

Key words: pretreatment HIV drug resistance; drivers and strategies to prevent PDR; low and middle-income countries;

Abstract

Pretreatment HIV drug resistance (PDR) has been increasing with scale-up of antiretroviral therapy (ART) in low- and middle-income countries (LMICs). Delay in responding to rising levels of PDR is projected to fuel a worldwide increase in mortality, HIV incidence and ART costs. Strategies to curb the rise in PDR include using ARVs with high-genetic barrier to resistance in first-line therapy and for prophylaxis in HIV exposed infants, enhancing HIVDR surveillance in populations initiating, receiving ART, and in those on pre-exposure prophylaxis, universal access and effective use of viral load tests, improving adherence and retention and minimizing ART programmatic quality gaps. In this review, we assess the drivers of PDR, and potential strategies to mitigate its rise in prevalence and impact in LMICs.

Introduction

Impressive gains have been made over the last 15 years in expanding access to antiretroviral therapy (ART) in low-and middle-income countries (LMICs). From fewer than 300,000 in 2003, there are now over 21.7 million people receiving ART in LMIC.[1] The wide-scale access to ART, has raised hopes for the elimination of AIDS as a public health threat by improving health for those infected and interrupting the spread of the virus . In 2014, UNAIDS set global targets for having 90% of people living with HIV knowing their status, 90% of those infected receiving ART, and 90% of those on ART having sustained viral suppression.[2] Achieving these targets by 2020 – just one year from today - and increasing them to 95%-95%-95% by 2030 is projected to result in the control of the HIV epidemic.[2]

The rise in HIV drug resistance (HIVDR), however, threatens the achievement of these targets. A meta-analysis of 63 studies conducted in LMICs showed that HIV drug resistance in persons before start of ART (pretreatment HIVDR, or PDR), has steadily increased worldwide from 2000 to 2016, coincident with the wide-scale rollout of ART.[3] The rise in PDR is especially high for the commonly used first-line, first generation non-nucleoside reverse transcriptase inhibitors (NNRTI) drugs (efavirenz and nevirapine).[3] In 2016, the prevalence of NNRTI PDR was estimated at 11.0% (7.5–15.9) in southern Africa, 10.1% (5.1–19.4) in eastern Africa, 7.2% (2.9–16.5) in western and central Africa, and 9.4% (6.6–13.2) in Latin America and the Caribbean, and 3.2% (1.8–5.6) in Asia.[3] These estimates include resistance emerging from either infections caused by a drug resistance strain (transmitted drug resistance, TDR) or resistance resulting from prior exposure to antiretroviral drugs (e.g. short-course prophylaxis for prevention of mother-to-child transmission [PMTCT], pre or post-exposure prophylaxis, or first-line ART restarters after a default or treatment interruption) (Fig 1).

The 2017 World Health Organization (WHO) HIV drug resistance global report shows that levels of NNRTI PDR had exceeded 10% in six of the eleven countries surveyed in 2014-2016 (Fig 2). [4] Prevalence of PDR was particularly high in specific sub-populations: (i) in persons restarting ART reporting prior exposure to ARVs, NNRTI PDR estimates were three times higher than in ARV-naïve people. [4,5](ii) PDR levels in women were estimated to be two-times higher than in men, [4] (iii) a recent meta-analysis of 50 studies globally showed comparatively high levels of

PDR in key populations, ranging from 1.3 times higher in men who have sex with men (MSM) to 3 times higher in persons who inject drugs (PIWD) when compared to the general population, [6] (iv) the level of HIVDR to NNRTIs is alarmingly high in infants who become infected despite use of PMTCT (using combination antiretroviral therapy for pregnant HIV-positive women and antiretroviral prophylaxis for HIV-exposed infants). A meta-analysis of WHO-recommended national surveys of pretreatment resistance in ART-naïve infants < 18 months s conducted between 2011 -2014 in 5 African countries among HIV-infected infants, showed that 1 in 2 infants are infected with virus harboring NNRTI resistance prior to treatment initiation. PDR to NNRTI was detected in nearly 2 in 3 HIV-infected infants in Zimbabwe,[7]; in Nigeria, where 25% of new pediatric HIV infections occur globally, PDR was detected in 47% of the infants, corresponding to an estimated annual ~20,000 children with NNRTI resistance before they reach 18 months.[8]

