against both drug classes in 79% (95% CI 67.7–89.9). No major PI DRMs were found. Pretreatment genotype data showed that more than 85% of these children were likely to have acquired DRMs while on ART [31]. In a cohort study of 198 HIV-infected children (17 years of age) in the Central African Republic on first-line ART regimens, 55% on treatment for a median of 3.4 years had virological failure. Greater than 50% of children with virological failure in whom genotyping results were available were resistant to first-generation NNRTIs and 24% had major PI DRMs [36]. A key issue highlighted by the authors of both of these studies is the need for routine virological monitoring in children on ART. In the Tanzanian study, < 5% of the children fulfilled WHO criteria for immunological failure at the time that they were diagnosed with virological failure and as a result would not have been identified as requiring a switch to a second-line ART regimen [31]. Accumulation of RT DRMs in children and adults from SSA with continued virological failure on first-line NNRTI-based ART as a result of limited availability of virological monitoring and associated delay in switching to second-line ART has been reported. New DRMs accumulated at an average rate of 1.45 (standard deviation (SD) 2.07) DRMs per year, 0.62 (SD 1.11) NNRTI DRMs and 0.84 (SD 1.38) NRTI DRMs per year, respectively, and the predicted susceptibility declined significantly after continued virological failure for all RT inhibitors [38].

In a meta-analysis of 51,347 children < 18 years of age included in 72 studies who were receiving first-line ART during 3 time periods (2000–2005, 2006–2009, 2010–2015), 64.7% (95% CI 57.5–71.8) in the early, 74.2% (95% CI 70.2–78.2) in the intermediate and 72.7% (95% CI 62.6–82.8) in the recent time period achieved viral suppression after 12 months on ART. Rates were similar after 6 and 24 months on ART but were substantially lower (< 65% in all 3 time periods) using an intention-to-treat analysis. The authors expressed concern that viral suppression rates among children in LMICs were lower than those of adults in LMICs and lower than those of children in high-income countries and the lack of progress during the 3 time periods threatened the attainment of the UNAIDS 90-90-90 global treatment targets [20]. As highlighted in the WHO systematic literature review, there is a relative paucity of data focusing on ADR in adolescent populations despite this age group having been identified as being at high risk for poor adherence and lower rates of virological suppression [2••].

The very high levels of ADR due to NNRTI DRMs, frequently occurring in combination with Ns/tRTI DRMs, call into question the future role of NNRTI-based ART regimens in children.

More durable first-line ART regimens, including boosted PI-based or dolutegravir (DTG)-based regimens, for which there are currently very low levels of PDR and which have higher barriers to developing resistance, have been recommended by WHO since 2010 (LPV/r) and 2017 (DTG) [21, 22, 23••, 27, 39]. However, widespread implementation of first-line LPV/r-based ART in young children has been hampered by unavailability of heat-stable, palatable paediatric formulations, lack of fixed-dose combination formulations incorporating Ns/tRTIs and cost considerations. Only 14% of 748,638 children < 15 years of age were receiving boosted PI-based first-line ART in a 2015 WHO global survey on ARV drug use in 66 LMICs [2••].

South African studies investigating DRMs in children failing treatment on a PI-based first-line ART regimen report variable rates of major PI mutations. Pillay et al. (2014) found only 1 child with a major PI DRM (V82A) among

16 children (median age 5 years (2.7–7.5)) failing a LPV/r first-line regimen and the most common pattern for children failing LPV/r was the M184V mutation alone [32]. Meyers et al. (2015) reported that 8/75 (10.7%) children failing LPV/r-based first-line ART had significant PI DRMs including 2 with intermediate resistance to darunavir (DRV) [6]. Rossouw et al. (2015) found major PI DRMs in 32/65 (49%) children (median age 16.8 months (7.8–23.3) initiated on LPV/r-based first-line ART. Advanced clinical disease, severe malnutrition, high baseline viral loads and high rates of tuberculosis coinfection were present at the time of ART initiation in this cohort. Duration of PI treatment and previous use of ritonavir (RTV) as a single unboosted PI were found to be risk factors for development of PI DRMs [7]. Drug-drug interactions between LPV/r and rifampicin are known to reduce plasma concentrations of LPV/r which may lead to virological failure and development of PI DRMs [40, 41]. Although super-boosting of LPV/r with the addition of RTV oral solution in young children with HIV/TB coinfection has been investigated and shown to be effective in overcoming this interaction, implementation of this strategy is limited by non-availability, short expiry time and very poor palatability of RTV oral solution [40, 42].

