



HIV Drug Resistance in Children and Adolescents: Always a Challenge?

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Accepted: 8 March 2021 / Published online: 18 March 2021
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Abstract

Purpose of Review With the expanded roll-out of antiretrovirals for treatment and prevention of HIV during the last decade, the emergence of HIV drug resistance (HIVDR) has become a growing challenge. This review provides an overview of the epidemiology and trajectory of HIVDR globally with an emphasis on pediatric and adolescent populations.

Recent Findings HIVDR is associated with suboptimal virologic suppression and treatment failure, leading to an increased risk of HIV transmission to uninfected people and increased morbidity and mortality among people living with HIV. High rates of HIVDR to non-nucleoside reverse transcriptase inhibitors globally are expected to decline with the introduction of the integrase strand transfer inhibitors and long-acting combination regimens, while challenge remains for HIVDR to other classes of antiretroviral drugs.

Summary We highlight several solutions including increased HIV viral load monitoring, expanded HIVDR surveillance, and adopting antiretroviral regimens with a high-resistance barrier to decrease HIVDR. Implementation studies and programmatic changes are needed to determine the best approach to prevent and combat the development of HIVDR.

Keywords HIV · Antiretroviral resistance · Pre-exposure prophylaxis · Prevention of mother-to-child transmission · Children · Adolescents

Introduction

Since the first cases of HIV were reported in 1981, an estimated 32.7 million people have died from AIDS-related illnesses and 75.7 million people have become infected with HIV globally [1]. With the advances and scale-up of antiretroviral therapy (ART), there has been a significant decline in global mortality and improvement of life expectancy of people living with HIV

(PLHIV) [2, 3]. Despite this progress, major gaps persist in the prevention and identification of HIV infection, access to care and treatment, and retention in care [4]. In 2019, out of approximately 38 million people estimated to be living with HIV, 81% were aware of their HIV diagnosis, 67% were receiving ART, and 59% achieved virologic suppression [1]. Work remains in order to achieve the goals set by the World Health Organization (WHO) and the Joint United Nations Programme on HIV and AIDS (UNAIDS) to eliminate AIDS as a public health threat by 2030, diagnose 95% of all PLHIV, provide treatment to 95% of those diagnosed, and ensure that 95% of PLHIV on treatment achieve sustained virologic suppression [5].

The introduction of new efficacious and better tolerated antiretroviral drugs (ARV) and ART regimens has been vital in controlling the HIV epidemic [6, 7]. Furthermore, major advances have been made in HIV testing, care, and treatment paradigms [8–10]. ART eligibility was expanded from initial guidance for immunologically suppressed patients with CD4 counts <200 cells/mm³, to PLHIV with a CD4 count ≤500 cells/mm³ plus other high-risk groups in 2013, and subsequently to all PLHIV regardless of CD4 count in 2015 [11, 12]. Prevention of mother-to-child HIV transmission (PMTCT)

This article is part of the Topical Collection on *Infectious Disease Epidemiology*

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achieved a dramatic reduction of perinatal HIV transmission and infant morbidity and mortality globally, with new HIV infections among children having declined by 52%, from ~310,000 in 2010 to 150,000 in 2019 [1, 13–15]. The PMTCT paradigm has also contributed to viewing “treatment as prevention” and the introduction of the concept of “undetectable=untransmittable” (U=U) and pre-exposure prophylaxis (PrEP) with ARVs among uninfected people at risk for acquiring HIV [12, 16, 17].

The “test and treat” strategy of universal voluntary HIV testing and immediate ART initiation was shown by mathematical modeling to significantly reduce new HIV infections [18], and has been recommended by WHO and most national HIV treatment guidelines for all PLHIV since 2016 [12]. In recent years, randomized population-based trials in sub-Saharan Africa, the center of the global HIV epidemic, have demonstrated that this approach resulted in >90% of PLHIV being aware of their diagnosis, 88–97% of those diagnosed with HIV received ART, and ≥87% of PLHIV receiving ART achieved virologic suppression [9, 19–22]. In 2019, 68% of adult PLHIV had access to ART, while 53% of children living with HIV aged 0–14 years had access to ART [1].