PDR has critical clinical and public health implications. Studies have shown association between NNRTI PDR with poor virological outcomes, impaired immune recovery, reduced durability of NNRTI-based regimens, increased switching to 2nd line and increased mortality.[5,9–13] Critically, rising rates of PDR coupled with treatment failure pose a putative risk to the success of the ongoing scale-up of ART programs globally.[14]

There are similar concerns about the effect of rising resistance on the efficacy of HIV pre-exposure prophylaxis (PrEP) and the potential impact of resistance acquired while on PrEP on TDF-based first line ART regimens. A review of findings from PrEP trials of TDF or emtricitabine/tenofovir show that emergence of drug resistance occurs infrequently (<0.1%) in patients with breakthrough infections, but was 46% among patients initiating PrEP with unrecognized sero-negative acute infections (HIV infected but having a negative serologic test result for HIV antibodies).[15,16] A modeling study from three independent mathematical models, however forecasted that the positive outcome associated with the infections averted using PrEP outweigh the potential threat of resistance emergence [17]. Nonetheless there are potential concerns associated with the use of PrEP in settings where TDF/FTC is erroneously started during undiagnosed HIV-1 infection.

Recent studies though conflicting have suggests that the effect of PDR appears to differ by regimen with , a lesser impact of PDR to tenofovir- and NNRTI containing first-line regimen, when NNRTI mutations occur as single class resistance and not in association with NRTI mutations.[18,19] Some studies also suggest the potential clinical impact of pretreatment

minority drug resistant variants although findings are still inconclusive.[20–23] Nonetheless a recent modeling study using data from sub-Saharan Africa projects that delays in responding to NNRTI PDR levels exceeding 10%, could negatively impact the attainment of the UNAIDS 90-90-90 targets if not timely addressed. This includes a projected increase in 16% (890,000) more AIDS-related deaths, 8.7% (450,000) more new infections and 7.7% (US\$ 6.5 billion) increased expenditure for ART programs between 2016 and 2030.[10] In this perspective piece, we review approaches to control and respond to the high levels of pretreatment drug resistance so as to protect the gains of ART and ongoing progress for epidemic control. This includes adaptation of several strategies already implemented in the WHO global guidelines as summarized in table 1 as well as other approaches discussed below.

1. Responding to increasing levels of PDR with updated guidelines to prioritize first-line ARVs with a high genetic barrier to resistance

As recommended by WHO, it is critical for countries with high levels of NNRTI PDR defined by a prevalence of PDR above 10% in populations starting ART, to use a first-line regimen that remains active in the face of rising NNRTI resistance.[13,24] The high occurrence of PDR to NNRTIs is partially attributed to its low genetic barrier to resistance, which typically leads to the rapid emergence of drug resistance in patients experiencing treatment failure with subsequent transmission of the resistant virus.[25] Use of ARVs with a high genetic barrier to resistance may therefore also minimize the emergence and transmission of HIV drug resistance. As from July 2018, WHO ART guidelines recommend the use of dolutegravir (DTG)-based regimen as the preferred first-line ART.[24] DTG is an integrase-based inhibitor with superior efficacy, tolerability and has a high-genetic barrier to resistance compared to NNRTI-based ART in clinical trials conducted in western settings. [26] DTG is also available as a fixed dose generic formulation with TDF and lamivudine at a price broadly comparable to that of EFV-based ART.[27] Timely adaptation of the WHO recommendations would be critical to prevent the negative effects of PDR especially in countries reporting high PDR prevalence to NNRTIs. By mid-2018, 92 LMICs had adopted or were in the process of adopting TDF/3TC /DTG as the preferred first-line therapy.[28] The US President's Emergency Plan for AIDS Relief (PEPFAR) has been accelerating the transition to DTG in countries supported by the programme.[29] DTG based regimens are predicted to be efficacious in naive patients and are particularly needed in areas where high NNRTI PDR has been documented. [30,31]