Approval of paediatric dosing for DTG in children > 6 years of age and weighing > 30 kg (United States Food and Drug Administration) and > 15 kg (European Medicines Agency) has been obtained. Studies investigating dosing of DTG for children < 6 years of age are ongoing. Data on patterns of ARV resistance in children treated with DTG-based first-line ART regimens outside clinical trials is not yet available.

Second-Line Antiretroviral Therapy

In children, second-line ART may be required following treatment failure on an NNRTI-based or PI-based first-line treatment regimen. Data on second-line ART following failure on INSTI-based first-line ART is not yet available.

Following NNRTI-Based First-Line Antiretroviral Therapy

Following NNRTI-based first-line ART treatment failure, a boosted PI-based second-line regimen has been recommended by WHO for both adults and children. Recently, WHO has recommended a second-line regimen comprising DTG plus 2 Ns/tRTIs in children for whom approved DTG dosing and formulations are available, and LPV/r plus 2 Ns/tRTIs in children at an age or weight at which approved DTG dosing is not available. Atazanavir in combination with ritonavir (ATV/r) is an alternative to LPV/r but its use is constrained by lack of suitable formulations for children < 6 years of age and < 15-kg body weight and the lack of a fixed-dose combination formulation with Ns/tRTIs or coformulation with RTV [23••].

As a result of poor access to or implementation of virological monitoring of children on first-line ART and delays in switching children to second-line ART in LMICs, reliable data on the risk factors, need for, and effectiveness of second-line ART regimens in children and adolescents is very limited.

In a study involving 277 children from Indonesia, Thailand and Vietnam with a median age of 7.5 years (interquartile range (IQR) 5.3–10.3) at the time of switching to second-line ART (containing 3TC (90%), TDF (43%), zidovudine (AZT) or abacavir (ABC) (30%), LPV/r (91%), ATV/r (7%)), virological failure on second-line ART occurred in 73/277 (27%). Genotyping at the time of second-line treatment failure was available in 50/73 (68%) children. The following spectrum of DRMs was reported: M184V in 56%, ≥ 1 thymidine analogue mutation (TAM) in 40%, > 4 TAMs in 10%, Q151M in 4%, any major LPV mutations in 8%, > 6 LPV mutations in 2% and any major ATV mutations in 4% [37••].

A recent multicentre analysis of cohorts of children and adolescents treated with second-line ART in LMICs was performed to estimate cumulative rates and predictors of virological failure defined as 2 consecutive viral load measurements > 1000 copies/ml after ≥ 6 months on second-line treatment. Among 928 children from 12 treatment cohorts in 14 countries in Asia and SSA who were receiving PI-based second-line ART, the virological failure rate after 24 months on the second-line regimen was 16.4% (95% CI 13.9–19.4). Adolescents (10–18 years of age) had a significantly higher treatment failure rate than younger children (3–9 years of age), 14.5 (95% CI 11.9–17.6) compared to 4.5 (95% CI 3.4–5.8) per 100 person-years. Adolescence and a shorter duration on first-line ART before switching to second-line treatment (< 24 months) were identified as significant risk factors for treatment failure [43•]. Although the virological failure rates reported in this study are lower than those for children on first-line ART regimens, particularly NNRTI-based regimens, and comparable to outcomes of second-line ART in adult cohorts in LMICs, the high rates among adolescents are likely to contribute to higher mortality rates and HIV transmission rates in this age group. In addition, genotyping that would allow the differentiation of PI resistance from poor adherence to the PI-based second-line regimen is not widely available, and availability of DRV and DTG is currently limited in many LMICs.

Following PI-Based First-Line Antiretroviral Therapy

Following LPV/r-based first-line ART treatment failure, WHO 2016 guidelines recommended RAL plus 2 Ns/tRTIs for children younger than 3 years of age and either EFV or RAL plus 2 Ns/tRTIs for children 3 years of age or older. If RAL is unavailable, WHO recommends continuing on LPV/r-based treatment unless there is progression of clinical disease

or adherence is compromised by poor palatability of the liquid LPV/r formulation in which case switching to a NVP-based regimen may be considered [22].

Updated interim guidance from WHO (July 2018) recommends a DTG-based second-line regimen following LPV/r-based first-line treatment failure in children of an age and weight for which DTG is approved and if DTG is available [23••]. Prospective data supporting the effectiveness and durability of these approaches to second-line ART following failure of LPV/r-based first-line ART in children is lacking.

