Review

Determinants of HIV drug resistance and public health implications in low- and middle-income countries

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Introduction

Efforts over the past decade to scale-up antiretroviral therapy (ART) in low- and middle-income countries (LMICs) have been successful. At the end of 2011, >8 million people were receiving ART in LMICs [1]. Treatment of millions of HIV-infected patients will inevitably be accompanied by emergence and transmission of HIV drug resistance (HIVDR), which can threaten the long-term effectiveness of available regimens [2–6].

As of the end of 2010, 7.8% of 72 WHO surveys of transmitted HIV drug resistance (TDR) among recently infected populations performed in 26 LMICs [7] reported moderate (5–15%) levels of resistance. Although the majority of surveys document low levels of resistance, it is concerning that more recent surveys show moderate levels of TDR [7–12]. Furthermore, a recent publication found a significant association between increasing rates of TDR and time since ART roll-out in six African countries [13]. Reports of moderate levels of TDR merit attention as increasing levels of HIVDR in LMICs represent a threat to the long-term success of global efforts aimed at sustained expansion of ART access [8,14].

As of the end of 2010, 40 WHO surveys assessing viral suppression rates and emergence of HIVDR in populations 12 months after ART initiation have been implemented in 12 countries. 12-Month follow-up data are currently available from 29 clinics [7]. Among patients with virological failure 12 months after ART initiation, 72.1% had resistance to any drug and 69.5% had non-nucleoside reverse transcriptase
inhibitor (NNRTI) resistance. Although levels of NNRTI resistance were significant, predicted levels of nucleoside reverse transcriptase inhibitor (NRTI) susceptibility suggested that the NRTI backbone of currently recommended second-line regimens would likely be effective in the majority.

Despite major progress, routine standardized HIVDR surveillance data are lacking in most LMIC settings. Policy makers should be aware that HIVDR surveillance, when routinely implemented, informs about: the extent to which HIVDR is being transmitted in specific populations and geographic areas; the prevalence of HIVDR in patients initiating first-line ART (pre-therapy resistance) and the predicted efficacy of available first-line regimens; the proportion of patients failing first-line ART with wild-type virus and therefore the need to strengthen adherence counselling to limit inappropriate switches; the prevalence of HIVDR in patients failing first-line ART with detected HIVDR and the predicted efficacy of empiric second-line and future salvage regimens; and ART programme functioning in providing population-based ART in a manner that optimizes patient outcomes and minimizes emergence of preventable HIVDR.

In high-income countries, although not entirely evidence-based practice, HIVDR testing of individual patients is routinely used to tailor antiretroviral (ARV) regimen selection and predict treatment response. However, in most LMICs resistance testing is neither routinely available nor recommended for individual patient management [15]. Even with recent technological advancements, it is unlikely that HIVDR testing for patient care will be routinely available for millions of patients in the near future in these settings. Furthermore, limited availability of alternative regimens restricts treatment change based on genotypic test results [16]. The absence of accessible resistance testing to monitor individual patient care in LMICs requires an intensification of efforts to optimize population-based ARV treatment and to minimize emergence and transmission of preventable HIVDR [17].

The human and financial implications of HIVDR are significant. Transmitted and acquired HIVDR can negatively affect morbidity and mortality and have major public health implications if they are not prevented and controlled in a timely manner [18,19]. Moreover, HIVDR limits treatment options and requires switching to costly second-line regimens that frequently produce more long-term toxicity [20–24]. Furthermore, the current annual cost of a second-line protease inhibitor (PI)-based regimen is 4× higher than that of recommended first-line NNRTI-based regimens [25]. TDR in recently-infected patients is associated with virological failure in patients who receive ≥1 drug to which the virus had lost susceptibility [14]. Emergence of moderate-to-high levels of HIVDR in treated patients can significantly increase the cost of ART in all countries, limiting the pace and successes of HIV treatment scale-up in LMICs [26].

Over the next decade, a significant proportion of the estimated 33 million HIV-infected individuals will require ART. Successfully initiating and maintaining such large populations on effective first-line treatment for as long as possible will be crucial in achieving the same reductions in morbidity and mortality that have been observed to date.