However, the use of DTG may be limited in women and children, pending evidence from ongoing studies. A recent study from Botswana showed a safety signal for the risk of neural tube defects in infants born to women who are on DTG at the time of conception, raising the need for alternative regimen in countries where a reliable and effective contraceptive cannot be assured pending findings from ongoing studies.[32] As recommended by WHO, it is critical for countries with PDR levels $\geq 10\%$ to use non-NNRTI regimens in women of childbearing potential. When DTG is not a suitable option, this may include protease inhibitor (PI) such as ritonavir-boosted atazanavir. If implementation of atazanavir is a challenge due to cost (nearly 3x that of DTG or efavirenz), it may be a valid alternative to use efavirenz-based regimen with close virological ART monitoring and promptly switch to second-line ART upon treatment failure. Alternatively one can use resistance testing in settings where this is feasible, affordable and available. Such strategies may possibly be more cost-effective, provided that adequate and robust systems for routine viral load monitoring and/or resistance testing exist and a rapid switch for women with treatment failure can be ensured.

Similarly, WHO recommends the use of a raltegravir-base ART in neonated and ritonavir-boosted lopinavir PI-based regimen in children younger than six years, pending evidence to support the use of DTG in this group.[24] However, although the recommendation to use PIs in children has been in place since 2013,[33] implementation has been hindered by a low supply of child-friendly palatable formulations (pellets or granules which can be crushed and mixed with fluids). As a result of high cost and the limited availability of PIs, nearly 77% of young children are still placed on sub-optimal NNRTI-based regimens.[27] It is anticipated that the supply of pediatric-based PIs will improve in 2019 following commitment by pharmaceutical companies to increase production of lopinavir-ritonavir pellet-based formulation and the recently approved granule-based formulations.[27]

Another issues is the use of DTG in some middle-income countries outside the medicine patent pool. These countries have limited or no access to the low-cost generic DTG formulation. In such cases, it will be critical to prioritize the use of non NNRTI-based regimens in groups that are more-at-risk of having PDR. These include persons reporting previous ARV use before re-starting ART and key populations (PWID, MSM and commercial sex workers). In addition, it may be prudent to use a non-NNRTI based regimen in women of child-bearing potential reporting previous ARV use even in countries with NNRTI PDR $< 10\%$, given the risk of transmission to the fetus with peri-partum virologic failure.

2. HIVDR prevention in HIV-exposed infants

In an era of limited pediatric HIV treatment options, it is even more important to focus on prevention of PDR in this vulnerable population. High levels of PDR in infants arise mainly from exposure to sub-therapeutic regimens ingested during breastfeeding or from the sub-therapeutic prophylaxis given to HIV-exposed infants. Moreover there is serious lack of potent pediatric regimens.[34,35] Development of new pediatric formulations lags far behind that for adults due to a smaller market size and challenges of conducting clinical trials in children. In response, since 2013 WHO has brought together cross-sectoral collaborations, including manufacturers, research networks, funding bodies, supply and procurement organizations, policy makers and regulatory agencies with the aim of ensuring accelerated development and uptake of optimal pediatric ARVs.[36] However, much still needs to be done, as evidenced by the experience with lopinavir-ritonavir pellets, which remain inaccessible to most countries due to limited production and high prices.[27]

Strategies to prevent PDR and improve outcomes for infants with HIV include [37]: i) preventing the transmission of HIVDR from mother-to-child by providing an effective ARV combination that rapidly reduces the plasma levels of viral load for women initiating treatment in the pre-partum period; ii) ensuring appropriate frequency of monitoring maternal viral loads during pre-partum and throughout breast-feeding, complemented with enhanced adherence interventions and use of integrase inhibitor-based regimens for those experiencing treatment failure so as to facilitate effective viral suppression; iii) preventing drug resistance acquired from either the sub-therapeutic infant prophylaxis or exposure to a sub-optimal maternal regimen ingested during breastfeeding. This latter could be achieved by using triple ARV prophylaxis with higher genetic barrier for resistance in infants coupled with timely diagnosis of HIV infection. The current PMTCT regimens in infants in LMICs comprise either monotherapy of nevirapine or a dual combination of nevirapine/zidovudine in high-risk infants. There is limited evidence to support the use of triple prophylaxis for infants for PMTCT.[38] However, mono- or dual regimens could be associated with increased risk in the emergence of resistance during breakthrough infections or infants initiated on prophylaxis with undetected infection. The use of a triple ARVs prophylaxis regimens could help to prevent emergence of resistance in these infants, as is the case in high-income settings and potential MTCT for very high risk babies. [37] [39] The argument for triple ARV prophylaxis is further augmented by the rising levels of HIVDR in

pregnant and breastfeeding women, which may increase risk of transmission as the same class of drugs are used for infant prophylaxis.[40,41] In addition, the use of the recommended birth testing by use of DNA-PCR could help prevent placing HIV-infected children on sub-therapeutic prophylactic regimens.