Third-Line Antiretroviral Therapy

There is currently no standardised third-line ART regimen recommended for all children with treatment failure on second-line ART although interim guidance from WHO recommends DRV/r (not recommended < 3 years of age and dosed twice daily in PI-experienced patients) plus DTG (dosed twice daily in INSTI-experienced patients) plus 1–2 Ns/tRTIs optimised if possible using information from genotyping [23••]. There are very few studies on the safety and efficacy of third-line ART regimens in children and adolescents. One study investigated outcomes among 54 Thai adolescents from 8 study sites with a median age of 14.3 years (IQR 12.4-15.4) at the time of switching to third-line ART who were treated with third-line regimens containing DRV/r, ETR, tipranavir/ritonavir or RAL and followed for 48 weeks. The indication for switching was treatment failure in 44 children and toxicity due to LPV/r-associated hyperlipidaemia in 10 children. In the children with treatment failure, genotyping done prior to switching showed that 50% had triple-class resistance (NRTI, NNRTI and major PI DRMs) and the remainder had similar mutations documented during previous testing. The 10 adolescents switched for toxicity were virally suppressed and did not undergo genotyping. The third-line regimens in all 54 adolescents comprised a median of 4 (range 4–6) ARVs. One child died from a non-ARV-associated cause and 2 were lost to follow-up. Six adverse events that may have been related to third-line ARVs included headache, gastrointestinal symptoms, rash, lipoatrophy and elevated triglycerides. A statistically significant improvement in median cholesterol and triglycerides among the 10 adolescents with hyperlipidaemia was reported. The median CD4 count in 47 adolescents with available data increased significantly from 16 to 21% and 410 to 607 cells/mm^3 after 48 weeks, and 72% and 66% of 50 adolescents with available data had HIV-1 RNA < 400 and < 50 copies/ml respectively after 48 weeks. Ninety percent of the adolescents who switched for toxicity remained virally suppressed after 48 weeks. Among 17 (31%) adolescents with HIV-1 RNA ≥ 1000 copies/ml, genotyping showed an ETR DRM score ≥ 4 in 2 (15%) and ≥ 1 major DRV DRM in 7 (54%) [44••].

A study from South Africa described 35 children with a median age of 8.8 years (IQR 5.5–11) who had received various first-line and second-line ART regimens for a median of 6.9 years (IQR 5–9.9) and subsequently started a DRV/r-, RAL- or ETR-containing ART regimen. At the time of the study, DTG was not available in South Africa [45•]. The main eligibility criterion for treatment with a DRV/r-, RAL- or ETR-containing regimen was the presence of PI resistance on genotyping (LPV/r or ATV/r mutation score of ≥ 15 using the Stanford genotypic resistance interpretation algorithm [10]). An important finding was that 12 of the 35 children (34.3%) had received only a PI-based first-line ART regimen (all RTV or LPV/r-based first-line ART but including single-drug substitutions from RTV to LPV/r, a single NRTI switch or temporary 3TC monotherapy) prior to the development of PI DRMs and switch to an expert committee-guided, individually tailored DRV/r-, RAL- or ETR-containing regimen. This was in keeping with HIV treatment guidelines in the Western Cape province of South Africa which makes provision for genotyping children with virological failure on PI-based first-line ART before deciding on second-line treatment [46]. In addition, 18 children (54%) had mutations conferring low- (n = 17, 48.6%) or intermediate-level (n = 1, 2.9%) resistance to DRV/r, and 16 children had mutations conferring low (n = 6, 17.1%), intermediate (n = 8, 22.9%) or high (n = 2, 5.7%) resistance to ETR prior to starting a DRV/r-, RAL- or ETR-containing regimen. After a median of 2 years (IQR 1.3–4) on treatment, 29/30 (96.7%) and 23/30 (76.7%) subjects with available results had HIV-1 RNA levels of < 400 and < 50 copies/ml, respectively [45•].

The limited available data suggests that treatment regimens containing 1 or more of DRV/r, an INSTI or ETR may be effective in children and adolescents failing treatment on first-line or second-line PI-based ART. Children and adolescents frequently have high rates of virological failure on PI-based ART regimens that may occur as a result of poor treatment adherence, poor tolerance or side-effects of medication, or PI resistance. Genotyping is needed to confirm or exclude PI resistance and guide the combination of ARVs used in a third-line regimen until new standardised regimens have been formulated.