Growing concerns about HIVDR emergence and transmission should not prevent initiatives to expand use of ARVs, but should be used to strongly advocate for adjustments in ART programme functioning intended to minimize emergence and transmission of HIVDR.

This article explores factors contributing to the emergence of HIVDR in LMICs, summarizes the WHO global strategy to assess and prevent HIVDR and describes a number of public health interventions that ART programmes should implement to further characterize policy implications of HIVDR emergence.

**Factors contributing to emergence of drug-resistant HIV in low- and middle-income countries**

Factors contributing to the development of HIVDR in LMICs can be broadly divided into four categories: ARV drug and regimen factors; virus factors; patient factors; and programme-related factors. Assessment and characterization of these factors and their interactions in local contexts can be achieved through routine surveillance, monitoring and evaluation activities, and operational research. Data generated through these activities can be used to develop well-informed and targeted public health interventions to optimize patient care and minimize the emergence of HIVDR.

**Antiretroviral therapy drug and regimen factors**

Treatment optimization is one of five key pillars of the Treatment 2.0 initiative [27], recently launched by the WHO and UNAIDS. In this context, WHO-recommended first-line ART regimens in LMICs include the use of two NRTIs and one NNRTI [15]. Efficacy of these regimens has been well-established by clinical trials and observational studies [28–31] conducted in both high-income and LMICs [32–34]. A recognized limitation of NNRTI-based regimens is their low genetic barrier to resistance. The genetic barrier of an ART regimen, defined as the number of mutations required to overcome drug-selective pressure, is an important factor in the emergence of HIVDR. Rapid selection of NNRTI resistance results from the inability of HIV to acquire high-level resistance to first-generation NNRTI
for the prevention of mother-to-child transmission in preserved susceptibility to AZT [50,51].

while conferring cross-resistance among NRTIs, results selected for the resistance mutation K65R, which, patients failing TDF-containing NNRTI-based regi-
mens select for the resistance to TDF [48,49]. By contrast, the majority of fer increasing levels of pan-NRTI resistance, including stavudine-containing regimens and subsequently con-
will accrue in patients who remain on a failing AZT- or analogue mutations. Thymidine analogue mutations may accrue in patients who remain on a failing AZT- or stavudine-containing regimens and subsequently con-
ger increasing levels of pan-NRTI resistance, including resistance to TDF [48,49]. By contrast, the majority of patients failing TDF-containing NNRTI-based regi-
mens select for the resistance mutation K65R, which, while conferring cross-resistance among NRTIs, results in preserved susceptibility to AZT [50,51].

Suboptimal regimens such as single-dose (sd)NVP for the prevention of mother-to-child transmission (PMTCT), drug–drug interaction and inappropriate prescribing practices [52,53] may represent a significant risk factor for HIVDR selection [54].

Optimal use of ARV drugs requires high adherence to all drug components. Use of regimens with high pill burden reduces patient adherence thus favouring emergence of HIVDR [55,56]. By contrast, use of fixed-dose combinations has important programme-related implications that support the public health approach to ART scale-up and minimize HIVDR. Fixed-dose combinations maximize the likelihood of having a constant supply of required ARVs at a programme level, facilitating rational prescribing and minimizing the need to maintain a separate supply chain for different drugs [56], thus improving patient adherence and reducing the cost of drug production, packaging, shipping, storage and dispensing [57].

Interactions between drugs can affect the selection of HIVDR by reducing ARV concentrations to subtherapeutic levels. Due to the frequency of HIV–tuberculosis coinfection, the most frequent case of drug interaction involving ART in LMICs is the concomitant use of rifampicin and NNRTIs. Rifampicin reduces plasma NVP drug levels (by 20–58%) and EFV levels (by 26%), although the latter is often not clinically relevant [58,59]. Despite the fact that clinical efficacy of NNRTI-based regimens does not seem to be affected, NNRTI drug levels may vary significantly among individuals, and selection of HIVDR due to suboptimal levels in a proportion of patients may occur. Larger appropriately designed studies are needed to resolve this important clinical question.