3. HIVDR prevention in populations receiving pre-exposure prophylaxis

Tenofovir is a component of both the PrEP regimen and the first line ART. Therefore resistance to tenofovir emerging from PrEP's use could compromise the effectiveness of first-line ART. Findings from clinical trials show infrequent occurrence of resistance in patients failing PrEP (<0.1%), while resistance is very common (41%) in people starting PrEP [16] More data is needed from real-life settings in countries where the HIV prevalence is very high and the regular procurement of HIV diagnostic tests may be a challenge; in these contexts, the risk of providing PrEP in people with unrecognized HIV infection should not be underestimated. Based on current evidence, emergence of drug resistance in PrEP could be minimized through accurate diagnosis of early stage HIV infection prior initiation of PrEP. This could be facilitated by the development of low cost nucleic-acid tests (NAT) for detection of acute infections prior to PrEP initiation. Close monitoring of adherence and breakthrough infections may also aid in timely detection of infection and withdrawal of PrEP to prevent emergence and accumulation of resistance. An effective long-term solution may involve the use of non-overlapping ARV-classes between PrEP and ART, and in longer-acting versions of PrEP, which prevent the need for daily adherence, both of which are being explored in ongoing clinical trials.

4. Enhanced surveillance and monitoring of drug resistance

It is critical to continuously monitor the emergence of HIV drug resistance to ensure sustained efficacy of the limited available drugs in LMICs, in line with WHO recommendations for standardized national representative surveys to assess PDR and ADR (table 1).[42] National-level estimates of HIV drug resistance generated from these survey help national programmes to select appropriate first, second, and third line ART regimens.

In addition, WHO also recommends continuous monitoring of program quality indicators (also known as Early Warning Indicators, EWIs) which are clinic level factors associated with the emergence of preventable HIV drug resistance.[42] This includes clinic level monitoring of on-time pill pick up, retention in care, loss-to-follow-up, drug stock-outs, viral load testing completion and suppression rates and timely switch to second line ART of patients failing first-line first-line ART. Information obtained from EWI monitoring is vital in improving the delivery of ART quality services at both the clinic and national level. [43] The assessment of clinic functioning should be followed by the identification of locally sustainable solutions, including stronger systems for drug procurement and supply chain, education and awareness of HIVDR among patients and health care workers and differentiated care models to maximize adherence and retention.

The integration EWI monitoring into routine monitoring and evaluation systems of national AIDS programme is expected to facilitate real time assessment and response to sub-optimal program functioning as recommended by WHO.[43]

Despite their critical role, not enough countries have regularly implemented these surveys, partially due to cost limitations. Potential complementary approaches include:

- Conducting surveys in population at highest risk of developing drug resistance e.g. conducting PDR surveys among key populations, and acquired drug resistance (ADR) survey in groups with high virological non-response rates such as adolescents.
- Leveraging routinely collected programmatic data to conduct ADR surveys using remnant viral-load specimens from patients experiencing virological failure. WHO is developing survey methods to guide countries on the use of this approach.[44]
- Big data analyses, involving non-sequencing data such as the EWIs and other related databases (like ART coverage, viral load test availability, HIV prevalence and incidence, socio-economic survey data, etc.) to predict HIVDR hotspots. A similar approach for use of proxy indicators has been proposed for the monitoring of the Global Action Plan on antimicrobial resistance [45]as well as in estimating the burden of difficult to diagnose diseases such as melioidosis.[46]
- HIVDR surveys in individuals on PrEP. Global Evaluation of Microbicide Sensitivity program (GEMS) has been evaluating different models for HIVDR surveillance in PrEP and WHO is also developing guidelines for use by national programs scaling up PrEP interventions. [47]
- The cost of HIVDR test is still a barrier to its wider use in LMIC where it is currently utilized to test specimens from second-line failures and in the context of surveillance. Reducing

overall cost of HIVDR testing is critical and this can be achieved through development of innovative approaches, like next generation sequencing (NGS) on (pooled) representative patient samples combined with advanced statistical analyses to estimate prevalence of key HIVDR mutations.

