HIV drug resistance in sub-Saharan Africa: public health questions and the potential role of real-world data and mathematical modelling

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Abstract

The prevalence of pretreatment resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) is >10% in many low-income countries. As a consequence, several sub-Saharan African countries have implemented, or are considering the introduction of, non-NNRTI-based first-line antiretroviral therapy (ART) for treatment-naïve and treatment-experienced patients. This is occurring at a time when ART programmes are expanding, in response to the World Health Organization guidelines, which recommend ART initiation regardless of CD4 cell count. Both those developments raise important questions regarding their potential impact on HIV drug resistance and the impact of HIV drug resistance on clinical outcomes. Those issues are particularly relevant to sub-Saharan Africa, where standardised ART regimens are used and where viral load monitoring and resistance testing are often not done routinely. It is therefore essential to forecast the impact of the implementation of universal ART, and the introduction of drugs such as dolutegravir to first-line regimens, on HIV drug resistance in order to inform future policies and to help ensure sustainable positive long-term outcomes. We discuss important public health considerations regarding HIV drug resistance, and describe how mathematical modelling, combined with real-world data from the four African Regions of the International epidemiology Databases to Evaluate AIDS consortium, could provide an early warning system for HIV drug resistance in sub-Saharan Africa.

Keywords: HIV drug resistance, universal test-and-treat, dolutegravir, sub-Saharan Africa, mathematical modelling

Introduction

The widespread emergence and transmission of HIV drug resistance (HIVDR) has impaired the success of the currently recommended first-line antiretroviral therapy (ART) regimens including efavirenz in sub-Saharan Africa (SSA). The prevalence of pretreatment non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance ranges from 8% in Cameroon to 15% in Uganda [1]. As many countries in the region consider shifting to dolutegravir-containing regimens, surveillance and monitoring of HIVDR will be key to ensuring the durability of this new drug. The introduction of universal test-and-treat policies [2] will increase the number of individuals on ART from 20 million in mid-2017 to approximately 30 million by 2020. This rapid expansion of ART programmes might impact the occurrence of HIVDR, particularly in under-resourced health systems with little capacity for virological monitoring. In this article we discuss important public health considerations regarding HIVDR in SSA, namely the potential impact of universal test-and-treat policies on HIVDR, and the potential implications of HIVDR on the effectiveness of dolutegravir-based ART. We also identify gaps in current knowledge, and describe how we could address current and future challenges in the field using real-world data from the International epidemiology Databases to Evaluate AIDS (IeDEA), a large consortium of HIV cohorts, and mathematical modelling.

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Universal test-and-treat policies and the emergence of HIV drug resistance in sub-Saharan Africa

Randomised controlled trials have shown the benefits of early ART initiation in terms of individual patient outcomes and a reduction in HIV transmission rates [3,4]. However, there are concerns that early ART initiation may increase the prevalence of antiretroviral drug resistance owing to compromised adherence, as patients who feel healthy might be less likely to be fully adherent [5]. Data regarding the impact of early ART on adherence and the development of HIVDR are limited and inconsistent. In a prospective study of 473 patients from Uganda, those who initiated ART with a CD4 cell count ≥250 cells/mm^3 were twice as likely to have treatment interruptions of >72 hours in the first 90 days of ART, as assessed by electronic pill bottles. As a consequence, they were nearly three times as likely to have an HIV viral load >400 copies/mL at 120 days than those with CD4 cell count <250 cells/mm^3 [6]. However, a study of 900 patients from South Africa found that CD4 cell count at ART initiation was not associated with adherence <95% in the first 12 months on ART (assessed by visual analogue scale and pill count) [7]. In terms of the impact of early ART initiation on HIVDR, in a cohort study from Europe, patients who initiated ART immediately (within 3 months of having a CD4 cell count and viral load measured while AIDS-free), were slightly more likely to develop drug resistance within 7 years than those who initiated ART at CD4 <500 cells/mm^3, or <350 cells/mm^3 [8]. In contrast, in the HPTN052 trial, which showed decreased HIV transmission between serodiscordant couples with ART initiation at a CD4 cell count of 350–550 versus <250 cells/mm^3, the risk of drug resistance was higher in the delayed versus early ART initiation arm [9].