In populations exposed to ARVs prior to initiation of first-line ART, there is a higher likelihood of pretreatment resistance [60]. In LMICs, ARV exposure prior to ART initiation most commonly occurs in women and infants who have received ARVs for PMTCT, particularly where sdNVP is used. The risk of selecting NVP resistance varies across different studies but ranges from 15% to 30% in women and may be as high as 50% in infants infected despite PMTCT [61]. NVP-resistant variants selected by sdNVP tend to fade from the circulating majority of quasispecies over time [62]. However, since infants should be started on treatment at time of diagnosis, NVP-resistant variants can significantly affect treatment efficacy [63].

Virus factors
Presence of pretreatment HIVDR is strongly associated with virological failure and further acquisition of HIVDR after the first year of NNRTI-based first-line ART regi-
men [8,13,14].

The mutations T215Y/F are frequently selected for by NRTIs (most commonly AZT); however, studies demonstrate that in the absence of drug selective pressure, rather than reverting to ‘wild type’, intermediate or ‘revertant states’ predominate. The presence of T215Y/F revertants signals past exposure of the virus to NRTIs. Although revertant mutations at position 215 do not affect drug susceptibility, their presence can favour virological failure and rapid selection of HIVDR when NRTI-containing regimens are intro-
duced [5,64].
The presence of TDR facilitates virological failure and further selection of drug-resistant variants due to failure of the ART regimen to fully suppress viral replication. One study showed that patients with TDR might be expected to accumulate more NRTI cross-resistance at time of virological failure, leading to ever increasing numbers of patients being treated with functional bPI monotherapy at time of switch to second-line treatment [65].

HIVDR may be more readily selected for in certain HIV subtypes compared with others, and mutation patterns may differ across subtypes. For example, after exposure to sdNVP, more HIVDR is observed in HIV-1 subtype D as compared with subtype A [66]. Polymorphisms present in subtype C affect the propensity of the virus to select for K65R compared with subtype B [67], although this finding has not been reported to be associated with increased frequency of virological failure [68].

Patient factors

Antiretroviral therapy adherence

Sustaining scale-up of ART in LMICs largely depends upon the ability of ART programmes to deliver ART in a way that minimizes treatment interruptions through drug supply continuity and maximizes adherence to first- and second-line regimens. Adherence to ART is a predictor of virological suppression [64,69–72], emergence of HIVDR, disease progression [73–75] and death [76–78].

Factors associated with poor adherence in resource-rich and resource-limited settings were shown to be untreated depression, active substance abuse, poor insight into disease and treatment, being an adolescent or young adult, higher pill burden, more frequent dosing and forgetfulness [79]. In sub-Saharan Africa, the following predictors of poor adherence were more prevalent: cost or structural barriers, such as pharmacy stock-outs or lack of transportation to the health facility for ART refills [80,81], food insecurity [82], and non-disclosure of HIV status to a loved one for fear of being stigmatized [83].

Emergence of NNRTI resistance is associated with unplanned treatment interruptions of ≥48 h [84,85]. Treatment interruptions can be due to suboptimal adherence at an individual patient level but also to financial difficulty in securing ARVs and drug stock-outs at ART clinics. Studies have documented drug stock-outs [85–87] and lack of access to medication [88] as important reasons for missed ARV doses in many LMIC settings.

Adherence is especially challenging among children for a variety of reasons. One important factor is drug palatability, which is particularly important for young children. While many available paediatric fixed-dose combinations are dispersible and can be dissolved in water to give a sweet fruit-flavoured solution, some liquid formulae – in particular bPIs such as lopinavir and ritonavir – are not readily water-soluble; thus, manufacturers have had to create syrup formulations that have a high alcohol content and unpleasant taste [89–91].

Children also depend upon caregivers for their treatment and multiple factors related to a child’s caregiver can result in poor adherence and selection of HIVDR [92]. If caregivers are themselves unwell, they may not be able to attend clinic visits with their child or collect medications as needed. Ensuring that >1 caregiver is aware of a child’s status and medication schedule is important when maximizing ART adherence in paediatric populations.

Orphans living with HIV frequently face the greatest challenges in terms of adherence. While orphans in institutional care typically have high levels of adherence (since care is often provided by trained caregivers), those who are raised in the households of relatives have poorer outcomes and are more likely to default or be non-adherent to care [93].