Conclusion

This review highlights the multiple ways in which antiretroviral resistance impacts infants and young children. These include transmitted drug resistance from a pregnant or breastfeeding mother to her child, pretreatment drug resistance occurring as a result of transmitted drug resistance or acquired following exposure to ARVs used as part of PMTCT programmes and acquired drug resistance in children with treatment failure on first-, second- or third-line ART regimens. High levels of pretreatment drug resistance to NNRTIs among

infants and young children identified through national surveillance programmes and large studies necessitate the need for urgent and widespread implementation of PI-based or DTG-based first-line ART regimens for children. Access to virological monitoring in all children on ART and genotype resistance testing in children with treatment failure on PI-based regimens is needed to improve treatment outcomes.

Compliance with Ethical Standards

Conflict of Interest J Nuttall has received payment as a member of HIV paediatric advisory boards for GlaxoSmithKline, Johnson and Johnson and Mylan, and received speaker honoraria from Mylan. V Pillay declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. UNAIDS. 90-90-90: An ambitious treatment target to help end the AIDS epidemic. Geneva; 2014.
2.•• World Health Organization. HIV drug resistance report. 2017. **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.**
3. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS Data 2017. 2017. http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf. Accessed 4 Aug 2018.
4.• 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. J Antimicrob Chemother. 2017;72(2):365–71. https://doi.org/10.1093/jac/dkw463 **Highlights the increasing rate of pretreatment drug resistance to NNRTIs in sub-Saharan African children < 12 years of age and the impact of PMTCT exposure.**
5.•• 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. Clin Infect Dis. 2017;65(12):2018–25. https://doi.org/10.1093/cid/cix698 **Provides data on rates of pretreatment drug resistance and frequencies of various NNRTI and NRTI mutations in children < 18 months of age.**
6. Meyers T, Sawry S, Wong JY, Moultrie H, Pinillos F, Fairlie L, et al. Virologic failure among children taking lopinavir/ritonavir-containing first-line antiretroviral therapy in South Africa. Pediatr Infect Dis J. 2015;34(2):175–9. https://doi.org/10.1097/inf.0000000000000544.
7. Rossouw TM, Feucht UD, Melikian G, van Dyk G, Thomas W, du Plessis NM, et al. Factors associated with the development of drug resistance mutations in HIV-1 infected children failing protease inhibitor-based antiretroviral therapy in South Africa. PLoS One. 2015;10(7):e0133452. https://doi.org/10.1371/journal.pone.0133452.
8. Tadesse B, Kinloch N, Baraki B, Lapointe H, Cobarrubias K, Brockman M, et al. High levels of dual-class drug resistance in hiv-infected children failing first-line antiretroviral therapy in Southern Ethiopia. Viruses. 2018;10(2). https://doi.org/10.3390/v10020060.
9. Gupta RK, Gregson J, Parkin N, Haile-Selassie H, Tanuri A, Andrade Forero L, et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. Lancet Infect Dis. 2018;18(3):346–55. https://doi.org/10.1016/s1473-3099(17)30702-8.
10. Stanford HIV drug resistance database, major HIV-1 drug resistance mutations. 2018. https://hivdb.stanford.edu/assets/media/resistance-mutation-handout-oct2018.85a4841b.pdf. Accessed 16 Nov 2018.
11. World Health Organization. Guidelines on the public health response to pretreatment HIV drug resistance. In: Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: second edition June 2016. 2017.
12. Boerma RS, Boender TS, Sigaloff KC, Rinke de Wit TF, van Hensbroek MB, Ndembi N, et al. High levels of pre-treatment HIV drug resistance and treatment failure in Nigerian children. J Int AIDS Soc. 2016;19(1):21140. https://doi.org/10.7448/ias.19.1.21140.
13. Kuhn L, Hunt G, Technau KG, Coovadia A, Ledwaba J, Pickerill S, et al. Drug resistance among newly diagnosed HIV-infected children in the era of more efficacious antiretroviral prophylaxis. AIDS (London, England). 2014;28(11):1673–8. https://doi.org/10.1097/QAD.0000000000000261.
14. Salou M, Butel C, Konou AA, Ekouevi DK, Vidal N, Dossim S, et al. High rates of drug resistance among newly diagnosed HIV-infected children in the National Prevention of Mother-to-child Transmission Program in Togo. Pediatr Infect Dis J. 2016;35(8):879–85. https://doi.org/10.1097/inf.0000000000001203.
15. Kityo C, Sigaloff KC, Sonia Boender T, Kaudha E, Kayiwa J, Musiime V, et al. HIV drug resistance among children initiating first-line antiretroviral treatment in Uganda. AIDS Res Hum Retrovir. 2016;32(7):628–35. https://doi.org/10.1089/aid.2015.0215.
16.•• Inzaule SC, Osi SJ, Akinbiyi G, Emeka A, Khamofu H, Mpazanje R, et al. High Prevalence of HIV Drug Resistance Among Newly Diagnosed Infants Aged <18 Months: Results From a Nationwide Surveillance in Nigeria. J Acquir Immune Defic Syndr. 2018;77(1):e1–7. https://doi.org/10.1097/qai.0000000000001553 **Recent study using WHO-recommended HIV drug resistance surveillance protocol highlighting the very high rate of pretreatment NNRTI resistance irrespective of knowledge of PMTCT-exposure status among infants and young children diagnosed through the EID programme.**
17. Shao ER, Kifaro EG, Chilumba IB, Nyombi BM, Moyo S, Gaseitsiwe S, et al. HIV-1 drug mutations in children from northern Tanzania. J Antimicrob Chemother. 2014;69(7):1928–32. https://doi.org/10.1093/jac/dku087.
18. Andrade SD, Sabido M, Monteiro WM, Benzaken AS, Tanuri A. Drug resistance in antiretroviral-naive children newly diagnosed