These approaches will require proof-of-principle, validation and scaling strategies before wide adaptation in LMICs

5. HIVDR prevention in populations receiving ART

Controlling PDR largely depends on limiting the emergence and transmission of drug resistance in patients on treatment. Several factors contribute to the development of HIVDR (Fig 2) and they mainly affect adherence to take ARVs as prescribed. Potential ways for mitigating HIVDR in populations on ART include:

a). Improving access to and appropriate clinical use of viral load monitoring

Expanding and consolidating universal access to regular viral load monitoring is critical for early identification of virological failure and limiting the emergence and accumulation of drug resistant strains.[48] Of equal importance is the use of viral load test in guiding the switch of stable patients from efavirenz- to DTG based first-line regimen as recommended in the 2018 WHO HIV treatment guidelines. [24] In the absence of viral load tests, some patients failing treatment could be switched to DTG while having resistance to the co-administered nucleosides (tenofovir and lamivudine). Indeed high levels of resistance to the NRTI backbone are common in patients failing NNRTI-based first-line ART in LMICs.[4,49] Findings from the TenoRes study showed a high level of thymidine analogue mutations in patients failing TDF based ART which could partially be attributed to historical stavudine-TDF substitutions without confirmation of viral suppression, or in PDR that persists at the time of TDF failure.[50] These findings further highlight the need for viral-load scale-up to support the planned large-scale treatment substitutions to DTG-based ART to prevent emergence of resistance in patients with undiagnosed virological failure. The accumulated NRTI resistance in absence of viral load tests may compromise DTG switches in the real world, although data are needed to inform this hypothesis.[51,52]

Access to viral load testing is unfortunately limited in many LMICs. A recent review of data from 45 high burden HIV countries showed that in 2017 nearly half of the patients on ART did not

receive at least one viral load test, indicating the need for accelerated access.[44] There are also substantial differences between countries, with some like Namibia, having viral load testing coverage as high as 91%, while others, such as Tanzania, reporting less than 10% coverage. Ongoing strategies to improve access include use of dried blood spots (DBS) to increase testing access to remote settings and use of point-of-care tests for decentralized access. [53,54]

Although a combination of laboratory-based testing and point-of-care tests may help improve testing access, more still needs to be done to ensure universal access and efficient use of available capacity. Studies indicate under-utilization of existing capacities[55] and lack of or delayed action on the test results.[56,57] A recent review of programmatic data in Kenya showed that only 4.1% of patients with unsuppressed viral load received a confirmatory viral load test,[56] while another study in Uganda showed that only 66% of patients with confirmed virological failure were switched to second line ART. Median time to treatment switch after confirmation of virological failure was also longer estimated at a median of eight months. [58]

This calls for addressing the gaps in the “viral load monitoring cascade” i.e. from i) routine viral load testing to ii) enhanced adherence counseling (EAC) in case of a viral load test result of $\geq 1,000$ cps/ml iii) a follow-up confirmatory viral load test after 3-6 months and iv) timely treatment switch to appropriate second-line ART if viral load remains ≥ 1000 cps/ml. All the gaps in the steps of this cascade need to be adequately addressed. Strategies for improving viral load testing access has been reviewed elsewhere [54,59] and include creating demand by increasing treatment literacy among communities, use of nurse-led viral load champions, use of m-health for timely identification of patients in need of viral-load tests and timely relay and use of test results, improving clinician-laboratory interface for timely testing and utilization of test results, task shifting approaches that empower nurses to make regimen changes to second-line, improved awareness among clinical staff of the high risk of drug resistance among failures, and increasing access to more tolerable and dosing-friendly second-line ART (e.g. atazanavir or darunavir in place of lopinavir).