Stigma and discrimination

HIV-associated stigma continues to be a major barrier to effective HIV prevention and treatment. Although stigmatizing attitudes have lessened as access to treatment has expanded, this shift in attitudes does not lessen the fear of stigma among HIV-infected individuals, within their relationships, families and communities [94].

The threat of social stigma may prevent people living with HIV from revealing their status to others and serves as a barrier to ART adherence [95]. Notably, people living with HIV may fear that taking medications in the presence of others will result in inadvertent disclosure of their HIV status [96]. Conversely, disclosure of HIV infection status has been reported as being protective against virological failure [97]. Among children studied in Uganda, a threefold higher rate of non-adherence was observed among children whose caregivers were not willing to inform others about the child’s status [98].

Programme factors

Various ART programme factors are related to emergence of population level HIVDR. Factors include demand for services that outstrip available capacity, limited human resources and infrastructure, fragile drug procurement and supply management systems, high cost for (and lack of) routine viral load monitoring, sustaining high-quality service while decentralizing care, and weak monitoring and evaluation of systems designed to assess quality of care and treatment outcomes [99]. Moreover, historically, healthcare systems in LMICs have not been designed to provide chronic
care, which includes adherence support and systems to trace patients with unknown treatment outcomes.

A potential risk associated with the expansion of treatment could be related to overcrowding and understaffing at ART sites, resulting in a reduced ability to dedicate time to each patient for counselling, reinforcing adherence messages, and tracing patients who do not return to clinic. Studies show that during ART programme roll-out, patients initially received rigorous monitoring, which became less stringent when patient numbers at a given site started to increase [34,100]. Notably a reduction in quality and intensity of patient monitoring by ART sites decreases patient retention, leading to higher proportions of treatment interruptions, and more patients with unknown treatment outcomes [100].

Virological monitoring
Viral load measurement is a more sensitive indicator of treatment failure compared with clinical or immunological parameters; however, many LMICs lack capacity to perform routine viral load monitoring leading to prolonged periods of virological failure prior to change of regimen [15,101]. Ongoing viral replication in the setting of drug selective pressure is a major determinant of HIVDR selection. Maintaining patients on a failing first-line NRTI-containing regimen is associated with accumulation of multiple NRTI mutations leading to NRTI cross-resistance. High population level NRTI cross-resistance will result in compromised efficacy of second-line and salvage regimens containing NRTIs [29]. Additionally, maintaining populations on failing regimens increases community viral load, which is likely to lead to increasing levels of TDR in newly infected individuals.

When available, viral load testing should be used to detect treatment failure in order to rapidly introduce adherence interventions or changes in therapy, which will suppress viral replication and reduce the risk of resistance accumulation, thus preserving second-line options. Although current modelling of ART efficacy does not unanimously support the implementation of systematic viral load monitoring in LMIC [65,102,103], the situation may change in the near future if ‘functional’ bPI monotherapy as a second-line regimen due to imputed NRTI resistance accumulated during prolonged first-line failure is shown to be associated with worse clinical or virological outcome. Data from ongoing clinical trials (for example, EAR-NEST) will help to address this question. Hopefully, technical improvements such as use of dried blood spots and point-of-care technologies may make routine viral load testing feasible for an increased number of ART programmes.

Adherence support
Adherence to ART is well-recognized as an essential component of individual and programmatic treatment success. However, because ART is life-long, maintaining a high level of adherence is particularly challenging. Fortunately, several studies report that adherence in developing countries compares favourably to that reported in the developed world, allaying some fears of the rapid emergence and spread of resistant virus in resource-limited settings [79]. Engagement of family or community members in adherence education and home visits can be particularly useful as is psychosocial support and community efforts to reduce HIV-associated stigma [104].

HIV prevention messaging
Given that a primary source of TDR is populations failing ART, these populations are the ideal target for prevention messages aimed at decreasing rates of resistance transmission. In addition, when HIV-infected patients access care and treatment, there is a unique opportunity at every encounter to convey prevention messages aimed at reducing HIV-related risk behaviours, which have the value of not only reducing HIV incidence but also TDR.

HIVDR can also be transmitted by drug-naive individuals who are unaware of their infection and thus transmit drug-resistant HIV to their partners. Expanded coverage of HIV diagnostic testing is therefore necessary to increase awareness among individuals of their HIV serostatus, and to offer appropriate counselling and access to treatment.

