HIV drug resistance in low-income and middle-income countries

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After 15 years of global scale-up of antiretroviral therapy (ART), rising prevalence of HIV drug resistance in many low-income and middle-income countries (LMICs) poses a growing threat to the HIV response, with the potential to drive an increase in mortality, HIV incidence, and costs. To achieve UNAIDS global targets, enhanced strategies are needed to improve quality of ART services and durability of available ART regimens, and to curb resistance. These strategies include roll out of drugs with greater efficacy and higher genetic barriers to resistance than those that are currently widely used, universal access to and improved effectiveness of viral load monitoring, patient-centred care delivery models, and reliable drug supply chains, in conjunction with frameworks for resistance monitoring and prevention. In this Review, we assess contemporary data on HIV drug resistance in LMICs and their implications for the HIV response, highlighting the potential impact and resistance risks of novel ART strategies and knowledge gaps.

Introduction

Global scale-up of antiretroviral therapy (ART) for HIV-1 infections has averted an estimated 7·8 million deaths and contributed to preventing 30 million new infections in low-income and middle-income countries (LMICs) between 2004, and 2014.[1] More than 21 million people with HIV worldwide are now receiving ART, just over half of all people infected.[2] Nine of ten people with HIV reside in LMICs, most of them in sub-Saharan Africa and Asia, the two regions most affected by the global epidemic.[2] The WHO-defined public health approach to ART roll out is based on simplified, standardised treatment protocols to facilitate effective care delivery in settings with limited clinical expertise and poor access to antiretroviral drugs and laboratory montoring.[3]

The UN has committed to the goal of ending the AIDS pandemic as a public health threat by 2030, ensuring that by 2020, 90% of people with HIV know their HIV status, 90% of those infected are receiving ART, and 90% of those on ART have sustained viral suppression.[2] Ensuring that 90% of people on ART have sustained viral suppression is crucially important to maximise individual health and survival and to reduce HIV incidence.[2] In coming years, ever-larger numbers of people must initiate and be successfully maintained on effective ART for life if global targets are to be achieved.[4]

However, after 15 years of ART scale-up,[2] rising HIV resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) in many LMICs poses a growing threat.[5,6] First-generation NNRTIs efavirenz and nevirapine remain the most widely used core drugs of first-line therapy and peripartum prophylaxis in mothers and newborn babies for prevention of mother-to-child transmission of HIV (PMTCT), but these drugs are vulnerable to selecting drug-resistance mutations because of their low genetic barrier to resistance, with just a single mutation resulting in complete loss of drug activity.[7] The global rise in HIV drug resistance has been forecasted to drive an increase in mortality, HIV incidence, and overall ART programmatic costs if no changes are made to standards of care in many LMICs.[8]

Major gaps in the quality of ART service delivery remain across many settings, including poor ART adherence, high attrition of patients, unreliable drug supply chains, and suboptimal viral suppression rates.[9] To sustain gains in the ART scale-up, enhanced strategies to optimise the durability of available ART regimens and curb resistance are needed. The introduction of the integrase inhibitor dolutegravir as part of a new low-cost fixed-drug combination in many LMICs offers great potential for effective and more durable therapy.[10] The proposed transition of people who are already on NNRTI-based first-line regimens to dolutegravir raises new challenges related to HIV drug resistance.

In this Review, we discuss data on HIV drug resistance (including pretreatment and acquired resistance) in LMICs and implications for the HIV response and highlight the potential impact and resistance risks of novel ART strategies, such as accelerated ART initiation (treat-all policy), dolutegravir, PMTCT, and pre-exposure prophylaxis (PrEP). Furthermore, we assess knowledge gaps and opportunities for addressing resistance.

Pretreatment drug resistance

The term pretreatment drug resistance defines drug resistance mutations detected in people with HIV before they start ART, resulting from either previous exposure to antiretroviral drugs (eg, PMTCT, PrEP, post-exposure prophylaxis, or interrupted first-line ART) or transmission of a drug-resistant strain.[5]

Pretreatment resistance to NNRTIs is associated with poor virological outcomes, impaired immune recovery, reduced durability of first-line regimens, and increased mortality.[11,12] A modelling study using data from sub-Saharan Africa estimated that in a situation in which NNRTI-associated pretreatment drug resistance is over 10% (mean 15%), 16% of AIDS deaths (890 000), 9% of new infections (450 000), and 8% of ART programme costs (US$6·5 billion) in the period 2016–30 would be attributable to HIV drug resistance.[8]

Global epidemiological data indicate a substantial rise in pretreatment resistance to NNRTIs after the ART scale-up, which is most pronounced in sub-Saharan Africa.[5,6] A meta-analysis on pretreatment drug resistance to NNRTIs in LMICs, which included 358 datasets representing 56 044 adults in 63 countries, estimated

prevalences in 2016 of 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, 9·4% (6·6–13·2%) in Latin America and the Caribbean, and 3·2% (1·8–5·6%) in Asia.[6] Estimated increases in the absolute prevalence of pretreatment resistance between 2015, and 2016, ranged from 0·3% in Asia to 1·8% in southern Africa. The most common NNRTI-associated mutations, in the reverse transcriptase gene, were Lys103Asn, Tyr181Cys, and Gly190Ala. The 2017 WHO HIV Drug Resistance Report[5] reported the worrisome finding that in six of 11 countries surveyed (Argentina, Guatemala, Namibia, Nicaragua, Uganda, and Zimbabwe) pretreatment resistance to NNRTIs surpassed 10% for people who were ART naive. Notably, these proportions were nearly two times higher in women than in men, and exceeded 10% in eight of the 11 countries surveyed.[5] Additionally, recent data point to high pretreatment resistance in Angola (16%),[13] Cuba (22%),[14] Mexico (12%),[15] Papua New Guinea (16%),[16] and South Africa (14%).[17]

Moreover, NNRTI-associated pretreatment resistance is higher among people initiating ART with previous antiretroviral drug exposure (22%) than among those who are antiretroviral naive (8%).[5,6] These data are particularly concerning, because this group is likely to be an increasing proportion of first-line ART initiators in some LMICs.