Despite growing ART coverage among PLHIV, virologic suppression is not uniform across diverse regions and populations [9]. The prevalence of virologic suppression in PLHIV who received ART in 2018 was reported to range from 59 to >95% in Asia and the Pacific, 47 to 83% in Western and Central Africa, 73 to >95% in Eastern and Southern Africa, and 80 to >95% in Western and Central Europe and North America [23]. Compared to adults, children living with HIV have significantly lower rates of virologic suppression, especially infants and young children aged <2 years, and those treated with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART regimens [24, 25•, 26]. Virologic suppression rates are also lower among adolescents [27–31], women [32–34], homeless people [35–37], injection drug users [38, 39], and substance users [37, 40].

HIV drug resistance (HIVDR), in addition to prompt linkage to care, ART adherence, early initiation of effective ART that is well tolerated, and accounts for food and drug interactions, is one of the key factors associated with achieving and sustaining virologic suppression among PLHIV [41–48]. HIVDR negatively affects the effectiveness of ART and decreases rates of virologic suppression, leading to treatment failure, immunologic decline, and increased HIV morbidity and mortality. HIVDR to certain ARV classes, such as NNRTIs [49•, 50•], recommended as the first-line ART and PMTCT regimen in low- and middle-income countries through 2018 [51], posed a considerable challenge to achieving the last two of the 95-95-95 global targets and preventing the spread of HIV.

Suboptimal adherence to ART has long been identified as a major contributor to the development of HIVDR among

PLHIV [47, 48], and is considered a potential risk for developing HIVDR among PrEP users who become diagnosed with HIV [52]. In resource-limited settings facing the highest burden of the HIV epidemic, challenges with procurement of ARVs and suboptimal HIV services are two other major contributors to the development of HIVDR among PLHIV [53, 54]. Suboptimal access to, and long turnaround times for HIV viral load (VL) and HIVDR testing, and the limited capacity to translate those results into clinical practice also remain challenging in resource-limited settings [54, 55]. Major barriers to suboptimal access to HIVDR testing include its high cost and the need for complex laboratory infrastructure which are often unavailable in resource-limited settings [54]. Moreover, the cascade of HIV care and treatment remains vulnerable to the global economic and health challenges such as the ongoing Coronavirus Disease 2019 (COVID-19) pandemic. Current estimates of the impact of the COVID-19 pandemic on the care of PLHIV suggest that disruptions to provision of HIV services and shortages of ARVs may lead to an almost doubling of HIV-related deaths and mother-to-child transmission of HIV in sub-Saharan Africa alone [56]. The development of HIVDR is another serious consequence to consider in the settings of potential shortages in ARVs and disruptions in HIV care.

In recent years, the impact of HIVDR on treatment outcomes, particularly among pediatric and adolescent populations [24, 25•, 26, 57], men who have sex with men (MSM) [58], and injection drug users [59], has become a growing concern. Alarming rates of HIVDR to NNRTIs have been reported in association with expanded access to ART, PMTCT, and prolonged use of failing ART regimens in patients without virologic suppression [24, 46, 50•, 60]. The introduction and scale-up of highly efficacious integrase strand transfer inhibitors (INSTIs) that have a high barrier to resistance [41, 61, 62] as the preferred first- and second-line ARVs [51, 63–67] has brought new hope that the scope of HIVDR may be reduced in the future. The recent (2020) approval of dolutegravir (DTG) for use in infants and young children by the US Food and Drug Administration (FDA) has positioned this INSTI as the preferred ARV for these vulnerable populations as well [68]. At the same time, the scale-up of PrEP and anticipated introduction of long-acting ARVs into clinical practice globally has generated questions about their impact on HIVDR in the coming years. This review will discuss the evolution and epidemiology of HIVDR globally with a special emphasis on pediatric populations and current data on HIVDR among novel ARVs.