Retention on antiretroviral therapy
Minimizing ART interruption and ensuring retention on ART and care is crucial to further reduce AIDS-related morbidity and mortality. Patients who disengage from care are at risk of selecting for HIVDR by virtue of unplanned ART treatment interruptions [84,85] and for transmitting HIV (and potentially drug-resistant virus) to others due to unsuppressed viraemia.

As ever larger populations are maintained on ART, maximizing population-level retention on therapy and minimizing the proportion of patients with unknown outcomes will become an increasingly important public health priority [105,106].

Losses from care have been reported to be as high as 25–50% 1 year after initiation of ART and reasons are often multifactorial [105–107]. Reasons include information systems that do not permit communication within and between ART clinics. This reason is especially true in settings where different medical record keeping systems are used, electronic records are unavailable, and unique national ART patient identifiers do not exist. Additionally, in many LMICs, deaths may
Table 1. World Health Organization recommended ART options for the prevention of mother-to-child transmission

Option A
Mother
Antepartum AZT (from 14 weeks)
sdNVP at onset of labour
AZT+3TC during labour and delivery
AZT+3TC for 7 days postpartum
Infant
Breastfeeding population
Daily NVP (from birth until 1 week after all exposure to breast milk)
Non-breastfeeding population
AZT or NVP for 4–6 weeks

Option B
Mother
Triple ARV (from 14 weeks until 1 week after all exposure to breast milk has ended)
AZT+3TC+LPV/r
AZT+3TC+ABC
AZT+3TC+EFV
TDF+3TC or FTC+EFV
Infant
For all exposed infants
AZT or NVP for 4–6 weeks

Based on [113]. ABC, abacavir; ART, antiretroviral therapy; ARV, antiretroviral; AZT, zidovudine; EFV, efavirenz; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; NVP, nevirapine; sdNVP, single-dose nevirapine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

go unreported because national death registries do not exist, or ART programmes lack consistent access to these registries. Furthermore, limited human and financial resources are available to actively trace patients who do not return to clinic or for drug pick-ups and patients themselves may not be able to afford the financial and social costs associated with care.

Modelling using data from Côte d’Ivoire demonstrated cost-effectiveness of four different interventions to prevent losses to follow-up and improve survival [108]. Interventions included eliminating ART copayments and payments for opportunistic infection treatment, improving personnel training, and providing meals and reimbursing transportation for participants.

Expanded antiretroviral therapy and prevention of mother-to-child transmission access

The 2010 WHO HIV treatment guidelines changed the criteria for ART initiation from CD4+ T-cell count ≤200 cells/mm³ to CD4+ T-cell count ≤350 cells/mm³, translating to an estimated 50% increase in the number of people eligible for ART [1].

The estimated median time from seroconversion to CD4+ T-cell count <200 and <350 cell/mm³ is 7.93 and 4.19 years, respectively [109]. By changing the criteria for ART initiation from <200 to <350 cell/mm³, populations will be exposed to ART for a mean additional 3.7 years. As HIVDR is an inevitable consequence of population ART exposure, the longer the exposure to ARVs, the greater is the risk of HIVDR emergence [110].

Modelling data suggest that initiation of patients at higher CD4+ T-cell counts will likely lead to a decrease in HIV incidence [111]. Due to substantially reduced HIV incidence, the number of new resistant infections is also anticipated to decrease [111]. However, among patients who do become infected, an increasing proportion are likely to carry drug-resistant virus [112].

The revised 2010 WHO PMTCT guidelines reflect a general tendency to promote earlier ART initiation, which provides the additional benefit of further reduction in mother-to-child transmission [113]. However, in this context, the implication on the selection of HIVDR in women and children can vary according the specific strategies being adopted. In mothers, for example, the adoption of triple ARV therapy (‘option B’; Table 1) may result in a higher risk of HIVDR selection due to ART interruption once breastfeeding has ceased; this is especially true if a woman stops an NNRTI-based regimen without appropriate continuation of NRTIs for 7 days. For this and other programmatic reasons, the WHO is now considering recommending ‘option B’, where triple ART is initiated during pregnancy and continued indefinitely thereafter. In children infected during the breastfeeding period, both options are likely to result in HIV resistance to NNRTIs and 3TC [114].