b. HIV drug resistance testing for individual clinical management

A complementary strategy for optimal treatment monitoring may include the use of drug resistance tests. In LMIC, where the public health approach to HIV treatment includes the use of a standard first and second line ART, HIVDR tests may serve to optimize treatment, henceforth

minimizing emergence and accumulation of drug resistance mutations and the subsequent onward transmission. Of equal importance is the need to rule out patients who are failing treatment without resistance so as to minimize unnecessary switches to more expensive or less-tolerated regimens. Studies indicate that drug resistance mutations are less commonly selected in patients failing drugs with high-genetic barrier such as DTG or PIs.[60,61] In such cases, switching regimen in absence of confirmed presence of resistance could prematurely burn a precious class of drugs and the use of HIVDR tests may overall improve the durability of the limited available drug options in these settings. Several countries in LMICs like Brazil,[62] Botswana,[63] Kenya,[64] Uganda[65] Malawi, and South Africa[66] have already adopted individualized resistance testing for second-line failures; and a multi-center randomized clinical trial is currently testing the efficacy of immediate resistance testing at the time of first-line failure in Uganda and South Africa.[67]

HIVDR genotyping technologies are becoming increasingly affordable, as reviewed elsewhere.[68,69] Briefly, Sanger assays are currently considered as the gold standard, and they are the most widely available genotyping technology in LMICs. They have also been widely validated for use with DBS. Their wide expansion is however limited by a high capital and test cost. The cost for commercial-based Sanger sequencing has however been declining with current costs being as low as 30-50 USD/test for the CDC/Thermofisher assay.[69] There are also advancements for development of low-cost novel point mutation assays (PMAs) for use at point of care[70,71] as well as adaptation of next-generation sequencing (NGS) which is anticipated to reduce costs through multiplexing in high-throughput facilities.[72] The cost of PMAs is expected to be as low as 18 USD for oligonucleotide ligation assays (OLA) which targets the major RTI mutations while NGS cost may be as low as ~5 USD per sample with multiplexing of large number of samples.[72]

More efforts are needed to make HIV drug resistance tests more affordable for routine use for individual patient management in LMICs. In the past years, financial support from multi-national organizations under the Diagnostics Access Initiatives have accelerated the development of low-cost CD4 and viral-load technologies, including point-of-care devices.[73] Similar support should be extended to innovators and manufacturers of HIVDR technologies. This could lead to more innovative technologies that combine viral load and HIVDR testing. In addition, collective negotiations by international entities, like CHAI or UNITAID, could further lower the overall costs of both the technologies and the tests.

Novel approaches are also needed to implement HIVDR tests for routine clinical management in LMICs. This includes prioritizing resistance testing in situations where its use is likely to be more cost-effective, such as in patients failing second-line ART after at least 12 months of therapy to minimize switches to expensive third line ART, in pregnant and breastfeeding women to enhance treatment monitoring and effectively prevent risk of vertical transmission, in children and adolescents who have poor adherence, high risk of failure and fewer treatment options, and in highly treated patients failing third line ART.

c. Person-centered care for improved adherence and retention

Improving patient's ART adherence and retention in care is paramount to minimize the emergence of HIVDR in treated patients. This will also likely address the high levels of PDR attributed to patients restarting treatment after previous disengagement from care. A first step in this process is a better understanding of the complex barriers to adherence both among patients and healthcare providers, which has been reviewed previously. Notably, the majority of these barriers are structural (e.g. transportation costs and limited social support), health system-based (drug stockouts and staff mis-treatment) or associated with persistent HIV stigma (e.g. lack of disclosure).[74–77] Consequently, although HIV adherence counseling is often relied upon as a means to help patients overcome adherence challenges, much broader efforts to respond directly to the complex root factors are needed. To do so, differentiated care models are being implemented, including ART delivery at community points, ART care and delivery using adherence clubs or community-based groups as well as reserving facility-based care to most-at-need patients such as those with unsuppressed viremia.[78] Previous studies have showed better adherence and retention using the decentralized care models and there is a need to take them to scale in many LMICs.[79,80] Other interventions have been reviewed elsewhere and include the use of social-behavioral interventions such as using mobile phone text reminders, cognitive-behavioral therapy, education, use of treatment supporters, direct observation treatment, nutrition support, financial incentives and addressing mental health issues.[81]

d) Enhancing research into long-acting ART formulations and functional cure

Even with a multi-disciplinary approach and person-centered care enhancements, a more effective strategy that addresses adherence challenges is needed. Ongoing research into long-acting formulations of existing and new ARVs seems promising[82] and may help relieve the burden of adherence to daily medications in specific groups and situations. Efforts will however be needed to overcome the barriers for wider implementation of these formulations in LMICs.