By contrast, the reported prevalence of pretreatment resistance to NRTIs has remained low with no discernible trend in most regions.[6] The most common mutation was Met184Ile or Met184Val associated with lamivudine and emtricitabine, followed by the thymidine analogue mutations Asp67Asn and Met41Leu, which confer resistance to zidovudine. The prevalence of pretreatment resistance to the other key drug classes (ie, boosted protease inhibitors and integrase inhibitors) is negligible, reflecting their restricted use in most LMICs.[5,18]

Acquired drug resistance after virological failure of ART

NNRTI-based ART

Widely used standard first-line ART regimens combine a first-generation NNRTI, either efavirenz or nevirapine, with dual NRTIs, either lamivudine or emtricitabine, plus either tenofovir or zidovudine.[19] As the global cohort of people on ART has grown and matured, the numbers of patients experiencing virological ART failure with acquired resistance will inevitably grow. A systematic review and meta-analysis of adults in LMICs estimated that approximately 85% of those still alive and receiving ART had viral suppression over the first 5 years of ART (on-treatment analysis).[20] However, when all people who had died, stopped ART, or were lost to follow-up were considered as having virological failure (intention-to-treat analysis), the viral suppression rate declines to only 62% after 4 years on ART.[20] Reported viral suppression in children in LMICs is even lower than that in adults in LMICs and that in children in high-income countries.[21] These data suggest deficiencies in the performance of many ART programmes.[2,5]

Among patients failing first-line NNRTI-based ART, 70–90% of patients have acquired resistance to NRTIs, NNRTIs, or both classes of drug.[5,22] The mutational patterns and rate are largely similar for children and adults. A global assessment of patients with virological failure on first-line tenofovir-containing ART showed high tenofovir-associated resistance (reverse transcriptase mutations Lys65Arg or Lys65Asn, or Lys70Glu, Lys70Gly, or Lys70Gln) in LMICs (57% in sub-Saharan Africa, 39% in Asia, and 35% in Latin America).[22] Among patients who had tenofovir resistance, 83% also had lamivudine and emtricitabine resistance, 78% had NNRTI-resistance, and 65% had both types of resistance. The fact that the prevalence of tenofovir-associated resistance was lower in Europe (20%) and North America (22%) than LMICs supports the notion that resistance can be limited by stringent viral load monitoring.[22]

Protease inhibitor-based ART

Despite substantial rates of first-line virological failure, the number of people who switch to regimens based on second-line ritonavir-boosted protease inhibitors in LMICs has been low (<5% of all people on ART).[5] Inadequate switching is likely a result of a combination of factors, such as clinicians' inexperience or limited access to diagnostic tests or second-line drugs. As universal viral load monitoring is implemented (with better diagnostic ability to detect first-line failures), the number of people on second-line ART in sub-Saharan Africa is expected to grow from fewer than 1 million at present to around 4–6 million people by 2030, comprising up to 20% of all individuals on ART.[23]

Most mutations that confer resistance to protease inhibitors are in the gene encoding the viral protease. A meta-analysis of second-line ART outcomes in adults in sub-Saharan Africa, comprising a boosted protease inhibitor with dual NRTIs, found that a third did not achieve viral suppression, and that among patients who were viraemic, acquired resistance associated with protease inhibitors was infrequent (median 17% of patients) but increased with therapy duration.[24] Possible mechanisms of the rarity of protease-inhibitor-associated mutations include complete non-adherence (hence no mutational selective pressure), or mediation of protease inhibitor resistance by mutations outside the protease gene, specifically in the *gag* and *env* genes.[25,26] Several studies have provided evidence for the additional benefit of NRTI continuation in second-line therapy based on boosted protease inhibitors, especially if replaced with other or alternative types of NRTI,[27,28] whereas use of a protease inhibitor monotherapy resulted in inadequate virological control and selection of resistance.[28,29]

Notably, a meta-analysis of 12 cohorts representing 928 children and adolescents on second-line ART based on boosted protease inhibitors from 14 countries in Asia

and sub-Saharan Africa found high rates of virological failure, with exceptionally poor virological outcomes in adolescents,[30] calling for urgent attention to optimise HIV care in these vulnerable groups.

Clinical management of second-line failures is sub-optimal in many settings, especially in the absence of resistance tests to identify people who harbour clinically relevant resistance mutations and need an optimised third-line regimen. In several LMICs, including Botswana, Brazil, Kenya, South Africa, and Uganda, routine resistance genotyping is increasingly done in second-line failures. With growing demand over time, understanding the optimal combination therapy and clinical management of patients on third-line and salvage therapy will become increasingly important.

Effect of HIV-1 subtypes on drug resistance

Combinations of antiretroviral drugs are effective across the various (non-B) HIV-1 subtypes circulating in LMICs.[31] Nonetheless, both enzymatic and virological data indicate that naturally occurring polymorphisms in non-B subtypes can influence HIV susceptibility to antiretroviral drugs and the propensity of HIV to acquire certain resistance mutations.[32–34] To date, however, no evidence suggests that these intersubtype differences result in different virological outcomes for the various ART regimens. For instance, although tenofovir-associated Lys65Arg mutation in the viral reverse transcriptase gene is more likely to emerge in subtype C compared with other subtypes,[35–37] there is no evidence that subtype-C infection increases the risk of virological failure for patients receiving a tenofovir-containing regimen.[37] Overall, the knowledge of subtype-specific differences in mutation distribution and clinical relevance remains poor, despite the fact that more than 90% of HIV-1 infections globally are non-B subtypes.