with HIV-1 in Manaus, Amazonas. J Antimicrob Chemother. 2017;72(6):1774–83. https://doi.org/10.1093/jac/dkx025.
19. World Health Organization. Surveillance of HIV drug resistance in children newly diagnosed with HIV by early infant diagnosis December 2017.
20. Boerma RS, Boender TS, Bussink AP, Calis JC, Bertagnolio S, Rinke de Wit TF, et al. Suboptimal viral suppression rates among HIV-infected children in low- and middle-income countries: a meta-analysis. Clin Infect Dis. 2016;63(12):1645–54. https://doi.org/10.1093/cid/ciw645.
21. World Health Organization. Policy brief. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. What's new. 2015.
22. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach, 2nd ed. 2016.
23.•• World Health Organization. Policy Brief. Update on antiretroviral regimens for treating and preventing HIV infection and update on early infant diagnosis of HIV. HIV treatment - interim guidance. 2018. **The WHO policy shift on ART sequencing options to recommend DTG-based regimens in first-, second- and third-line ART for all eligible patients in whom approved dosing is available.**
24. Inzaule SC, Hamers RL, Noguera-Julian M, Casadellà M, Parera M, Rinke de Wit TF, et al. Primary resistance to integrase strand transfer inhibitors in patients infected with diverse HIV-1 subtypes in sub-Saharan Africa. J Antimicrob Chemother. 2018;73(5):1167–72.
25. World Health Organization. Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach. 2004.
26. Arrive E, Newell ML, Ekouevi DK, Chaix ML, Thiebaut R, Masquelier B, et al. Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. Int J Epidemiol. 2007;36(5):1009–21. https://doi.org/10.1093/ije/dym104.
27. World Health Organization. Antiretroviral therapy for HIV infection in infants and children: towards universal access. Recommendations for a public health approach. 2010 revision 2010.
28. World Health Organization. Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013.
29. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early antiretroviral therapy and mortality among HIV-infected infants. Engl J Med. 2008;359(21):2233–44. https://doi.org/10.1056/NEJMoa0800971.
30. Violari A, Lindsey JC, Hughes MD, Mujuru HA, Barlow-Mosha L, Kamthunzi P, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. N Engl J Med. 2012;366(25):2380–9. https://doi.org/10.1056/NEJMoa1113249.
31. 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 (London, England). 2017;31(1):61–70. https://doi.org/10.1097/qad.0000000000001273.
32. Pillay S, Bland RM, Lessells RJ, Manasa J, de Oliveira T, Danaviah S. Drug resistance in children at virological failure in a rural KwaZulu-Natal, South Africa, cohort. AIDS Res Ther. 2014;11(1):3.
33. 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. https://doi.org/10.1371/journal.pone.0144057.
34. Dow DE, Shayo AM, Cunningham CK, Reddy EA. Durability of antiretroviral therapy and predictors of virologic failure among perinatally HIV-infected children in Tanzania: a four-year follow-up. BMC Infect Dis. 2014;14:567. https://doi.org/10.1186/s12879-014-0567-3.
35. Mutwa PR, Boer KR, Rusine J, Muganga N, Tuyishimire D, Schuurman R, et al. Long-term effectiveness of combination antiretroviral therapy and prevalence of HIV drug resistance in HIV-1-infected children and adolescents in Rwanda. Pediatr Infect Dis J. 2014;33(1):63–9. https://doi.org/10.1097/INF.0b013e31829e6b9f.