These differences in the effect of timing of ART initiation on the development of HIVDR might be explained by differences in adherence: patients in clinical trials are generally more closely monitored, and may be more motivated to take treatment than those in routine care. Although the evidence that early ART initiation in itself influences the emergence of HIVDR is not compelling, there is reason to believe that the continued expansion of ART programmes might result in increased rates of HIVDR through suboptimal adherence and suboptimal retention in care in the context of resource-limited health systems. Along with HIVDR surveys, adherence monitoring and interventions to improve adherence should be studied in more depth in these settings.

Potential implications of HIV drug resistance on the success of dolutegravir-based antiretroviral therapy in sub-Saharan Africa

In many African countries, the prevalence of pretreatment NNRTI resistance mutations is >10%, the World Health Organization's threshold for countries to consider implementing non-NNRTI-based first-line ART [1,10]. As a consequence, many SSA countries have either started or are considering implementation of dolutegravir-based first-line ART, although recent concerns regarding its safety in early pregnancy may limit its use in women of childbearing age [11]. It is anticipated that dolutegravir will be used in both ART-naïve and ART-experienced patients; the latter will switch from their current NNRTI-based first-line regimens. This raises concerns regarding its use in settings where resistance testing is not standard of care, and where even viral load monitoring may not be performed routinely.

Dolutegravir has a high genetic barrier to resistance and development of resistance mutations has not been shown in clinical trials of treatment-naïve patients initiating dolutegravir-containing ART without pretreatment drug resistance [12,13]. In ART-naïve patients, dolutegravir was superior to efavirenz and to ritonavir-boosted darunavir in terms of virological outcomes, and much of that superior efficacy was due to dolutegravir's better tolerability [12,13]. However, in a study of dual therapy with dolutegravir and lamivudine in the US, three out of 120 patients had virological failure at 24 weeks, and one patient developed resistance mutations to both drugs (M184V and R263R/K) [14]. This patient was thought to be poorly adherent to ART as his plasma dolutegravir concentrations were below the limit of quantification on at least one occasion.

In treatment-experienced patients receiving dolutegravir, development of HIVDR is also uncommon, but has been reported in patients on dolutegravir monotherapy. In the DOMONO trial, ART-experienced patients who were virologically suppressed were randomly allocated to switch to dolutegravir monotherapy immediately or at 24 weeks [15]. Eight of 95 participants experienced virological failure and three developed integrase resistance mutations at 48 weeks. In another clinical trial from Spain, two of 31 patients who were randomly allocated to be switched to dolutegravir monotherapy developed integrase resistance [16]. The authors of both studies concluded that dolutegravir should not be used as monotherapy. Of note, ART-experienced patients in the studies described above were virologically suppressed at baseline, and patients with previously documented HIVDR were excluded. Routine viral load monitoring is not carried out in many SSA countries, so it is likely that many patients will switch to dolutegravir-based ART when they are not virologically suppressed. The DAWNING study, a multicentre trial that randomly allocated patients whose first-line ART was failing to receive dolutegravir-based or protease inhibitor-based ART provides some reassurance regarding the use of dolutegravir in patients who are not virologically suppressed [17]. Importantly, all patients had to have at least one active nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) predicted by resistance testing. Dolutegravir-based ART was superior to protease inhibitor-based ART, and no patients in the dolutegravir arm developed resistance mutations.

In summary, based on the available evidence, dolutegravir seems to be highly effective, both in ART-naïve and ART-experienced patients, provided that it is combined with a functional NRTI backbone. The TenoRes collaboration, which comprises data from clinical trials and observational studies, reported a prevalence of tenofovir resistance of 57% (370/654), and a prevalence of M184V/I mutation of 61% (401/654) in patients whose first-line ART regimens including tenofovir were failing [18]. Even though the high prevalence of NRTI resistance in patients with failing first-line ART in SSA may have important implications for the use of dolutegravir in settings without viral load monitoring, the long-term clinical significance of NRTI resistance in patients starting dolutegravir is not yet known. Interestingly, HIV-suppressed, treatment-experienced individuals with the M184V mutation switching to a dolutegravir/lamivudine dual therapy do not seem to have an increased risk of virological failure [19]. This finding is supported by results from *in vitro* studies, which showed that the presence of either of the NRTI resistance mutations M184I/V or K65R prevented the development of resistance to dolutegravir [20].