Despite the expansion of ART and PMTCT combination regimens, sdNVP remains widely used. The provision of an AZT and 3TC for 7 days postpartum (‘option A’; Table 1) can reduce the selection of NVP resistance and increase PMTCT efficacy. While this option includes prolonging paediatric NVP during the breastfeeding period, further decreasing postnatal transmission, this option is likely to result in a large proportion of children who do become infected despite prophylaxis having NRTI-resistant virus [115].

Expansion of more effective PMTCT interventions will reduce the number of children acquiring HIV infection; however, children infected despite PMTCT will be very likely to carry HIV-resistant mutants, which may affect first-line efficacy.

World Health Organization strategy to assess and prevent HIV drug resistance

Since 2004, the WHO has led global efforts to assess population-level HIVDR emergence and transmission in LMICs. The WHO developed a global HIVDR prevention and assessment strategy designed to promote the long-term effectiveness of available first- and second-line regimens, improve quality of care and optimize ART programme efficiency [116]. The original strategy includes three main elements.
Determinants of HIV drug resistance and public health implications

The first element is the monitoring of HIVDR early warning indicators (EWIs) [26]. EWI monitoring identifies factors at individual clinics known to create situations favourable to the emergence of HIVDR without requiring drug resistance testing. EWI monitoring forms the foundation of national HIVDR prevention and assessment strategies and provides a context for interpretation of surveys of transmitted and acquired HIVDR. The timely identification of ART clinics with suboptimal performance helps target appropriate interventions that can potentially reduce risk of HIVDR emergence and optimize patient care.

The second element is the surveillance of acquired HIVDR in populations on ART [117]. This prospective survey is performed at sentinel ART clinics for the purpose of assessing performance in achieving HIVDR prevention (defined as achieving viral load <1,000 copies/ml) in patients 12 months after ART initiation and for the purpose of describing detected HIVDR in patients failing first-line therapy. A threshold of 1,000 copies/ml was chosen due to the current sensitivity and reproducibility of standard commercial genotyping assays. Survey results provide site-specific assessments of viral load suppression, particularly relevant to clinics and programmes where viral load is not routinely performed, and results may be used for programmatic adjustment [117].

The third element is the surveillance of transmitted HIVDR in recently infected populations [118]. The WHO TDR survey uses small sample sizes and truncated sequential sampling to classify HIVDR prevalence as low (<5%), moderate (5–15%) or high (>15%) in a specific geographical area. The survey alerts programme planners to transmission of drug-resistant HIV. Survey results inform the selection of future first-line ART regimens, selection of current PMTCT, pre-exposure prophylaxis (PreP), post-exposure prophylaxis (PEP), and inform on functioning of HIV prevention programmes.

In 2012, the WHO strategy underwent revision to supplement and simplify current methods with the hope of improving feasibility. In addition to the surveys described above, three additional surveys are now recommended: nationally representative surveys to assess HIVDR in ART-naive children <18 months, surveys of HIVDR in adult patients prior to ART initiation, and cross-sectional surveys conducted in a representative sample of clinics to assess HIVDR in adults 12–15 months and 24–36 months after ART initiation and, in paediatric patients, 12–36 months after ART initiation. The WHO-recommended essential package for surveillance and monitoring of HIVDR is found in Figure 1.

Recommendations on public health actions when detecting specific HIV drug resistance thresholds

Because results from HIVDR surveys are intended to trigger specific public health actions, the WHO recommends that policy makers critically review survey results and implement appropriate interventions, which differ according to the detected level of transmitted or acquired drug resistance. Public health actions specific for different HIVDR thresholds were recently revised during a 2012 WHO expert consultation.

**Figure 1. 2012 World Health Organization recommended essential package for HIV drug resistance surveillance and monitoring**

![Diagram](https://via.placeholder.com/150)

**ART, antiretroviral therapy; HIVDR, HIV drug resistance.**
Surveys of transmitted HIV drug resistance

If TDR is classified as low (<5%) in a specific geographical area, no changes in current ART guidelines (PMTCT, ART, PEP and PrEP) are warranted; national programmes should make plans to repeat the survey in 2 years in the same geographical area.