Accelerated ART initiation

WHO recommends accelerating ART initiation in all individuals with HIV (the treat-all policy) as early as possible after diagnosis, regardless of CD4 cell count (the so-called test-and-treat strategy). Concerns that the more prolonged exposure to ART could increase the risk of acquired resistance have not been confirmed in high-income settings.[38] A review of the evidence suggested that accelerated ART initiation, including ART start on the same day as diagnosis, can lead to improved viral suppression.[39] Nonetheless, accelerated ART initiation could have long-term implications on retention, adherence, and drug resistance, and data from LMICs are not yet available. Modelling studies based on African data have predicted that early ART initiation, at high CD4 cell counts, could lead to a rise in NNRTI-associated pretreatment drug resistance levels, but this risk would be outweighed by substantial absolute reductions in the number of new HIV infections; additionally, the increased resistance risk could be mitigated by improving early failure detection and switching practices.[40,41] Close monitoring is therefore warranted as accelerated ART initiation is implemented.

Dolutegravir roll out in LMICs and uncertainties in the evidence base

Since 2014, dolutegravir has been increasingly used as part of first-line regimens in Europe and North America[42,43] because of improved tolerability, higher efficacy, higher genetic barrier to resistance, and fewer drug interactions than other antiretroviral drugs. In July, 2017, WHO recommended the use of alternative, non-NNRTI-based (ie, based on either dolutegravir or protease inhibitors) first-line ART in countries in which at least 10% of patients who are antiretroviral naive have virus with pretreatment resistance to NNRTI, and in all people who report prior antiretroviral drug exposure.[44] Since September, 2017, a new low-cost generic fixed-dose combination of tenofovir, lamivudine, and dolutegravir has been offered to 92 LMICs through the Medicines Patent Pool at a similar or lower price than NNRTI-based ART (median $75 per patient per annum).[10] Several countries in sub-Saharan Africa and Brazil are in the process of transitioning all first-line patients to this combination. Moreover, the US President's Emergency Plan for AIDS Relief (PEPFAR) programmes will accelerate access to the fixed-dose combination for all patients supported by the programme.[45] A future transition from first-line ART containing efavirenz to dolutegravir in adults who are initiating ART has been forecasted to be effective and cost-effective in sub-Saharan Africa, at any prevalence of NNRTI pretreatment resistance.[46] Because of the resultant lower need of more expensive second-line protease inhibitor regimens, overall programme cost would be reduced.[46]

Although this transition could blunt the impact of rising NNRTI resistance and yield improved ART outcomes, the transition also presents new challenges. First, the speed of the transition to fixed-dose tenofovir, lamivudine, and dolutegravir should depend on a country's situation, taking into account training and supply chain readiness, pricing and availability, current NNRTI-associated pretreatment resistance prevalence, and available laboratory capacity. Second, evidence is scarce to support the roll out of dolutegravir for specific groups of patients (ie, those with tuberculosis co-infection, young children, and pregnant women). Interaction with the tuberculosis drug rifampicin could reduce dolutegravir concentrations when used concomitantly, although preliminary data suggest that doubling the dose of dolutegravir results in high viral suppression in HIV and tuberculosis co-infected adults receiving rifampicin-based tuberculosis therapy.[47] A potential safety issue related to neural tube defects in infants born to women who were taking dolutegravir at the time of conception has raised concerns.[48,49] Following these concerns, the WHO interim guidelines recommend the use of dolutegravir in women of reproductive age only when a

consistent and reliable contraception is assured. This implies the need for alternative regimens for women in LMICs who have limited access to effective contraception.

Third, the need for viral load and resistance testing might be increased with roll out of combined tenofovir, lamivudine, and dolutegravir. A blanket transition to the fixed dose combination (in absence of viral load testing) carries the risk that patients who already have acquired resistance to the NRTI backbone are switched to functional monotherapy, recognisant of the fact that dolutegravir maintenance monotherapy studies have reported high virological failure with acquisition of integrase inhibitor resistance mutations.[50,51] Preliminary data thus support an approach of transition to combined tenofovir, lamivudine, and dolutegravir in the presence of confirmed viral suppression. Additionally, in four clinical trials of antiretroviral-naive patients who received first-line dolutegravir plus dual NRTIs, patients with virological failure did not carry any resistance mutations to either integrase inhibitors or NRTIs;[52–55] these results suggest that blanket switches of all patients who are viraemic from dolutegravir-based first-line ART to protease-inhibitor-based second-line treatment could be premature, potentially wasting resources and unnecessarily exposing patients to drug toxicity. Individual resistance testing to guide the clinical management of patients on tenofovir, lamivudine, and dolutegravir is likely to be cost-effective, and countries like Botswana and Brazil have already implemented this as standard of care.[56] Implementation science studies will be important early in the roll out to inform optimal laboratory monitoring strategies.

Fourth, a study in people who were integrase inhibitor-naive indicated that major mutations are likely to be rare across circulating HIV-1 subtypes in sub-Saharan Africa, only occurring at low-resistance detection thresholds.[18] However, the extent to which HIV-1 subtype affects mutational pathways of resistance (eg, integrase mutations Arg263Lys in subtype B versus Gly118Arg in non-B subtype)[57,58] and virological response of integrase inhibitor-based regimens remains unclear.

Antiretroviral drugs for HIV prevention and risk of drug resistance

PMTCT in infants and children

A meta-analysis on pretreatment drug resistance in children, including 19 studies representing 2617 children in 13 countries, found a prevalence of 42·7% in children exposed to PMTCT and 12·7% in children not exposed, with NNRTI mutations found in 32·4% and in 9·7% of these children, respectively.[59] Surveys of pretreatment resistance among children aged less than 18 months who were diagnosed with HIV through early infant diagnosis in five sub-Saharan African countries between 2011, and 2014, found that 53% had resistance to NNRTIs and 8·8% had resistance to NRTIs, and resistance was particularly high in those exposed to PMTCT.[60] High prevalence of pretreatment resistance to NNRTIs in infants strongly supports WHO's 2013 recommendation that all children younger than 3 years should start first-line regimens based on boosted protease inhibitors, irrespective of previous PMTCT exposure. These data highlight the urgent need to overcome barriers to the scaling up of paediatric protease inhibitor-based regimens and to accelerate the study and approval of integrase inhibitors for use in young children.