Overview of the Global HIV Drug Resistance Landscape

The use of HIVDR testing in resource-limited settings requires authorization and is limited to PLHIV who are

consistently failing ART, whereas HIVDR testing is performed routinely in PLHIV initiating and failing ART in resource-rich settings [69]. The prevalence of HIVDR globally is studied through surveillance mainly for nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and NNRTIs, and increasingly for protease inhibitors (PIs) and INSTIs. The focus on HIVDR surveillance on NRTIs and NNRTIs is logical, given that they comprised first-line ART regimens until recently, require fewer genetic mutations to reduce viral susceptibility, and have a lower genetic barrier to resistance compared with PIs and INSTIs [69]. There is essentially no cross-resistance between drug classes (e.g., resistance to NRTIs does not translate into resistance to NNRTIs, PIs, or INSTIs), but there is significant cross-resistance within certain drug classes, because most HIVDR mutations reduce the susceptibility to multiple ARVs of the same class [69].

HIVDR is typically divided into three main categories: acquired HIV drug resistance (ADR), transmitted HIV drug resistance (TDR), and pretreatment HIV drug resistance (PDR) [49••]. ADR develops when HIV mutations emerge in individuals receiving ART, often secondary to poor adherence or treatment interruption. TDR is detected in individuals with no history of previous ARV exposure (i.e., treatment-naïve) and occurs when individuals are infected with virus that has HIVDR mutations. PDR is detected either in treatment-naïve individuals or in individuals with prior ARV exposure (i.e., treatment-experienced) who are initiating ART. PDR can be either transmitted or acquired drug resistance, or both [49••]. The prevalence of ADR, TDR, and PDR differ between resource-rich and resource-limited settings due to the differences in factors affecting development of HIVDR outlined in Table 1.

ARV, antiretroviral; *ART*, antiretroviral therapy; *HIVDR*, HIV drug resistance; *INSTI*, integrase strand transfer inhibitor; *PMTCT*, prevention of mother-to-child transmission of HIV; *PrEP*, pre-exposure prophylaxis; *NNRTI*, non-nucleoside reverse transcriptase inhibitor; *VL*, viral load

HIV Drug Resistance in Resource-Rich Settings

PLHIV in resource-rich settings have wider and more ample access and experience with diverse ARVs and, therefore, have had historically higher rates of HIVDR. In a large study of almost 85,000 samples from treatment-naïve and treatment-experienced adult PLHIV in the USA during 2012–2018, 33% of samples demonstrated reduced susceptibility to at least one ARV [70]. NNRTI resistance was common (~75% of samples with any resistance) and PI and INSTI resistance were significantly less common (8% and 17%, respectively) in 2018 [70]. During 2015–2016, a French study reported prevalence rates of TDR in treatment-naïve PLHIV, with PI and INSTI resistance of 11% and 9%, respectively [71]. In

contrast, 2013 data from the UK reported low rates of TDRs at 6.6%, including PI resistance at 1.7%, and no major INSTI resistance among treatment-naïve PLHIV [36].

More concerning are the data on the increasing prevalence of INSTI TDRs in an urban US setting within a cohort in Washington, DC, USA, during 2004–2013 (0.0 to 1.4%, $p=0.04$) [72]. While the overall INSTI ADRs remained low at 1.8% in this US study in 2013 [72], 40% of INSTI-experienced patients in a recent study (2008–2017) from Italy were reported to have at least one major INSTI resistance mutation, with a preponderance of INSTI resistance among patients with higher HIV VL [73]. These data suggest that despite the high resistance threshold of INSTIs, with the increasing use of these ARVs globally, INSTI-experienced patients will need to be monitored closely for the INSTI HIVDR.

Reassuringly, the rate of multiclass ADR in heavily treatment-experienced PLHIV in resource-rich settings has decreased over the past decade, with a prevalence of three-class (NRTI, NNRTI, PI) resistance at only 6.7% and four-class (NRTI, NNRTI, PI, INSTI) resistance at <2% in 2014 [74]. Despite relatively low rates of three- or four-class ADR, heavily treatment-experienced PLHIV remain a vulnerable cohort of patients with an urgent need for novel ARV agents.

HIV Drug Resistance in Resource-Limited Settings

Data from resource-limited settings suggest high rates of PDR and TDR to NRTIs and NNRTIs. Surveillance by the WHO during 2014–2018 reported that 12 out of 18 low- and middle-income countries (5 from sub-Saharan Africa, 5 from the Americas, 2 from Western Pacific) had NNRTI PDR >10% [49••]. A 2016 systematic review and meta-regression analysis of 56,044 adult PLHIV from 63 low- and middle-income countries found NNRTI PDR prevalence to be between 7.2 and 11.0% [60]. It was estimated that the increase in prevalence of PDR between 2015 and 2016 was higher in southern Africa (1.8%) compared to Asia (0.3%) [60].