Gaps in current knowledge: the place for using IeDEA cohort data and mathematical modelling to predict and monitor HIV drug resistance in sub-Saharan Africa

While treatment guidelines and drug prescribing policy are usually based on results from randomised controlled trials, such studies often give little insight into the real-world effectiveness of the interventions evaluated. Clinical trials usually have strict inclusion and exclusion criteria, provide close follow-up and monitoring of patients, and adherence is usually better than in routine care. Observational cohorts are often able to provide generalisable data from many more patients in settings that reflect real-world use of interventions. However, in terms of predicting how HIVDR will affect the success of universal test-and-treat policies and the introduction of new drugs to first-line ART regimens in SSA, both clinical trials and observational cohorts have limitations. The vast majority of studies published to date were conducted in North America or Europe, in clinical settings that differ substantially from SSA. Although we can be confident that dolutegravir-based first-line triple therapy will lead to favourable virological outcomes in SSA, data on its use among patients whose NNRTI-based first-line therapy was failing are insufficient to date.

The scarcity of HIVDR surveillance data in resource-limited settings, together with the fact that those data are usually not linked with observational cohorts, presents challenges for assessing and predicting the transmission of HIVDR. Mathematical models offer a unique opportunity to bridge this gap [21] by combining observational data on rates of HIV diagnosis, treatment, and virological response with cross-sectional HIVDR surveillance data from local settings. Mathematical models have been used to address several key questions regarding HIVDR in various populations, and they are increasingly being used to inform policy [2,10,21]. Box 1 and Table 1 briefly discuss several examples.

The African regional cohorts of the IeDEA consortium provide the ideal platform to explore many of the outstanding research

Box 1. HIV drug resistance mathematical models

The HIV Synthesis Model, developed by Phillips *et al*, captures resistance to the different antiretroviral classes and its effect on treatment outcome [22-24]. More specifically, it models HIVDR in terms of the presence or absence of every mutation specific to the antiretrovirals in use. Agent-based models such as the HIV Synthesis Model have the advantage of being able to represent complex processes, like the process of acquiring resistance mutations. However, the drawback of using such models is that many assumptions are made but may not be verifiable. This can be avoided by using simpler models, such as compartmental models. Abbas *et al* [25], Nichols *et al* [26], and Supervie *et al* [27] have developed deterministic compartmental models to model HIV drug resistance and calibrated them with data from South Africa, Zambia and Botswana, respectively. These three models capture resistance in a simpler way than the HIV Synthesis Model. The South African Transmission Model [25] has only two layers (absence/presence of resistance) to model resistance, while the HIV-transmission models developed by Nichols *et al* [28] and Supervie *et al* [27] represent the main resistance mutations (K65R and M184V mutations for nucleoside reverse transcriptase inhibitors) (Table 1).

Table 1. Examples of how mathematical models have been used to address key HIV drug resistance questions:

Model	HIV drug resistance questions
HIV Synthesis Model: individual-based model calibrated with sub-Saharan African data	• Assessing the impact of viral load monitoring on HIVDR [29] • Predicting the impact of HIVDR on mortality [24,30] • Assessing the effectiveness and cost-effectiveness of interventions such as dolutegravir-based ART in settings with a relatively high prevalence of HIVDR [22,23]
Deterministic compartmental model calibrated with Ugandan and Kenyan data	• Assessing the impact of increasing second-line ART coverage (28); and earlier ART initiation (32) on HIVDR
South African Transmission Model: compartmental model calibrated to replicate the South African HIV-1 epidemic	• Assessing the impact of PrEP on HIVDR [25]
Macha HIV Transmission model: deterministic compartmental model calibrated with Zambian data	• Assessing the impact of PrEP [26] on HIVDR
PrEP Intervention Transmission model: compartmental model integrating PrEP and ART and calibrated with data from Botswana	• Assessing the impact of PrEP on HIVDR [27]
PrEP intervention model: compartmental model representing the MSM population in San Francisco	• Assessing the impact of PrEP on HIVDR [31]

ART: antiretroviral therapy; HIVDR: HIV drug resistance; MSM: men who have sex with men; PrEP: pre-exposure prophylaxis

questions highlighted in this article, as they comprise large cohorts of patients on ART from 23 countries across West, Central, East, and Southern Africa [32]. The Consortium collects routine clinical data of patients managed largely in primary healthcare settings, and has a strong capacity for data management and analysis, with a long track record of research that influences policy. Few cohorts measure or collect HIVDR data, but many have the infrastructure to collect them, provided dedicated funding is available.