PMTCT in women of reproductive age

Since 2015, WHO recommends that all pregnant woman with HIV start life-long ART, the so-called Option B+. Reports of suboptimal adherence and retention during and after pregnancy raised concerns that this strategy could promote drug resistance.[61,62] Early follow-up data from programmes in Malawi and Uganda showed reasonable virological control and low levels of acquired resistance,[63,64] although data from a Rwandan programme reported a concerning increasing trend of higher viraemia and acquired resistance with prolonged ART duration.[65] Further implementation research on how to ensure optimal adherence and retention and avoid cycles of ART stops and restarts is needed to optimise long-term outcomes.

PrEP

Following 2015 WHO recommendations, PrEP is being rolled out in key populations (such as sex workers, men who have sex with men, and people who inject drugs) and in broader population groups in LMICs that are considered at substantial risk for HIV infection.[66] The efficacy of daily tenofovir combined with emtricitabine exceeds 90%, but efficacy is highly correlated with adherence, and individuals with a breakthrough infection are theoretically at high risk of acquired resistance. In trials, resistance to tenofovir or emtricitabine was rare (0·1% of users), and in most cases occurred when PrEP was unintentionally prescribed to individuals with undiagnosed acute HIV infection.[67] The potential benefits of PrEP in sub-Saharan Africa have been predicted to outweigh the risks associated with resistance, and the magnitude of PrEP-induced resistance is expected to be small compared with acquired resistance during ART.[68] Nonetheless, as PrEP is scaled up in LMICs, resistance could increase, particularly in settings where many HIV infections remain unrecognised, warranting continuous monitoring.

Framework to curb HIV drug resistance

Population-based surveillance and prevention

The global response to emerging antimicrobial resistance has received increasing attention worldwide. As part of these concerted efforts, WHO is spearheading the Global Action Plan on HIV drug resistance (2017–21), a 5 year framework articulating a global consensus and co-mmitment to minimising HIV drug resistance and preventing it from undermining attainment of global HIV

targets.[69] Continuous population-based surveillance remains a crucial component to understand the scientific basis and clinical implications of HIV drug resistance in all regions and to inform appropriate ART algorithms. WHO recommends standardised surveys to assess pretreatment drug resistance and acquired resistance in adults and children and so-called early warning indicators of HIV drug resistance, with the aim of obtaining nationally representative estimates that inform strategies to improve ART service delivery and guide selection of first-line, second-line, and third-line regimens. For instance, aggregated data on rising prevalence of pretreatment resistance NNRTI have resulted in updated 2017 guidelines to define the public health response,[44] as a supplement to the 2016 consolidated ART guidelines.[19] Nonetheless, to date many countries have experienced challenges in implementing WHO-recommended surveys because of cost and feasibility issues. Consequently, representative data on HIV drug resistance are scarce and usually lag behind in many settings, potentially causing the underestimation of prevalence estimates. The collection of early warning indicators should be improved now that WHO has harmonised them with monitoring indicators of PEPFAR and The Global Fund to Fight AIDS, Tuberculosis and Malaria and integrated them into the 2017 update of the WHO patient-centred monitoring guidelines.[70] Novel laboratory technologies that measure HIV drug resistance are increasingly affordable, which could facilitate surveillance in LMICs.[71,72] Briefly, Sanger assays are the gold standard, although high capital and test costs have limited availability of these assays to a few reference laboratories in LMICs. Next-generation sequencing could have the potential to substantially reduce testing costs through multiplexing in high-throughput facilities, although the requirements for bioinformatics expertise are still complex.[71,72] As health information systems improve, new opportunities arise for dynamic approaches that could help countries to understand in real time the effects of implemented changes on the quality of their ART programmes, with the potential that these approaches could result in decreased drug resistance rates. This type of information could prove to be complementary to the WHO-recommended surveys (panel 1).

***Panel 1*: Framework to curb HIV drug resistance**

- The WHO Global Action Plan for HIV drug resistance (2017–21) is a framework for countries and national and international partners, aiming to articulate synergistic actions that will be required to prevent HIV drug resistance from undermining efforts to achieve global targets on health and HIV, and to provide the most effective treatment to all people with HIV. The action plan has five strategic objectives: prevention and response, monitoring and surveillance, research and innovation, laboratory capacity, and governance and enabling mechanisms.[69]
- Enhanced quality of ART delivery is needed to consolidate long-term gains, including implementation of first-line ART regimens with greater efficacy, implementation of genetic barriers (eg, fixed-dose combination tenofovir, lamivudine, and dolutegravir), expanded access to second-line and third-line regimens, universal access to and effective use of viral load testing, improved capacities for resistance testing, and patient-centred care models. Special attention is needed for vulnerable groups, such as children, adolescents, and pregnant women.
- WHO-recommended resistance surveys to provide nationally representative estimates that inform strategies to improve ART service delivery and guide selection of first-line, second-line, and third-line regimens. Special attention is needed for the roll out of novel ART strategies, such as accelerated ART initiation, PrEP, option B+, and fixed-dose tenofovir, lamivudine, and dolutegravir.
- WHO normative guidance in response to emerging drug resistance is crucial to formulate an effective public health response.[44]

ART=antiretroviral therapy. PrEP=pre-exposure prophylaxis.

Patient-centred care

Enhanced services of ART delivery and novel ART strategies are prerequisites to consolidate long-term gains. These methods include use of first-line ART regimens with greater efficacy higher genetic barriers to resistance (eg, dolutegravir), expanding access to second-line and third-line regimens and universal access to viral load testing, and improving capacities for resistance testing. The wide implementation of treat-all strategies and PrEP will decrease HIV incidence, but also calls for enhanced frameworks to monitor emerging HIV drug resistance during their scale-up. To improve service quality, adherence and retention, outcomes, and efficiency and to reduce costs, differentiated patient-centred care models are being implemented to tailor intensity of HIV services to the specific needs of different groups of individuals across the cascade of care, potentially reducing unnecessary burdens on the health system.[73,74] Opportunities also exist for a stronger role for community and health information technology applications to improve quality of care.