36. Mossoro-Kpinde CD, Gody JC, Mboumba Bouassa RS, Mbitikon O, Jenabian MA, Robin L, et al. High levels of virological failure with major genotypic resistance mutations in HIV-1-infected children after 5 years of care according to WHO-recommended 1st-line and 2nd-line antiretroviral regimens in the Central African Republic: a cross-sectional study. Medicine. 2017;96(10):e6282. https://doi.org/10.1097/md.0000000000006282.
37.•• 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. JAIDS J Acquir Immune Defic Syndr. 2016;72(4):380–6. https://doi.org/10.1097/qai.0000000000000971 **One of the few studies on second-line PI-based ART outcomes in children and adolescents with data on genotyping.**
38. Boender TS, Kityo CM, Boerma RS, Hamers RL, Ondoa P, Wellington M, et al. Accumulation of HIV-1 drug resistance after continued virological failure on first-line ART in adults and children in sub-Saharan Africa. J Antimicrob Chemother. 2016;71(10):2918–27. https://doi.org/10.1093/jac/dkw218.
39. World Health Organization. HIV treatment. Transition to new antiretrovirals in HIV programmes. Geneva; 2017. July 2017.
40. Ren Y, Nuttall JJ, Egbers C, Eley BS, Meyers TM, Smith PJ, et al. Effect of rifampicin on lopinavir pharmacokinetics in HIV-infected children with tuberculosis. J Acquir Immune Defic Syndr. 2008;47(5):566–9. https://doi.org/10.1097/QAI.0b013e3181642257.
41. McIlleron H, Ren Y, Nuttall J, Fairlie L, Rabie H, Cotton M, et al. Lopinavir exposure is insufficient in children given double doses of lopinavir/ritonavir during rifampicin-based treatment for tuberculosis. Antivir Ther. 2011;16(3):417–21. https://doi.org/10.3851/imp1757.
42. Rabie H DP, Lee J, Kindra G, Coovadia A, Pillay S et al. Lopinavir ritonavir (1:1 ratio) in the presence of rifampicin is not inferior to lopinavir ritonavir (4:1 ratio) in the absence of rifampicin in human immune deficiency virus (HIV) children. In: Interim analysis of an open label sequential non-randomized pharmacokinetics study.7th International Workshop on HIV Pediatrics, 17–18 July 2015. Vancouver, Canada; 2015.
43.• Boerma RS, Bunupuradah T, Dow D, Fokam J, Kariminia A, Lehman D, et al. Multicentre analysis of second-line antiretroviral treatment in HIV-infected children: adolescents at high risk of failure. J Int AIDS Soc. 2017;20(1):21930. https://doi.org/10.7448/ias.20.1.21930 **Highlights the disproprtionately high risk of second-line PI-based ART treatment failure in adolescents.**
44.•• Prasitsuebsai W, Sophonphan J, Chokephaibulkit K, Wongsawat J, Kanjanavanit S, Kosalaraksa P, et al. Treatment outcomes of third-line antiretroviral regimens in HIV-infected Thai adolescents. Pediatr Infect Dis J. 2017;36(10):967–72. https://doi.org/10.1097/inf.0000000000001638 **One of the very few studies on third-line ART in adolescents.**
45.• Nuttall J, Pillay V. Characteristics and early outcomes of children and adolescents treated with darunavir/ritonavir-, raltegravir- or etravirine-containing antiretroviral therapy in the Western Cape Province of South Africa. S Afr Med J. 2018;108(2):105–10. https://doi.org/10.7196/SAMJ.2017.v108i2.12573 **Describes a cohort of children and adolescents with PI resistance who accessed individualised ART regimens comprising third-line ARVs via a decentralised treatment programme.**
46. Western Cape Government Health. The Western Cape antiretroviral treatment guidelines. 2013.