## BRIEF REPORT

# Impact of HIV Drug Resistance on HIV/AIDS-Associated Mortality, New Infections, and Antiretroviral Therapy Program Costs in Sub–Saharan Africa

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To inform the level of attention to be given by antiretroviral therapy (ART) programs to HIV drug resistance (HIVDR), we used an individual-level model to estimate its impact on future AIDS deaths, HIV incidence, and ART program costs in sub–Saharan Africa (SSA) for a range of program situations. We applied this to SSA through the Spectrum-Goals model. In a situation in which current levels of pretreatment HIVDR are over 10% (mean, 15%), 16% of AIDS deaths (890 000 deaths), 9% of new infections (450 000), and 8% ($6.5 billion) of ART program costs in SSA in 2016–2030 will be attributable to HIVDR.

**Keywords.**  cost; death; drug resistance; HIV; incidence; mathematical model.

The Joint United Nations Programme on HIV/AIDS (UNAIDS) has set the ambitious global goal of increasing the number of people on antiretroviral therapy (ART) who have viral load suppression, with the dual aim of eliminating AIDS as a public health threat and ending new infections by 2030 [1]. Since the start of the scale-up of ART in the early 2000s, levels of human immunodeficiency virus (HIV) drug resistance (HIVDR) have been increasing gradually [2, 3] and HIVDR has been shown to compromise the effect of commonly used drug regimens [4, 5]. If levels of HIVDR are allowed to further increase, they may compromise the ability to reach the UNAIDS goal of 90% of all people taking ART having suppressed viral load. Moreover, high levels of HIVDR are likely an indication of gaps in ART service

delivery (such as suboptimal retention on ART, poor population-level adherence to ART, high levels of unknown treatment outcomes, and stock-outs of antiretroviral drugs) and signal the need for programmatic improvements. The actual and potential impact of HIVDR has not previously been estimated. We used a model of HIV/ART programs to estimate the impact of drug resistance from 2016 to 2030 in key outcomes of AIDS deaths, new infections, and ART program costs. Subsequently, using the Spectrum Goals model, we used these estimates of impact to estimate the absolute level of impact in sub–Saharan Africa as a whole [6].

## METHODS

### Modeling Approach

We use the HIV Synthesis Model, an individual-based simulation model of HIV transmission, progression, and the effect of ART, considering specific drugs and resistance mutations. The model has been described in detail (eg, [7, 8]). For this project, we initially based the demographics of the population studied and HIV epidemic and ART program features around those for Malawi, although by sampling parameters relating to sexual behavior, HIV testing, ART adherence, rate of treatment interruption, ART monitoring strategy, switch rate after first-line regimen failure, we generated diverse situations likely to reflect a range of settings in SSA with respect to aspects such as HIV prevalence, ART uptake, HIV incidence, and transmitted HIVDR. We restricted attention to situations (ie, model runs) in which HIV prevalence was between 8%–30% in 1999 and between 8%–25% in 2004, and also to those in which the level of HIVDR amongst ART-naive treatment initiators was below 20% in 2014, as evidence based on data to this date suggest that levels are below this [9–11].

For each setting situation generated, we look at the projected outcomes from 2016 to 2030 under the assumption of (1) no change in the rates of resistance acquisition and transmission (indicated as "with HIVDR" scenario in Table 1), and (2) a hypothetical (ie, counterfactual) scenario in which resistant virus disappears in those in whom it is present (leaving all people with drug-sensitive virus only) and there is no new acquisition or transmission of resistant virus ("without further HIVDR" scenario). We assume that from 2016, viral load monitoring has been introduced (using the World Health Organization (WHO) criteria of a confirmed value >1000 copies/mL to define failure [12]), that efavirenz with tenofovir and emtricitabine/lamivudine remains the first-line regimen for the duration, with atazanavir plus zidovudine and emtricitabine or lamivudine used in second-line regimens, and darunavir plus dolutegravir plus tenofovir plus emtricitabine or lamivudine as third-line. The