Access to and effective use of viral load testing

Access to routine viral load monitoring, crucial for early detection of virological failure and averting unnecessary switching,[75] is being accelerated in many LMICs. However, a large collaborative analysis of African cohorts found that even when routine viral load monitoring was in place, around 44% of patients with confirmed virological failure were not switched to another regimen, and 22% of patients under routine viral load monitoring and 30% of those receiving targeted viral load monitoring switched regimens

Panel 2: Knowledge gaps in addressing HIV drug resistance

- Need for up-to-date survey data on HIV drug resistance across all settings, with global systems for quality assurance.
- Standardisation of definitions of virological failure, drug resistance mutations, clinically relevant resistance detection thresholds for sequence analysis, and affordable and simple bioinformatics analysis.
- Impact of implementing novel ART strategies, including so-called treat-all strategies, PrEP, option B+, and fixed-dose combination tenofovir, lamivudine, and dolutegravir, in terms of retention, adherence, and drug resistance.
- Implementation science around the transition to tenofovir, lamivudine, and dolutegravir—eg, need for viral-load and resistance testing, durability and sequencing of ART lines, mutational resistance patterns in HIV-1 non-B subtypes, resistance to cytosine analogues, tenofovir, and dolutegravir components of the regimen, and resuppression after intensive adherence counselling.
- Virological mechanisms and optimal clinical management of patients with virological failure and acquired resistance to bPI and integrase inhibitor-based regimens.
- Activity of integrase inhibitor-based regimens in patients with an impaired NRTI-backbone and in non-standard combinations (eg, with bPI).
- Efficacy of recycled NRTIs and their use in second-line ART.
- Optimal strategies for clinical management, regimen sequencing, and adherence and retention support in children, adolescents, and post-partum women.
- Optimal combination therapy and clinical management of patients on third-line ART.

ART=antiretroviral therapy. PrEP=pre-exposure prophylaxis. NRTI=nucleoside reverse transcriptase inhibitors. bPI=boosted protease inhibitors.

Search strategy and selection criteria

We searched PubMed for original research, reviews, and viewpoint articles describing HIV drug resistance in low-income and middle-income countries. We used a search strategy combining medical subject headings and free text search terms for "HIV", "antiretroviral therapy", "drug resistance", and "low and middle-income countries". Articles published in English from July 1, 2013, to July 1, 2018, were reviewed for relevance. Reference lists of relevant articles were also screened for additional references. We also reviewed WHO treatment guidelines and reports, and abstracts presented at the main international HIV conferences during the past 2 years (ie, the International AIDS Society Conference on HIV Science, Conference on Retroviruses and Opportunistic Infections, and International Workshop on HIV Drug Resistance).

without any evidence of virological failure.[76] Therefore, more efforts are needed not only to achieve universal access to viral load monitoring, but also to strengthen functional capacities.[77,78] Implementation research will be essential for understanding the performance of viral load testing, including current and optimum testing frequencies, test results returned to patients, actions taken within appropriate timeframes, and interventions that work to achieve renewed suppression. Patient communities are increasingly claiming their rights to have access to optimal care, demanding their viral loads to be suppressed, which should serve as a further impetus for this work.[79]

The potential using long-acting antiretrovirals for treatment and prevention

Long-acting antiretrovirals are a promising approach to enable gains in optimising adherence and minimising treatment failure and acquired resistance, which are crucial both for treatment and PrEP.[80] For instance, the landmark phase-2B LATTE trial[81] found that a combination of two long-acting injectable agents, cabotegravir and rilpivirine, was well tolerated and had similar efficacy to that of daily oral triple-drug ART for maintaining viral suppression through 96 weeks.[81] However, the consequences of interrupting long-acting antiretrovirals are unclear; extended exposure to subtherapeutic concentrations of residual drug might increase the risk of selecting drug-resistant HIV variants.[82] A case of drug-resistant virus has been reported in a woman who received long-acting rilpivirine in a phase 1 PrEP trial[83] and who became infected with a wild-type HIV strain, which then selected for the Lys101Glu mutation in the reverse transcriptase gene under prolonged residual rilpivirine exposure.[83] There are still numerous health system and individual barriers to the wide implementation of long-acting antiretrovirals in key populations in LMICs, such as the need for drug development with improvements in potency, pharmacokinetics, and pharmacodynamics, simplified delivery approaches, research on patients' preferences, specific clinical infrastructure, provider training, and laboratory monitoring.

Conclusions

Rising prevalence of HIV drug resistance threatens achievements to date in controlling the epidemic, and have the potential to increase the costs of national ART programmes to untenable levels. The commitment of policy makers and national governments remains essential to achieving global HIV targets. Substantial knowledge gaps remain in addressing resistance in LMICs, in relation to the contemporary epidemiological situation, optimal clinical management, and diagnostic algorithms (panel 2). A range of measures can be taken to minimise HIV drug resistance and maintain global HIV control. Roll out of fixed-dose combination tenofovir, lamivudine, and dolutegravir provides a unique opportunity to improve

durability and effectiveness of ART, provided it is implemented in conjunction with improved quality of services and appropriate monitoring frameworks, such as robust drug supply chains, enhanced functional capacity for viral load monitoring, patient-centred community-based care delivery models, and routine HIV drug resistance surveillance as an integral part of national ART programmes. Implementation science will be crucial in generating real-world evidence on these multifaceted approaches to evaluate and maximise their effect.

Contributors

RLH conceptualised the Review, did the literature search, and wrote the first draft of the manuscript. TFRdW and CBH provided additional references, and commented on and contributed to subsequent versions. We all read and approved the final paper.

Declaration of interests

TFRdW and CBH are members of the WHO Steering Group on HIV Drug Resistance. We declare no competing interests. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

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References

1 UNAIDS. '15 by 15': a global target achieved. 2015. http://www.unaids.org/sites/default/files/media_asset/UNAIDS_15by15_en.pdf (accessed May 1, 2018).