Unfortunately, the rates of ADR in resource-limited settings have generally increased over time. Surveillance of ADR in 9 low- and middle-income countries by the WHO during 2014–2018 identified a prevalence of NNRTI PDR ranging from 50% in Eswatini to 97% in Uganda among PLHIV receiving ART for ~12 months. Among PLHIV receiving ART for ≥48 months, most of the surveyed countries had higher rates of NNRTI, NRTI, and dual-class NNRTI and NRTI ADR [49••]. Similarly, in a systematic review of seven studies in resource-limited settings, the majority of which were in sub-Saharan Africa, overall ADR was detected in 7.2% of patients on ART for 6–11 months, compared to 20.7% of patients on ART for ≥36 months [75]. The development of multi-class drug resistance also increased over time (3.7% and 21.6% at

Table 1 Challenges and solutions to the development of HIVDR

Challenges	Solutions
ART and patient factors	
<ul style="list-style-type: none"> • Suboptimal ART and PrEP adherence • Infant PMTCT exposure to NNRTIs, leading to higher PDR in infants with perinatal HIV* • Widespread use of NNRTIs as a first-line ART in young children* • Prolonged breastfeeding of HIV-exposed infants with suboptimal maternal adherence and viral suppression* • ARVs toxicity and drug-drug and food-drug interactions • Inadequate access to ARVs* 	<ul style="list-style-type: none"> • Using potent INSTIs as first- and second-line ART regimens across all populations including pregnant and breastfeeding women, infants, and young children • Simplified formulations and dosing of ARVs in infants and young children • Routine medication review to address drug-drug and food-drug interactions • Dual ART regimens and long-acting injectable ARVs to decrease toxicity, drug-drug, and food-drug interactions and improve ART and PrEP adherence • Addressing ARV forecasting and procurement gaps for ART and PrEP • Roll out of novel ARVs and therapies with high resistance barrier • Stronger patient engagement, education, and adherence support with focus on vulnerable populations
Laboratory and testing related factors	
<ul style="list-style-type: none"> • Limited access to HIV viral load (VL) monitoring* • Limited access to HIV drug resistance (HIVDR) testing* • Suboptimal HIVDR surveillance* 	<ul style="list-style-type: none"> • Point-of-care VL testing • Affordable HIVDR testing, preferably combined with VL testing • Expanded HIVDR surveillance at initiation of ART and in people with unsuppressed VL
Health system factors	
<ul style="list-style-type: none"> • High cost and limited capacity to conduct HIVDR* • Suboptimal health system capacity to address VL failure, HIVDR, and support adherence* 	<ul style="list-style-type: none"> • Decreased cost and increased implementation of HIVDR surveillance • Increased health system capacity to monitor VL and manage VL failure and HIVDR • Modeling and cost-effectiveness analysis • Implementation and operational research

*These factors are known to have a stronger impact on HIVDR in resource-limited settings compared with resource-rich settings

6–11 months and ≥ 36 months, respectively) [75]. Not surprisingly, the extent of ADR is most pronounced in PLHIV experiencing virologic failure. Among 171 treatment-experienced PLHIV with virologic failure in Uganda, Kenya, Tanzania, and Nigeria during 2013–2019, ADR were observed for NNRTIs in 82.5%, for NRTIs in 66.7%, and for PIs in 1.8% of participants, respectively [76]. These data collectively highlight the importance of routine VL monitoring for early identification and management of virologic failure in the context of developing ADR.

HIV Drug Resistance in Pregnant Women, Children, and Adolescents

High rates of NNRTI HIVDR are reported among women in resource-limited settings and contribute to the significant rise in TDR among infants and young children living with HIV. A South African study (2011–2012) detected NNRTI HIVDR in more than half (65%) of pregnant women living with HIV [77], and a study of a large cohort of mother-infant pairs from South Africa, Brazil, and Argentina showed that women with detectable viremia were more likely than women with virologic suppression to transmit HIVDR to their infants [78], emphasizing the importance of optimizing ART regimens and maintaining virologic suppression throughout pregnancy.