**Table 1. Impact of HIVDR Between 2016–2030[a]**

| Scenario Until 2030 | Of those on ART, Percent With Viral Load <1000 copies/mL | AIDS Deaths (per year)[b] | HIV Incidence (adults 15–49)/100 PY | Cost of First-Line ART ($)[b,c,d] | Cost of Second-Line ART ($)[b,c,d] | Cost of Third-Line ART ($)[b,c,d] | Overall ART Cost ($)[b,c,d] |
|---|---|---|---|---|---|---|---|
| **Current level of PDR <10% (mean ~ 5.7%)** | | | | | | | |
| (1) With HIVDR | 89% | 16 000 | 0.19 | 50M | 21M | 1.0M | 72M |
| (2) Without further HIVDR | 95% | 14 000 | 0.17 | 55M | 12M | 0.7M | 68M |
| Effect of HIVDR | 6% Median 6% (5%–7%) lower viral suppression rate in those on ART | 13% Median 12% (3%–23%) attributable to HIVDR | 7% Median 8% (0%–23%) HIV incidence attributable to HIVDR | Lower cost of 1st-line drugs | Higher cost of 2nd-line drugs | Higher cost of 3rd-line drugs | 6% Median 6% (2%–9%) of ART costs attributable to HIVDR |
| **Current level of PDR ≥10% (mean ~ 15%)** | | | | | | | |
| (1) With HIVDR | 85% | 26 000 | 0.48 | 71M | 38M | 2.0M | 111M |
| (2) Without further HIVDR | 93% | 22 000 | 0.43 | 79M | 22M | 1.4M | 102M |
| Effect of HIVDR | 8% Median 8% (6%–10%) lower viral suppression rate in those on ART | 16% Median 16% (7%–25%) attributable to HIVDR | 9% Median 9% (0%–26%) HIV incidence attributable to HIVDR | Lower cost of 1st-line drugs | Higher cost of 2nd-line drugs | Higher cost of 3rd-line drugs | 8% Median 8% (4%–11%) of ART costs attributable to HIVDR |

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; HIVDR, HIV drug resistance; PDR, pretreatment HIV drug resistance; PY, person-years.

[a]Mean and, for effect of drug resistance, median; 90% range over model runs /situations. This is the projected average impact in the context of low income settings in sub–Saharan Africa with an adult population size of 10 million.

[b]In context of country with adult population size of 10 million.

[c]Discounted at 3% per year.

[d]Costs of antiretroviral drugs (including 20% for supply chain) for first-line $120, second-line $343, and third-line $962. Other unit costs are shown in Supplementary Methods.

rate of switching to a second-line regimen after first-line failure is increased from 0.05 to 0.2 per 3 months before 2016, to 0.5 per 3 months after 2017. This was done so that we could look at the impact of drug resistance in the context of close to an optimal switching strategy—our estimates of health impact are conservative in this respect. We present the median and 90% range over situations (model runs) for the impact of drug resistance on HIV incidence, AIDS deaths, and ART program costs.

Having used the HIV Synthesis model to estimate the impact of HIVDR, we then extrapolated this to sub–Saharan Africa as a whole by applying the proportion of AIDS death, new infections, and ART costs attributable to HIVDR to the fast-track projected estimates of these obtained using the Spectrum Goals model [6].

### Modeling of ART and HIVDR

HIVDR is modeled in terms of the presence or absence of mutations specific to the drugs in use. A distinction is made for each mutation as to whether it is present only in low abundance and is thus transmissible. The probability of selection of drug-resistant virus among people on ART is determined by the number of active drugs in the regimen (determined by the presence of relevant resistance mutations), viral load, and the individuals' current ART adherence. Mutations acquired while on ART are lost from majority virus (at a mutation-specific rate) after the drug selecting for it is discontinued, although these mutations remain in minority virus. Mutations present in minority virus reemerge in majority virus when 1 of the corresponding drugs is started. The probability of transmission of HIV from a condomless sex partner depends on the viral load in the source partner. The presence of drug resistance in in the partner does not directly influence the risk of transmission, only via any effect on viral load. For a newly infected person, the probability that the source partner has resistant virus in the majority circulating virus is determined by the prevalence of resistance among those with HIV having condomless sex. Not all resistance mutations present in majority virus in the source partner are established in the circulating virus of the newly infected person. The probability of transmission of drug resistance mutations is mutation-specific. Once a virus with a mutation is transmitted and established in the new host, there is a tendency for a loss of drug-resistant mutation from majority virus over time; again, mutation-specific. A series of comparisons of model outputs with observed data for a range of ART-related variables are shown in the Supplementary Material.

## RESULTS

We generated 2500 HIV epidemic/program situations in total. The characteristics of these situations in 2015 are reported as the median (5%–95% range): HIV prevalence (median, 8%; range 4%–17%), HIV incidence (0.36 per 100 person years; range, 0.12–1.26), proportion diagnosed (median, 86%; range, 68%–93%), proportion on ART (median, 64%; range, 47%–78%).

Table 1 shows the outcomes projected for 2016–2030 for scenarios "with HIVDR" and "without further HIVDR." Table 1 also shows the percentage or absolute difference between these scenarios, which indicates the impact that HIVDR is projected to have over 2016–2030. This is shown separately in the context of setting situations with current level of pretreatment HIVDR (PDR) <10% and over 10%. In the former case, we estimate a 6% lower viral suppression rate in those on ART, 13% higher number of AIDS deaths per year, 7% higher HIV incidence, and 6% higher ART costs, which are all attributable to HIVDR. In settings with current level of PDR ≥10%, an 8% lower viral suppression rate in those on ART, 16% higher number of AIDS deaths per year, 9% higher HIV incidence, and 8% higher ART costs are attributable to HIVDR. The median and 90% range over model runs presented conveys the uncertainty and variability across settings in these estimates of attribution.