2 UNAIDS. Global AIDS update 2017: ending AIDS. Progress towards the 90–90–90 targets. 2017. http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf (accessed May 1, 2018).

3 Ford N, Ball A, Baggaley R, et al. The WHO public health approach to HIV treatment and care: looking back and looking ahead. *Lancet Infect Dis* 2018; **18:** e76–86.

4 US President's Emergency Plan for AIDS. PEPFAR strategy for accelerating HIV/AIDS epidemic control (2017–2020). Factsheet, September 2017. https://www.pepfar.gov/documents/organization/274400.pdf (accessed May 1, 2018).

5 WHO, CDC, The Global Fund. HIV drug resistance report 2017. http://apps.who.int/iris/bitstream/10665/255896/1/9789241512831-eng.pdf?ua=1 (accessed April 1, 2018).

6 Gupta RK, Gregson J, Parkin N, et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. *Lancet Infect Dis* 2018; **18:** 346–55.

7 Stanford University. HIV drug resistance database. NNRTI resitance notes. https://hivdb.stanford.edu/dr-summary/resistance-notes/NNRTI/ (accessed June 1, 2018).

8 Phillips AN, Stover J, Cambiano V, et al. Impact of HIV drug resistance on HIV/AIDS-associated mortality, new infections, and antiretroviral therapy program costs in sub–Saharan Africa. *J Infect Dis* 2017; **215:** 1362–65.

9 WHO. Global report on early warning indicators of HIV drug resistance. Technical report. July 2016. http://apps.who.int/iris/bitstream/10665/246219/1/9789241511179-eng.pdf?ua=1 (accessed (accessed May 1, 2018).

10 Clinton Health Access Initiative. ARV market report:the state of the antiretroviral drug market in low- and middle-income countries, 2016–2021. 2017. https://clintonhealthaccess.org/content/uploads/2017/09/2017-ARVMarket-%0AReport_Final.pdf (accessed (accessed April 1, 2018).

11 Pinoges L, Schramm B, Poulet E, et al. Risk factors and mortality associated with resistance to first-line antiretroviral therapy: multicentric cross-sectional and longitudinal analyses. *J Acquir Immune Defic Syndr* 2015; **68:** 527–35.

12 Hamers RL, Schuurman R, Sigaloff KCE, et al. Effect of pretreatment HIV-1 drug resistance on immunological, virological, and drug-resistance outcomes of first-line antiretroviral treatment in sub-Saharan Africa: a multicentre cohort study. *Lancet Infect Dis* 2012; **12:** 307–17.

13 Afonso JM, Bello G, Guimaraes ML, Sojka M, Morgado MG. HIV-1 genetic diversity and transmitted drug resistance mutations among patients from the North, Central and South regions of Angola. *PLoS One* 2012; **7:** e42996.

14 Perez L, Kouri V, Aleman Y, et al. Antiretroviral drug resistance in HIV-1 therapy-naive patients in Cuba. *Infect Genet Evol* 2013; **16:** 144–50.

15 Ávila-Ríos S, García-Morales C, Matías-Florentino M, et al. Pre-treatment HIV drug resistance in Mexico and its impact on first-line antiretroviral treatment effectiveness: a nationally representative 2015 WHO survey. *Lancet Infect Dis* 2016; **3:** e579–91.

16 Lavu E, Kave E, Mosoro E, et al. High levels of transmitted HIV drug resistance in a study in Papua New Guinea. *PLoS One* 2017; **12:** e0170265.

17 National Institute for Communicable Diseases. Communicable diseases communiqué. Prospective sentinel surveillance of human immunodeficiency virus-related drug resistance. 2016. http://www.nicd.ac.za/assets/files/NICD Communicable DiseasesCommunique_Mar2016_final.pdf (accessed April 1, 2018).

18 Inzaule SC, Hamers RL, Noguera-Julian M, et al. Primary resistance to integrase strand transfer inhibitors in patients infected with diverse HIV-1 subtypes in sub-Saharan Africa. *J Antimicrob Chemother* 2018; **73:** 1167–72.

19 WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach–second edition. 2016. http://www.who.int/hiv/pub/arv/arv-2016/en/ (accessed April 1, 2018).

20 Boender TS, Sigaloff KCE, Mcmahon JH, et al. Clinical infectious diseases long-term virological outcomes of first-line antiretroviral therapy for HIV-1 in low- and middle-income countries: a systematic review and meta-analysis. *Clin Infect Dis* 2015; **61:** 1453–61.

21 Boerma RS, Boender TS, Bussink AP, et al. Suboptimal viral suppression rates among HIV-infected children in low- and middle-income countries: a meta-analysis. *Clin Infect Dis* 2016; **63:** 1645–54.

22 The TenoRes Study Group. Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multicentre retrospective cohort study. *Lancet Infect Dis* 2016; **16:** 565–75.

23 Estill J, Ford N, Salazar-Vizcaya L, et al. The need for second-line antiretroviral therapy in adults in sub-Saharan Africa up to 2030: a mathematical modelling study. *Lancet HIV* 2016; **3:** e132–39.

24 Stockdale AJ, Saunders MJ, Boyd MA. Effectiveness of protease inhibitor/nucleos(t)ide reverse transcriptase inhibitor–based second-line antiretroviral therapy for the treatment of human immunodeficiency virus type 1 infection in sub-Saharan africa: a systematic review and meta-analysis. *Clin Infect Dis* 2018; **66:** 1846–57.

25 Fun A, Wensing AMJ, Verheyen J, Nijhuis M. Human immunodeficiency virus gag and protease: partners in resistance. *Retrovirology* 2012; **9:** 63.

26 Rabi SA, Laird GM, Durand CM, et al. Multi-step inhibition explains HIV-1 protease inhibitor pharmacodynamics and resistance. *J Clin Invest* 2013; **123:** 3848–60.

27 Aboud M, Brites C, Lu H, et al. DTG versus LPV/r in second Line (DAWNING): outcomes by WHO-recommended NRTI backbone. Conference on Retroviruses and Opportunistic Infections (CROI); Seattle, Washington; March 4–7, 2018. 508.