Children with perinatal HIV can acquire HIVDR from their mother (TDR), ARV exposure through PMTCT (PDR and ADR), and failure to sustain virologic suppression on ART

(ADR). In two European studies (1993–2017), the prevalence of NRTI, NNRTI, and PI TDR was reported at 3.6–14.6%, 17.9–26%, and 0–10.4%, respectively, among children living with HIV [79, 80]. Rates of overall HIVDR in children living with HIV in resource-limited settings during 2004–2015 have been reported at 13–40%, and as high as 34–79% in those children with prior exposure to ARVs through PMTCT [24, 81–84]. A 2016 meta-analysis that included data from 19 studies with a total of 2617 children living with HIV aged ≤ 12 years from 13 countries in sub-Saharan Africa found a high prevalence of PDR at 42.7% among children exposed to ART through PMTCT compared to 12.7% among children without PMTCT ART exposure: NNRTI mutations were found in 32.4% and 9.7% of these children, respectively [24]. PDR to PIs in infants and young children with perinatal HIV has also been reported, albeit at low prevalence rates $< 3\%$ with the exception of one European study (Spain, 1993–2016) described above (10.4%) [24, 79, 80, 82, 83]. To our knowledge, INSTI TDR in infants or young children with newly diagnosed perinatal HIV have not been reported in resource-limited settings to date.

The rates of HIVDR in children living with HIV and adolescents with perinatal HIV are generally high in both resource-rich and resource-limited settings, likely due to a combination of prolonged ART exposure and ART adherence challenges. Within a cohort of 234 children and adolescents with perinatal HIV infection in the USA (2007–2009), 61% had resistance to at least 1 NRTI, 45% to at least 1 NNRTI, and 34% to at least 1 PI, and 18% had resistance in all 3 classes [57]. In comparison,

a study of 47 predominantly treatment-experienced children and adolescents in sub-Saharan Africa reported a prevalence of 87.2% with ≥ 1 NRTI resistance mutations, 65.9% with ≥ 1 NNRTI resistance mutations, and 63.8% with ≥ 3 PI resistance mutations [85]. Adolescents with recently diagnosed horizontally acquired HIV in the USA (2003–2005) were reported to have a high prevalence of HIVDR (18%), particularly to NNRTIs (15%) [86], suggesting that the duration of ART exposure does not necessarily correlate with the absence of HIVDR.

Evolution of HIV Drug Resistance

HIVDR evolves naturally when confronted by suboptimal pharmacokinetic exposure with selective pressures by diverse ARVs. Over the years of the HIV epidemic, HIVDR has been affected by changes in ART and PMTCT approaches, and the introduction of novel ARVs. For example, the evolution in the management of PMTCT from short course zidovudine to single dose nevirapine to “Option B+” with lifelong triple maternal ART throughout pregnancy and through breastfeeding have affected the trajectory of NRTI and NNRTI HIVDR among women and young children in resource-limited settings. Along with a significant reduction in perinatal HIV transmission, several studies from sub-Saharan Africa have shown a higher prevalence of NNRTI drug resistance in infants with perinatal HIV exposed to PMTCT compared to infants without PMTCT exposure [24, 82, 84, 87]. The high prevalence of NNRTI HIVDR resistance with PMTCT exposure and lower rates of virologic suppression in young children along with other considerations have accelerated first-line ART recommendations by the WHO for replacing NNRTIs with INSTIs in adults, including pregnant women living with HIV, and with PIs and INSTIs for newly diagnosed infants with perinatal HIV [51].