Table 2 shows the projected average impact of HIVDR on AIDS deaths, new infections, and ART costs in sub–Saharan Africa between the present and 2030 using the Spectrum Goals fast-track modeling. Results indicate that in a situation where pretreatment drug-resistance levels are generally below 10%, there is still a substantial impact of drug resistance, being responsible for an estimated 710 000 AIDS deaths, 380 000 new infections, and $5.0 billion extra ART costs by 2030. If levels of pretreatment drug resistance are over 10%, the impact is greater, with an estimated 890 000 AIDS deaths, 450 000 new infections, and $6.5 billion extra ART costs by 2030 attributable to HIVDR.

## DISCUSSION

Recently, elevated levels of non-nucleoside reverse transcriptase inhibitor (NNRTI) drug resistance among ART-naive individuals have been observed in several low- and middle-income countries, including Angola (14%), Botswana (8%), Cuba (8%), Mexico (10%), Papua New Guinea (16%), and South Africa (14%) [9–11]. The levels of NNRTI resistance reach almost 40% among ART starters with prior antiretroviral exposure [9, 11]. Our estimates indicate that, even in settings where pretreatment HIVDR levels are relatively lower (<10%), resistant virus is nevertheless responsible for a significant extra burden of new AIDS deaths and additional costs. Results underscore the need for countries to follow WHO recommendations to both monitor levels of HIVDR and ART program factors (or early warning indicators of HIVDR) associated with its emergence, and make any necessary program changes to reduce the rate with which resistance emerges, accumulates, and is subsequently transmitted [12–14]. We convey uncertainty and variability between settings in the impact of HIVDR through our 90% range over model runs. These bounds suggest that there is more uncertainty and variability around the impact of HIVDR on new infections than around the impact on AIDS deaths and costs.

It is important to emphasize that our estimates of the impact of resistance are based on there being no change in the regimens in use or introduction of baseline drug-resistance testing. While our modeling shows the importance and impact of HIVDR in determining program outcomes if this current situation continues, it does not address the practical questions of what the response should be in countries to finding high levels of pretreatment HIVDR and what level of HIVDR should trigger a public health response. Previous work has suggested a key role for introducing viral load monitoring, if not available [8]. In addition, increasing the frequency of viral load monitoring and using a lower threshold to define failure could be another response to high levels of transmitted drug resistance. Other potential future options include transitioning from efavirenz-based to dolutegravir-based first-line regimens, and possibly in some areas the use of individual-level drug resistance testing before or soon after the start of ART.

Although we show that drug resistance is a serious concern, it should not be used as a reason against expanding ART use to all individuals infected with HIV both for treatment and prevention, as is now recommended by WHO [12]. Modeling has

**Table 2. Projected Impact of HIVDR on AIDS Deaths, New Infections, and ART Costs in Sub–Saharan Africa 2016–2030.[a]**

|  | AIDS Deaths | New Infections | ART Costs |
|---|---|---|---|
| With HIVDR (Fast-track projections) | 5.6 million | 5.1 million | $ 83 billion |
| Current level of PDR <10% |  |  |  |
| Percentage attributable to HIVDR | 13% | 7% | 6% |
| Amount attributable to HIVDR | 710,000 | 380 000 | $5.0 billion |
| Current level of PDR ≥10% |  |  |  |
| Percentage attributable to HIVDR | 16% | 9% | 8% |
| Amount attributable to HIVDR | 890 000 | 450 000 | $6.5 billion |

Abbreviations: HIV, human immunodeficiency virus; HIVDR, HIV drug resistance; PDR, pretreatment HIV drug resistance.

[a]Using the Spectrum Goals Model estimates [6] by applying the impact of drug resistance as estimated using the HIV Synthesis Model.

shown that the benefits of "treat all" far outweigh the potential risks of HIVDR; in fact, while we should expect to see an increased proportion of ART initiators with drug-resistant virus, overall HIV incidence is predicted to decline [7, 15].

It is important to note in studying Table 1 that any comparisons across the <10% and >10% pretreatment HIVDR situations should be interpreted with caution, as such comparisons not only reflect the effect of HIVDR but also the presence of confounding. For example, settings in which population-level adherence to ART is lower tend to have higher levels of pretreatment HIVDR, but there are also direct effects of adherence on mortality, viral suppression, and HIV incidence, which are not mediated by drug resistance. Thus, there is confounding by the common cause of poor adherence. A further caveat is that the estimates in Table 1 are based on adults only. While fewer children are being infected, among HIV-positive children there are often high levels of acquired and transmitted drug resistance. In this respect, our results underestimate the full impact of HIVDR.

In summary, our results indicate that HIVDR inevitably causes attenuation of the potential full health benefits of ART and adds cost to the programs. While we cannot remove drug resistance completely, we can take measures to minimize its impact on health and ART program costs. To achieve the UNAIDS targets of 90-90-90 by 2020 and the elimination of AIDS as a public health threat by 2030, not only do millions of people need to be started and retained on ART, but the quality of service delivery in many countries needs be strengthened and routine HIVDR surveillance and response must become an integral part of ART programs.

## Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

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