28 Hill AM, Venter F. The unexpected success of NRTIs in second-line treatment. *Lancet Infect Dis* 2018; **18:** 3–5.

29 Paton NI, Kityo C, Hoppe A, et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. *N Engl J Med* 2014; **371:** 234–47.

30 Boerma RS, Bunupuradah T, Dow D, et al. Multicentre analysis of second-line antiretroviral treatment in HIV-infected children: adolescents at high risk of failure. *J Int AIDS Soc* 2017; **20:** 21930.

31 Clutter DS, Jordan MR, Bertagnolio S, Shafer RW. HIV-1 drug resistance and resistance testing. *Infect Genet Evol* 2016; **46:** 292–307.

32 Brenner B, Turner D, Oliveira M, et al. A V106M mutation in HIV-1 clade C viruses exposed to efavirenz confers cross-resistance to non-nucleoside reverse transcriptase inhibitors. *AIDS* 2003; **17:** F1–F5.

33 Ariyoshi K, Matsuda M, Miura H, Tateishi S, Yamada K, Sugiura W. Patterns of point mutations associated with antiretroviral drug treatment failure in CRF01_AE (subtype E) infection differ from subtype B infection. *J Acquir Immune Defic Syndr* 2003; **33:** 336–42.

34 Palma AC, Covens K, Snoeck J, Vandamme AM, Camacho RJ, van Laethem K. HIV-1 protease mutation 82M contributes to phenotypic resistance to protease inhibitors in subtype G. *J Antimicrob Chemother* 2012; **67:** 1075–79.

35 Coutsinos D, Invernizzi CF, Xu H, et al. Template usage is responsible for the preferential acquisition of the K65R reverse transcriptase mutation in subtype C variants of human immunodeficiency virus type 1. *J Virol* 2009; **83:** 2029–33.

36 Invernizzi CF, Coutsinos D, Oliveira M, Moisi D, Brenner BG, Wainberg M. Signature nucleotide polymorphisms at positions 64 and 65 in reverse transcriptase favor the selection of the K65R resistance mutation in HIV-1 subtype C. *J Infect Dis* 2009; **200:** 1202–06.

37 White E, Smit E, Churchill D, et al. No evidence that HIV-1 subtype C infection compromises the efficacy of tenofovir-containing regimens: cohort study in the United Kingdom. *J Infect Dis* 2016; **214:** 1302–08.

38 Lodi S, Günthard HF, Dunn D, et al. Effect of immediate initiation of antiretroviral treatment on the risk of acquired HIV drug resistance. *AIDS* 2017; **32:** 327–35.

39 Ford N, Migone C, Calmy A, et al. Benefits and risks of rapid initiation of antiretroviral therapy. *AIDS* 2018; **32:** 17–23.

40 Nichols BE, Sigaloff KC, Kityo C, et al. Averted HIV infections due to expanded antiretroviral treatment eligibility offsets risk of transmitted drug resistance: a modeling study. *AIDS* 2014; **28:** 73–83.

41 Nichols BE, Sigaloff KCE, Kityo C, et al. Increasing the use of second-line therapy is a cost-effective approach to prevent the spread of drug-resistant HIV: a mathematical modelling study. *J Int AIDS Soc* 2014; **17:** 19164.

42 DHHS. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2018. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf (accessed June 1, 2018).

43 European AIDS Clinical Society. Guidelines version 9.0, October 2017. http://www.eacsociety.org/files/guidelines_9.0-english.pdf (accessed June 1, 2018).

44 WHO. Guidelines on the public health response to pretreatment HIV drug resistance. 2017. http://apps.who.int/iris/bitstream/10665/255880/1/9789241550055-eng.pdf?ua=1 (accessed May 1, 2018).

45 President's Emergency Plan for AIDS Relief. PEPFAR 2018 country operation plan guidance for standard process countries. 2018. https://www.pepfar.gov/documents/organization/276459.pdf (accessed May 1, 2018).

46 Phillips AN, Cambiano V, Nakagawa F, et al. Cost-effectiveness of public-health policy options in the presence of pretreatment NNRTI drug resistance in sub-Saharan Africa: a modelling study. *Lancet HIV* 2018; **5:** e146–54.

47 Dooley K, Kaplan R, Mwelase N, et al. Safety and efficacy of dolutegravir-based ART in TB/HIV coinfected adults at week 24. Conference om Retroviruses and Opportunistic Infections; Baltimore, MD, USA; March 4–7, 2018. 33.

48 WHO. Statement: potential safety issue affecting women living with HIV using dolutegravir at the time of conception. May 18, 2018. http://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf (accessed June 1, 2018).

49 US Food and Drug Administration. Juluca, tivicay, triumeq (dolutegravir): FDA to evaluate– potential risk of neural tube birth defects. 2018. https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm608168.htm (accessed June 1, 2018).

50 Wijting I, Rokx C, Boucher C, et al. Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised non-inferiority trial. *Lancet HIV* 2017; **12:** e547–54.

51 Blanco JL, Rojas J, Paredes R, et al. Dolutegravir-based maintenance monotherapy versus dual therapy with lamivudine: a planned 24 week analysis of the DOLAM randomized clinical trial. *J Antimicrob Chemother* 2018; published online March 28. DOI:10.1093/jac/dky093 (preprint).

52 Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis* 2013; **13:** 927–35.

53 Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. *Lancet HIV* 2017; **4:** e536–46.

54 Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. *Lancet HIV* 2015; **2:** e127–36.

55 Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir–lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013; **369:** 1807–18.

56 WHO. Handbook of the Botswana 2016 integrated HIV clinical care guidelines. 2016. http://apps.who.int/medicinedocs/en/m/abstract/Js22413en/ (accessed June 1, 2018).

57 Han YS, Mesplède T, Wainberg MA. Differences among HIV-1 subtypes in drug resistance against integrase inhibitors. *Infect Genet Evol* 2016; **46:** 286–91.