These include enabling timely manufacture of low-cost generic drugs, simplified delivery approaches, assessing patient preferences and effective laboratory monitoring. A more lasting solution may require renewed focus and acceleration in functional cure research (sustaining virological control in absence of treatment). [83] Achieving wide-scale functional cure may potentially address the challenge of adherence and drug resistance and may be a more effective strategy to ensure a sustainable long-term control of the HIV epidemic. Two studies also suggest the possibility of achieving eradication HIV cure (eradicating all HIV virus from the body)[84,85]

e) Better understanding for biological determinants of drug resistance.

Current paradigm for HIV drug resistance interpretation is based on mutations occurring within the drug target genes. However ongoing research suggest potential effect of undiagnosed resistance in non-drug target genes especially for PI's and integrase.[86] Studies have shown the potential role of mutations in the *gag* and *env* genes[87–92] in mediating PI resistance as well as mutations in the polypurine tract in mediating INSTI resistance.[93,94] It is likely that such mutants could be transmitted during infections and potentially impact on treatment outcomes. There is thus a need for further studies to fully ascertain these mechanisms.

To support efforts to prevent, monitor and respond to HIVDR, WHO jointly with partners have developed a five-year global action plan (GAP, 2017-2021) which outlines key actions for country and global stakeholders.[14] Increased advocacy on investments in addressing drug resistance alongside the general implementation of the GAP is critical to preserve the ART gains in LMICs. There are also some gaps in knowledge to which more studies are required to effectively combat PDR, which have been highlighted, in previous reviews. [95–98]

In conclusion, rising levels of NNRTI PDR in LMICs are concerning with potential negative impact to the ongoing progress towards achieving HIV epidemic control by 2030. Potential ways to address PDR include use of alternative non-NNRTI regimens with high genetic barrier for both treatment and prophylaxis, use of sensitive nucleic-acid based tests for identifying acute infections prior PrEP initiation, enhancing population-based HIVDR surveillance in populations

initiating or receiving ART as well as those on PrEP and preventing emergence of drug resistance in populations receiving ART.

Future perspective

The adaptation of the recent WHO recommendations for use of DTG-based first-line regimen is expected to reduce the impact of the rising levels of NNRTI PDR. Safety concerns for its use in children ≤ 6 years and women of reproductive age warrants alternative approaches for these populations pending findings from ongoing studies. Nonetheless adaptation of other aforementioned approaches are critical to minimize the emergence and impact of PDR to current and future regimens in LMICs.

Executive summary

- Prevalence of NNRTI pretreatment HIVDR in LMICs has been increasing with ART rollout, and is
 - Twice as high in women compared to men
 - Twice as high in persons with prior ARV exposure compared to those ART naive
 - As high as 50% in HIV infected ARV naive infants
- NNRTI PDR of $\geq 10\%$ is projected to fuel an increase in 16% (890,000) more AIDS-related deaths, 8.7% (450,000) more new infections and 7.7% increased ART costs (US\$ 6.5 billion) within the course of 5 years if no action is taken
- Strategies to mitigate the impact of PDR include
 - Timely implementation of the WHO recommended DTG-based first-line regimen which has a higher genetic barrier to resistance
 - Preventing PDR in HIV exposed infants by use of triple ARV prophylaxis and more frequent viral load tests among pregnant and breastfeeding mothers
 - Enhanced surveillance and monitoring of HIVDR in populations initiating and receiving ART as well as those on PrEP
 - HIVDR prevention in populations receiving ART
 - Improving access to and effective use of viral load monitoring

- Use of HIV drug resistance testing for individual clinical management where recommended and feasible
 - Strengthening the collection and use of quality of care indicator to identify quality gaps and implement effective solutions.
 - Adapting person-centered care for improved ART adherence and retention to care
 - Enhancing research into long-acting ART formulations and functional cure
 - Better understanding of biological determinants of HIV drug resistance such as in patients failing protease-inhibitor regimens
- Conclusion and future perspective: Adoption of the recent WHO guidelines for use of DTG-based regimens is likely to address the impact of NNRTI-PDR in LMICs; however, alternative approaches are needed for women of reproductive age due to safety concerns for its use in these populations pending evidence from ongoing studies. Adaptation of quality ART delivery approaches are needed to prevent the emergence and transmission of HIVDR to both existing and new ARVs.