We have also recently developed a deterministic compartmental mathematical model that comprises three layers: treatment stage (e.g. diagnosis, treatment, viral suppression or failure); disease progression (represented by CD4 count strata); and the presence/absence of HIVDR (in process for future publication). Disease progression at each treatment stage, as well as the transition from one treatment stage to another, are estimated from observational data from the IeDEA Southern Africa cohorts and UNAIDS data. The model has the potential to address key questions regarding HIVDR in Southern Africa. Specifically, we aim to describe time trends and drivers of HIVDR, and to estimate how the spread of resistance is affected by alternative interventions. For example, we could assess the impact of enhanced laboratory monitoring (i.e. viral load and resistance testing) on the development of acquired drug resistance under universal test-and-treat conditions. Furthermore, we aim to assess to what extent changes in ART guidelines (e.g. dolutegravir-based first-line ART), can curb the transmission of resistance and improve clinical outcomes. As described above, a key question in this context is the potential impact of NRTI resistance on the effectiveness of dolutegravir-based ART. Finally, we hope to predict the potential development and spread of resistance to dolutegravir. The main difficulty of making such a prediction is the lack of long-term data regarding the impact of dolutegravir resistance on clinical outcomes. Nevertheless, we believe that, by integrating the accumulating clinical data or by making reasonable assumptions on such parameters based on comparable processes or settings [33], mathematical models will be helpful in providing risk assessments, and identifying key knowledge gaps that should be addressed by clinical, epidemiological, and laboratory studies.

Conclusion

Universal test-and-treat policies and the introduction of new drugs such as dolutegravir to first-line ART regimens have the potential to improve patient outcomes and reduce the transmission of HIV in SSA. However, it is important to monitor their implementation, and to forecast their effect on the development of HIVDR. The African regional cohorts of the IeDEA global consortium represent an ideal platform to provide data regarding the real-world effectiveness of novel ART strategies and mathematical models have the potential to help predict the emergence of HIVDR in SSA. Such research is essential to ensure positive long-term outcomes, and to inform future programmatic and policy changes, tailored to local settings.

References

1. World Health Organization. *HIV drug resistance report*. Geneva: WHO; World Health Organization; 2017. Available at: www.who.int/hiv/pub/drugresistance/hivdr-report-2017/en (accessed October 2018).
2. World Health Organization. *Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV*. Geneva: WHO; World Health Organization; 2015. Available at: www.who.int/hiv/pub/guidelines/earlyrelease-arv/en (accessed October 2018).
3. Lundgren JD, Babiker AG, Gordin F *et al.* Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373**: 795–807.
4. Cohen MS, Chen YQ, McCauley M *et al.* Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med* 2016; **375**: 830–839.
5. Nachega JB, Uthman OA, del Rio C *et al.* Addressing the Achilles' heel in the HIV care continuum for the success of a test-and-treat strategy to achieve an AIDS-free generation. *Clin Infect Dis* 2014; **59 Suppl 1**: S21–27.
6. Adakun SA, Siedner MJ, Muzoora C *et al.* Higher baseline CD4 cell count predicts treatment interruptions and persistent viremia in patients initiating ARVs in rural Uganda. *J Acquir Immune Defic Syndr* 2013; **62**: 317–321.
7. Iwuji C, McGrath N, Calmy A *et al.* Universal test and treat is not associated with sub-optimal antiretroviral therapy adherence in rural South Africa:THe ANRS 12249 TasP Trial. *J Int AIDS Soc* 2018; **21**: e25112.
8. Lodi S, Gunthard HF, Dunn D *et al.* Effect of immediate initiation of antiretroviral treatment on the risk of acquired HIV drug resistance. *AIDS* 2018; **32**: 327–335.
9. Palumbo PJ, Fogel JM, Hudelson SE *et al.* HIV drug resistance in adults receiving early vs. delayed antiretroviral therapy: HPTN 052. *J Acquir Immune Defic Syndr* 2018; **77**: 484–491.