INSTIs have also replaced the second-line PIs among PLHIV failing non-INSTI-based ART based on better tolerability, higher resistance threshold, lower cost, and potential for higher adherence [51]. Recent data suggest that regimens combining the INSTI, DTG, and with one or two NRTIs are capable of overcoming pre-existing NRTI resistance in treatment-experienced patients with virologic failure [88–90]. The most potent and currently preferred first- and second-line ART and INSTIs (DTG and bictegravir (BIC)) have a high-resistance barrier, but are not fully protected from HIVDR. An Italian study of 462 INSTI-experienced PLHIV detected low-level resistance to any INSTI in 42.9% of cases, and intermediate-level resistance to DTG in 15% of cases, supporting INSTI genotype testing in INSTI-experienced patients and encouraging continued support of adherence to INSTI-based ART regimens [73]. In this study, previous exposure to DTG, and not to first generation INSTIs (raltegravir

(RAL) or elvitegravir (EVG)), were associated with a decreased susceptibility to DTG, confirming its higher genetic barrier and lack of cross-resistance within this drug class. In a larger Canadian study of 1379 PLHIV receiving INSTI-based regimens with RAL, EVG, or DTG, INSTI resistance was reported in both treatment-naïve and treatment-experienced PLHIV, with a trend for DTG having a lower rate of resistance compared with RAL and EVG [91]. Risk factors for emergent INSTI HIVDR were similar to other reports and included low CD4 count (<200 cells/ μL) and $<80\%$ adherence to ART [91]. Real-world outcomes with HIVDR data for PLHIV on regimens with newer INSTIs such as BIC and cabotegravir (CAB) are sparse or not yet available. However, HIVDR surveillance is important as there is extensive cross-resistance between DTG, BIC, and CAB [92, 93]. With the majority of national and international guidelines now recommending INSTI-based ART regimens as the preferred first- and second-line regimens for PLHIV [51, 63–67], it will be crucial to monitor INSTI HIVDR globally.

The introduction of PrEP and dual ART regimens for prophylaxis and treatment of HIV has generated new questions about their impact on HIVDR. Currently, HIVDR has been rarely reported among PrEP users who became infected with HIV [16, 94]. HIVDR have been reported in cases when PrEP was initiated during acute HIV infection, or with suboptimal PrEP adherence. PrEP-related HIVDR has the potential to affect the selection of first-line ART regimen initiated by PrEP users who acquire HIV. It also poses a risk to the treatment of hepatitis B in those patients who acquire the infection while on PrEP. Recent preliminary data has shown that the long-acting injectable INSTI, CAB, is a safe and efficacious PrEP agent [95], reducing the challenge of medication adherence for people who have challenges with taking daily PrEP.

In recent years, ART regimens with two ARVs (3TC plus DTG or darunavir/ritonavir (DRV/r), DTG plus rilpivirine (RPV), or DTG plus DRV/r) have been introduced into clinical practice following studies that have shown them to be effective in achieving virologic suppression in treatment-naïve adults [90, 96, 97] and/or maintaining virologic suppression in treatment-experienced adults [98–103], with no evidence of the emergence of HIVDR mutations to either of the ARVs used. Studies have shown that dual ART regimens are non-inferior to standard triple ARV regimens, and provide the opportunity to reduce adverse effects of ARVs and simplify ART regimens [90, 97–100, 104, 105]. Currently recommended dual ART regimens are either INSTI-based, PI-based, or a combination of an INSTI with a boosted PI [63, 106]. Studies in treatment-naïve PLHIV receiving dual ART with DTG plus 3TC or 3TC plus DRV/r did not demonstrate any resistance mutation selection at virologic failure [90, 96]. Among 556 virologic suppressed PLHIV who switched from a triple or dual regimen (3TC plus boosted PI) to dual ART with DTG and 3TC, 12 patients experienced virologic failure. However, none

developed resistance mutations to DTG or 3TC [98]. PLHIV receiving dual ART with RAL plus DRV/r had a high rate (29.5%) of INSTI resistance at virologic failure [97]. Conversely, resistance mutations were rare in studies combining 2nd generation INSTIs, DTG, or long-acting CAB, with RPV [99, 100]. Dual ART regimens are promising treatment options for PLHIV who do not have pre-existing mutations to either ARVs with a low likelihood for development of HIVDR, with adequate ART adherence. HIVDR surveillance will allow a better understanding of the emergence of HIVDR in PLHIV receiving standard-of-care dual ART regimens.

Novel Approaches to Combat HIV Drug Resistance

Numerous novel therapeutic approaches to HIV treatment are undergoing studies, including the use of broadly neutralizing antibodies (bNAbs), long-acting ARVs, and ARVs from new drug classes. These novel approaches are vital in expanding HIV prevention and treatment options, particularly for PLHIV with multi-drug-resistant HIV infection. Long-acting oral or injectable ARVs are also beneficial in overcoming the need for daily medication usage, which can ultimately lead to improved medication adherence and lower HIVDR. A full review of these novel approaches is beyond the scope of this review; however, select agents will be described in brief below.