If TDR is classified as moderate (5–15%) for the NNRTI drug class in a specific geographical area, extra quality assurance of laboratory and epidemiological data should be performed to ensure accuracy of survey results. If no sequence quality assurance issues are noted and appropriate survey inclusion/exclusion criteria were followed, surveillance of TDR should be immediately repeated in the same geographical area to confirm the results and be expanded to additional areas.

A moderate TDR classification alerts programme planners to transmission of significant levels of HIVDR. National HIV programmes should react by reviewing potential sources of HIVDR transmission in the area surveyed through assessment of clinic factors favouring HIVDR emergence (EWIs), rates of viral load suppression 12 months after ART initiation at representative ART sites in the area of survey (WHO surveys of acquired HIVDR), performance of HIV prevention programmes to minimize HIVDR transmission and coverage of HIV testing services (high coverage of HIV testing increases awareness of HIV status and reduces the risk of unintended HIVDR transmission).

Before changing ART policy based on TDR survey results, policy makers should conduct representative surveillance of HIVDR in populations initiating ART. The prevalence of HIVDR in populations initiating ART will inform policy makers when/if they should consider changing first-line regimens (from NNRTI-based to PI-based regimens) at the population level, introducing baseline genotype testing at the individual level to guide therapy (where feasible) or intensifying viral load monitoring (for example, during the first 12 months following ART initiation).

If a survey conducted among pregnant women at antenatal care sites in a specific geographical area shows moderate levels of TDR, and results are confirmed by repeated surveys, policy makers should consider implementing full-scale national surveillance in a representative sample of all HIV-infected pregnant women. Policy implications include switching from NNRTI-based to PI-based PMTCT or performing resistance genotyping in all HIV-infected pregnant women to guide the decision on which PMTCT regimen will be most effective. Since policy decisions should take into account cost-effectiveness analysis, the WHO is exploring the possibility to develop specific guidance to help HIV/ART policy makers to interpret survey results using an economic lens.

When full-scale surveillance of HIVDR in HIV-infected pregnant women is not feasible, subanalyses of HIVDR prevalence in women initiating ART may be considered.

If high levels (>15%) of NNRTI TDR are detected, the same actions listed for moderate HIVDR should be taken. In this case, however, the WHO does not recommend repeating the survey in the same area to confirm the results because chance of gross misclassification (low as high or high as low) is ≤5/10,000 surveys [119], but instead recommends immediately performing full-scale national surveillance of HIVDR in populations initiating ART in order to inform first-line ART policy.

In order to inform selection of PMTCT regimens, full-scale surveillance of HIVDR among HIV-infected pregnant women should be conducted. These surveys will provide point prevalence estimates of HIVDR and will trigger public health actions based on cost-effectiveness thresholds. When full-scale surveillance of HIVDR in HIV-infected pregnant women is not feasible, subanalyses of HIVDR prevalence in women initiating ART may be considered (Table 2).

Surveys of acquired HIV drug resistance

WHO-recommended protocols for monitoring acquired HIVDR assess clinical performance in achieving HIVDR prevention in cohorts of patients initiating first-line ART. The WHO target of viral load suppression (HIVDR prevention) is ≥70% of patients with virological suppression (viral load <1,000 copies/ml) 12 months after ART initiation [117]. The threshold of ≥70% was chosen based on review of published literature and expert opinion, and considers patients lost to follow-up and those stopping ART as experiencing virological failure and therefore as having possible HIVDR.

At ART clinics not achieving rates of virological suppression among ≥70% of patients at 12 months, appropriate programmatic actions to be taken are based on the main reason(s) for failing to achieve the target, including pretreatment HIVDR, selection of HIVDR while on therapy, ART discontinuation (stop ART or loss to follow-up) and poor adherence.

When most virological failures are associated with detected pretreatment HIVDR, representative national surveillance of HIVDR in populations starting ART should be performed and intensified viral load monitoring or individual baseline HIVDR testing implemented based on country-specific cost-effectiveness thresholds.