58 Brenner BG, Thomas R, Blanco JL, et al. Development of a G118R mutation in HIV-1 integrase following a switch to dolutegravir monotherapy leading to cross-resistance to integrase inhibitors. *J Antimicrob Chemother* 2016; **71:** 1948–53.

59 Boerma RS, Sigaloff KCE, Akanmu AS, et al. Alarming increase in pretreatment HIV drug resistance in children living in sub-Saharan Africa: a systematic review and meta-analysis. *J Antimicrob Chemother* 2017; **72:** 365–71.

60 Jordan MR, Penazzato M, Cournil A, et al. Human immunodeficiency virus (HIV) drug resistance in African infants and young children newly diagnosed with HIV: a multicountry analysis. *Clin Infect Dis* 2017; **65:** 2018–25.

61 Haas AD, Tenthani L, Msukwa MT, et al. Retention in care during the first 3 years of antiretroviral therapy for women in Malawi's option B+ programme: an observational cohort study. *Lancet HIV* 2016; **3:** e175–82.

62 Haas AD, Msukwa MT, Egger M, et al. Adherence to antiretroviral therapy during and after pregnancy: cohort study on women receiving care in Malawi's option B+ program. *Clin Infect Dis* 2016; **63:** 1227–35.

63 Tenthani L, Haas AD, Tweya H, et al. Retention in care under universal antiretroviral therapy for HIV-infected pregnant and breastfeeding women ('option B+') in Malawi. *AIDS* 2014; **28:** 589–98.

64 Decker S, Rempis E, Schnack A, et al. Prevention of mother-to-child transmission of HIV: postpartum adherence to option B+ until 18 months in Western Uganda. *PLoS One* 2017; **12:** 0179448.

65 Gill MM, Hoffman HJ, Bobrow EA, et al. Detectable viral load in late pregnancy among women in the Rwanda option B+ PMTCT program: enrollment results from the Kabeho study. *PLoS One* 2016; **11:** e0168671.

66 WHO. WHO expands recommendation on oral pre-exposure prophylaxis of HIV infection (PrEP). Policy Brief. 2015. http://apps.who.int/iris/bitstream/handle/10665/197906/WHO_HIV_2015.48_eng.pdf;jsessionid=8B4B5945CC6A788D31B69A0D8C1E991F?sequence=1 (accessed June 1, 2018).

67 Riddell J, Amico KR, Mayer KH. HIV preexposure prophylaxis: a review. *JAMA* 2018; **319:** 1261–68.

68 van de Vijver DAMC, Nichols BE, Abbas UL, et al. Preexposure prophylaxis will have a limited impact on HIV-1 drug resistance in sub-Saharan Africa: a comparison of mathematical models. *AIDS* 2013; **27:** 2943–51.

69 WHO. Global action plan for HIV drug resistance 2016–2021. 2016. http://www.who.int/hiv/pub/drugresistance/hiv-drug-resistance-brief-2016/en/ (accessed May 1, 2018).

70 WHO. Consolidated guidelines on person-centred HIV patient monitoring and case surveillance. Guidelines. 2017. http://www.who.int/hiv/pub/guidelines/person-centred-hiv-monitoring-guidelines/en/ (accessed May 1, 2018).

71 Inzaule SC, Ondoa P, Peter T, et al. Affordable HIV drug-resistance testing for monitoring of antiretroviral therapy in sub-Saharan Africa. *Lancet Infect Dis* 2016; **16:** e267–75.

72 Inzaule SC, Hamers RL, Paredes R, Yang C, Schuurman R, Rinke de Wit TF. The evolving landscape of HIV drug resistance diagnostics for expanding testing in resource-limited settings. *AIDS Rev* 2017; **19:** 1–3.

73 Duncombe C, Rosenblum S, Hellmann N, et al. Reframing HIV care: putting people at the centre of antiretroviral delivery. *Trop Med Int Heal* 2015; **20:** 430–47.

74 Grimsrud A, Bygrave H, Doherty M, et al. Reimagining HIV service delivery: the role of differentiated care from prevention to suppression. *J Int AIDS Soc* 2016; **19:** 21484.

75 Sigaloff KCE, Hamers RLRL, Wallis CLCL, et al. Unnecessary antiretroviral treatment switches and accumulation of HIV resistance mutations; two arguments for viral load monitoring in Africa. *J Acquir Immune Defic Syndr* 2011; **58:** 23–31.

76 Haas AD, Keiser O, Balestre E, et al. Monitoring and switching of first-line antiretroviral therapy in adult treatment cohorts in sub-Saharan Africa: collaborative analysis. *Lancet HIV* 2015; **2:** e271–78.

77 Peter T, Ellenberger D, Kim AA, et al. Early antiretroviral therapy initiation: access and equity of viral load testing for HIV treatment monitoring. *Lancet Infect Dis* 2016; **17:** e26–29.

78 Saito S, Duong YT, Metz M, et al. Returning HIV-1 viral load results to participant-selected health facilities in national population-based HIV impact assessment (PHIA) household surveys in three sub-Saharan African countries, 2015 to 2016. *J Int AIDS Soc* 2017; **20** (suppl 7)**:** e25004.

79 The Lancet HIV. U=U taking off in 2017. *Lancet HIV* 2017; **4:** e475.

80 Benitez-Gutierrez L, Soriano V, Requena S, Arias A, Barreiro P, de Mendoza C. Treatment and prevention of HIV infection with long-acting antiretrovirals. *Expert Rev Clin Pharmacol* 2018; **11:** 507–17.

81 Margolis DA, Gonzalez-Garcia J, Stellbrink H-J, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet* 2017; **390:** 1499–510.

82 Markowitz M, Frank I, Grant RM, et al. Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial. *Lancet HIV* 2017; **4:** e331–40.

83 Penrose KJ, Parikh UM, Hamanishi KA, et al. Selection of rilpivirine-resistant HIV-1 in a seroconverter from the SSAT 040 trial who received the 300-mg dose of long-acting rilpivirine (TMC278LA). *J Infect Dis* 2016; **213:** 1013–17.