10. World Health Organization. *Guidelines on the public health response to pretreatment HIV drug resistance*. Geneva: WHO; World Health Organization,; 2017. Available at: www.who.int/hiv/pub/guidelines/hivdr-guidelines-2017/en (accessed October 2018).
11. World Health Organization. *Statement on DTG*. Geneva: World Health Organization; 2018. Available at: www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf (accessed October 2018).
12. Walmsley S, Baumgarten A, Berenguer J *et al.* Brief report: dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. *J Acquir Immune Defic Syndr* 2015; **70**: 515–519.
13. 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**: e127–136.
14. Taiwo BO, Zheng L, Stefanescu A *et al.* ACTG A5353: a pilot study of dolutegravir plus lamivudine for initial treatment of HIV-1-infected participants with HIV-1 RNA < 500,000 copies/mL. *Clin Infect Dis* 2017; **66**: 1689–1697.
15. 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; **4**: e547–e554.
16. 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. Epub ahead of print.
17. Aboud M, Kaplan R, Lombaard J *et al.* Superior efficacy of dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) compared with lopinavir/ritonavir (LPV/RTV) plus 2 NRTIs in second-line treatment: interim data from the DAWNING study. *IAS Conference on HIV Science*. July 2017. Paris, France. Abstract TUAB0105LB.
18. Gregson J, Tang M, Ndembi N *et al.* 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**: 565–575.
19. Reynes J, Meftah N, Montes B. Dual regimen with dolutegravir and lamivudine maintains virologic suppression even in heavily treatment experienced HIV-infected patients: 48 weeks results from a pilot study (DOLULAM). *HIV Drug Therapy*. October 2016. Glasgow, UK. Abstract P080.
20. Oliveira M, Ibanescu RI, Pham HT *et al.* The M184I/V and K65R nucleoside resistance mutations in HIV-1 prevent the emergence of resistance mutations against dolutegravir. *AIDS* 2016; **30**: 2267–2273.
21. Egger M, Johnson L, Althaus C *et al.* Developing WHO guidelines: time to formally include evidence from mathematical modelling studies. *F1000Res* 2017; **6**: 1584.
22. Phillips AN, Cambiano V, Miners A *et al.* Effectiveness and cost-effectiveness of potential responses to future high levels of transmitted HIV drug resistance in antiretroviral drug-naive populations beginning treatment: modelling study and economic analysis. *Lancet HIV* 2014; **1**: e85–e93.
23. 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–e154.
24. 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**: 1362–1365.
25. Abbas UL, Glaubius R, Mubayi A *et al.* Antiretroviral therapy and pre-exposure prophylaxis: combined impact on HIV transmission and drug resistance in South Africa. *J Infect Dis* 2013; **208**: 224–234.
26. Nichols BE, Boucher CA, van Dijk JH *et al.* Cost-effectiveness of pre-exposure prophylaxis (PrEP) in preventing HIV-1 infections in rural Zambia: a modeling study. *PLoS One* 2013; **8**: e59549.
27. Supervie V, Barrett M, Kahn JS *et al.* Modeling dynamic interactions between pre-exposure prophylaxis interventions & treatment programs: predicting HIV transmission & resistance. *Sci Rep* 2011; **1**: 185.
28. Nichols BE, Sigaloff KC, 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.
29. Phillips AN, Pillay D, Garnett G *et al.* Effect on transmission of HIV-1 resistance of timing of implementation of viral load monitoring to determine switches from first to second-line antiretroviral regimens in resource-limited settings. *AIDS* 2011; **25**: 843–850.
30. Cambiano V, Bertagnolio S, Jordan MR *et al.* Transmission of drug resistant HIV and its potential impact on mortality and treatment outcomes in resource-limited settings. *J Infect Dis* 2013; **207 Suppl 2**: S57–62.
31. Supervie V, Garcia-Lerma JG, Heneine W, Blower S. HIV, transmitted drug resistance, and the paradox of preexposure prophylaxis. *Proc Natl Acad Sci U S A* 2010; **107**: 12381–12386.
32. Egger M, Ekouevi DK, Williams C *et al.* Cohort profile: the international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa. *Int J Epidemiol* 2012; **41**: 1256–1264.
33. Vitoria M, Hill A, Ford N *et al.* The transition to dolutegravir and other new antiretrovirals in low-income and middle-income countries: what are the issues? *AIDS* 2018; **32**: 1551–1561.