When most virological failures are associated with acquired HIVDR, association of virological failure with patient/ART clinical factors (for example, patient adherence as estimated by on-time drug pick-up, previous ART exposure, self-reported adherence assessment, drug stock-out during the survey period, health staff/patient ratios, opening hours of the pharmacy...
Table 2. Public health actions for surveys of transmitted drug-resistant HIV

<table>
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<tr>
<th>Intensity</th>
<th>Description</th>
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<tbody>
<tr>
<td>Low-level transmitted HIVDR (&lt;5%; ANC, VCT/STI clinics, high-risk populations)</td>
<td>Repeat survey in 2 years in same geographical area. Consider expansion to additional areas based on ART coverage and roll-out. No changes in ARV guidelines (PMTCT, ART, PreP, PEP) based on survey data.</td>
</tr>
<tr>
<td>Moderate-level transmitted HIVDR (5–15%; ANC)</td>
<td>Perform careful quality assurance of laboratory and epidemiological data. Immediately repeat survey to confirm moderate classification in same area; perform TDR surveillance in additional areas of the country. Critically review possible sources of HIVDR transmission: assess HIVDR EWI data and data from surveys of acquired HIVDR from ART clinics in the same geographical region; review performance of HIV prevention programmes from individuals aware of their HIV infection in the area of the survey, and assess coverage of HIV testing services in the area of the survey to estimate the risk of unintended HIVDR transmission. Inform decision making around intensified viral load monitoring, individual drug resistance testing prior to ART initiation and first-line regimen selection, conduct HIVDR surveillance in populations initiating ART.</td>
</tr>
<tr>
<td>High-level transmitted HIVDR (&gt;15%)</td>
<td>Take actions 1–4 listed in 'Moderate-level transmitted HIVDR (5–15%)'. Immediately perform full-scale national surveillance in all HIV-infected pregnant women to estimate national point prevalence of TDR and trigger public health actions (switch to PI-based PMTCT or recommend HIVDR testing for all HIV-infected pregnant women) based on national cost-effectiveness thresholds.</td>
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ANC, antenatal care; ART, antiretroviral therapy; ARV, antiretroviral; EWI, early warning indicators; HIVDR, HIV drug resistance; PMTCT, prevention of mother-to-child transmission; PreP, pre-exposure prophylaxis; PEP, post-exposure prophylaxis; PI, protease inhibitor; STI, sexually-transmitted infection; TDR, transmitted HIV drug resistance; VCT, voluntary counselling and testing.

...and cost, if any, of ART) should be assessed to guide further site-specific action. Factors found to be associated with virological failure should be addressed through public health interventions or further characterized by operational research.

When survey results are driven by high rates of long-term follow-up, robust defaulter tracing and characterization of unknown outcomes and their determinants should be implemented.

When most virological failures are associated with undetected HIVDR (wild-type virus), ART adherence messaging should be evaluated and patient adherence to therapy supported.

An important result of surveys of acquired HIVDR are the observed HIVDR patterns at time of failure, which may inform the selection of second-line regimens, with the caveat that this population does not necessarily represent patients failing and switching to second-line ART. Indeed, in the real world, most switches to second-line therapy occur at time points well beyond the first 12 months when additional HIVDR may have emerged.

**Conclusions**

Global ART scale-up has been one of the most impressive and effective public health initiatives and the WHO Treatment 2.0 approach promises to capitalize on previous successes, while building stronger health systems to successfully initiate and maintain ever larger populations on ART. Lack of available HIVDR genotyping for individual patients should not limit prevention efforts to minimize emergence and transmission of HIVDR. While viral factors such as HIV subtype cannot be altered, a number of ART programmatic and patient factors have been identified which can be monitored and adjusted at local ART delivery levels to optimize programme functioning and minimize emergence of HIVDR. Additionally, standardized and routine surveillance of transmitted and acquired HIVDR and HIVDR at initiation of ART provide valuable data to guide public health prevention and treatment policy. As we enter a new era of HIV care and treatment, programme optimization efforts, including taking steps to minimize emergence of preventable HIVDR, must be a top priority for national ART programmes, international organization, funders and programme implementing partners. If preventive and corrective programme action is not taken today, successful population-level treatment response will be at significant risk in the future.

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Disclosure statement

SB is a staff member of the WHO. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or stated policies of WHO. The authors declare no competing interests.

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