Several novel ARVs recently approved by the FDA for use in adults include fostemsavir (FTR), ibalizumab (IBA), and doravirine (DOR). FTR, a prodrug of temsavir, is an attachment inhibitor that prevents HIV entry into the CD4 T-cell and is approved for heavily treatment-experienced adults with multi-drug-resistant HIV. FTR-related mutations have been reported at a high rate (48%) in PLHIV receiving FTR as functional monotherapy or with only one or two fully active ARVs through week 96 [107]. Regardless of this limitation, the efficacy and tolerability data support the use of FTR as a salvage treatment option in patients with multi-drug-resistant HIV. IBA is a novel monoclonal antibody administered every 4 weeks as an intravenous infusion. Despite IBA resistance observed to occur in PLHIV receiving IBA as monotherapy [108], antibodies to IBA have rarely been observed in clinical trials with IBA [109, 110]. Additionally, IBA has no reported cross-resistance with other ARVs [111] and even has synergistic *in vitro* effects with the fusion inhibitor, enfurvitide (T-20) [112], making it a promising agent for the treatment of multi-drug-resistant HIV. Lastly, DOR is a novel NNRTI with a higher genetic barrier to resistance compared to first-generation NNRTIs, nevirapine and efavirenz, and the second-generation NNRTI, RPV [113]. PLHIV who previously failed a first- or second-generation NNRTI-based ART

regimen had a high-level DOR resistance rate of 6–35% [114, 115].

DOR is currently being investigated for use in combination with islatravir (ISL), a long-acting first in-class nucleoside reverse transcriptase translocation inhibitor with multiple mechanisms of antiviral action. ISL in combination with DOR has demonstrated high potency and good tolerability at week 96 with no viral resistance identified [116]. A number of other novel therapeutic agents for the treatment of HIV are under investigation. While initial safety and tolerability studies have been successful, treatment with bNAbs is accompanied with its own set of challenges including inadequate or transient responses in patients with resistant viruses at baseline, and emergence of resistant bNAbs HIV mutations [117, 118]. Clinical trials are in progress for newer generations of bNAbs for treatment and prevention of HIV. Another novel agent under investigation is lenacapavir (LEN), which is a subcutaneous long-acting HIV-1 capsid inhibitor that is being developed in combination with other ARVs, and is capable of producing sustained therapeutic concentrations for at least 6 months after a single dose [119]. Resistance to lenacapavir in a phase 1b trial was shown to be rare, with no cross-resistance against the commonly used ARVs (NRTI, NNRTI, PI, and INSTI) [120]. Among 29 PLHIV who received monotherapy with LEN, a single mutation emerged in 2 participants who received LEN at doses several-fold lower than used in phase 2 trials [120]. Overall, these novel and investigational therapeutic approaches highlight the ongoing quest for HIV treatment options with higher acceptability, tolerability, and resistance barrier.

Conclusion

The evolution of ART regimens has contributed to the trajectory of HIVDR and solutions to address this therapeutic challenge. Despite significant progress in the introduction of novel, more potent, and better tolerated ARVs and ART regimens, HIVDR remains a significant challenge globally, particularly in some regions within resource-limited settings where HIV policies and programmatic and health care gaps limit HIVDR surveillance, prevention, and handling of virologic failure and HIVDR. The need for routine HIVDR surveillance and VL monitoring is significant and necessary to inform on future recommendations of first-line ART regimens. Point-of-care diagnostics have the potential improve the management of PLHIV with HIVDR at the time of initiating ART or at the time of failure. Implementation studies and programmatic changes are needed to determine the best approach to disseminating these services and increase health system capacity in order to combat the development of HIVDR. Novel therapeutic agents bring solutions to the challenge of virologic failure and HIVDR, but do not eliminate the need for the prevention,

monitoring, and management HIVDR in order to achieve the elimination of AIDS and control of HIV epidemic globally.

Declarations

Ethics Approval and Consent to Participate This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

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