Figures Legends

Fig 1: Pretreatment HIV drug resistance: Causes and impact

** Mainly HIV exposed infants receiving sub-therapeutic post exposure prophylaxis

Pretreatment resistance occurs either due to infection with a resistant virus or from persons initiating or reinitiating treatment after previous exposure to ARVs including PrEP/PEP, previous short course ART for PMTCT or persons reinitiating treatment after previous disengagement from care. Occurrence of pretreatment drug resistance impacts on both ARV prevention and treatment strategies

Fig 2: Prevalence estimates of PDR to EFV/NVP in nationally representative surveys from 11 LMICs

Graph showing estimates of pretreatment drug resistance from 11 low and middle-income countries reporting data to WHO from 2014-2017.

Fig 3: Factors associated with emergence of acquired HIV drug resistance in ART treated populations

Table 1: Summary of existing policies and related challenges for the prevention of pretreatment HIV drug resistance

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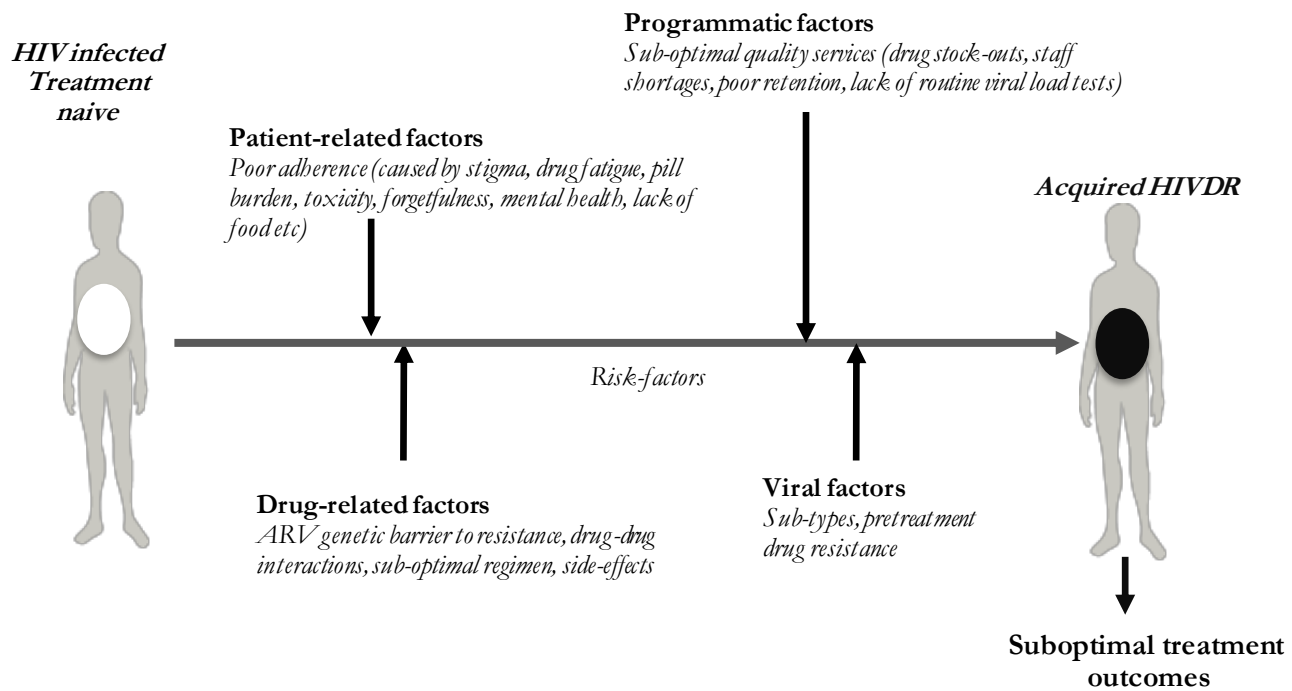


Figure 3: Factors associated with emergence of acquired HIV drug resistance in ART treated populations

