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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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Abstract

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 pre-treatment 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.

Key words: HIV; drug resistance; mathematical model; cost; death; incidence

Introduction

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 scale-up of ART in the early 2000's, levels of 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 HIVFT 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 sub-optimal retention on ART, poor population-level adherence to ART, high levels of unknown treatment outcomes and stock outs of antiretroviral drugs, and signal 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 2016-2030 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

Modelling 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 (e.g. 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 in respect of aspects, such as HIV prevalence, ART uptake, HIV incidence and transmitted HIVDR. We restricted attention to situations (i.e. model runs) in which HV prevalence was between 8% and 30% in 1999 and between 8% and 25% in 2004, and also to those in which the level of HIVDR amongst ART naïve treatment initiators was below 20% in 2014 as evidence based on data to this date suggests levels are below this level (9-11).

For each setting situation generated, we look at the projected outcomes from 2016 to 2030 under the assumption of (i) no change in the rates of resistance acquisition and transmission (indicated as w*ith HIV drug resistance* scenario in Table 1), and (ii) a hypothetical (i.e. counter-factual) 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 HIV drug resistance* scenario). We assume that from 2016 viral load monitoring is introduced (using the 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 rate of switching to a 2nd line regimen after 1st line failure is increased from 0.05-0.2 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).

Modelling of ART and HIVDR

HIVDR is modelled in terms of the presence or absence of mutations specific to the drugs in use. Distinction is made for each mutation as to whether it is present only in low abundance, and thus assumed non-transmissible, or if it is present in majority virus. 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 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 re-emerge in majority virus when one 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 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 is 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 (8% (4%-17%), HIV incidence (0.36 per 100 person years (0.12-1.26), proportion diagnosed (86% (68%-93%), proportion on ART (64% (47%-78%)).

Table 1 shows the outcomes projected for 2016–2030 for scenarios w*ith HIV drug resistance* and *without further HIV drug resistance*. 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 pre-treatment 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, 6% higher ART costs are all attributable to HIVDR. In settings with current level of PDR $\geq$ 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 HIV drug resistance on AIDS deaths, new infections and ART costs in sub-Saharan Africa between the present and 2030 using the Spectrum Goals fast-track modelling. Results indicate that in a situation where pre-treatment 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 pre-treatment 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 NNRTI drug resistance among ART-naïve 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 ARV exposure (9, 11). Our estimates indicate that, even in settings where pre-treatment 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 modelling shows the importance and impact of HIVDR in determining program outcomes if this current situation continues, it does not address the practical question of what should be the response in countries to finding of high levels of pre-treatment 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 response to high levels of transmitted HIV drug resistance. 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 use of individuallevel 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). Modelling has 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% pre-treatment 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 pre-treatment HIVDR, but also there are 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, amongst HIV positive children there are often high levels of acquired and transmitted drug resistance. In this respect, our results under-estimate 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. Whilst 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.

Conflicts of Interest

VC has received payment for lectures from MSD. No other authors have any relevant conflicts of interest with this work.

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Table 1. Impact that HIV drug resistance (HIVDR) is projected to have between 2016 and 2030 (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 and adult population size 10 million. PDR – pre-treatment drug resistance.

Scenario until 2030	**% of those on ART who have viral load < 1000 cps/mL**	**AIDS deaths +**	**HIV incidence (adults 15-49) / 100 person years**	**Cost of 1st line ART + * &**	**Cost of 2nd line + * &**	**Cost of 3rd line + * &**	**Overall ART cost + * &**
Current level of PDR < 10% (mean ~ 5.7%)							
(i) With HIVDR	89%	16,000 per year	0.19	$50m	$21m	$1.0m	$72m
(ii) Without further HIVDR	95%	14,000 per year	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%)							
(i) With HIVDR	85%	26,000 per year	0.48	$71m	$38m	$2.0m	$111m
(ii) Without further HIVDR	93%	22,000 per year	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

+ in context of country with adult population size of 10 million. * discounted at 3% per year & Costs of ARV drugs (incl 20% for supply chain) 1st line $120, 2nd line $343, 3rd line $962. Other unit costs are shown in Supplementary Methods.

Table 2. Projected impact of HIV drug resistance (HIVDR) on AIDS deaths, new infections and ART costs in sub-Saharan Africa between 2016 and 2030. Using the Spectrum Goals model estimates (6), by applying the impact of drug resistance as estimated using the HIV Synthesis Model

	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 biillion
Current level of PDR ≥ 10%			
Percentage attributable to HIVDR	16%	9%	8%
Amount attributable to HIVDR	890,000	450,000	$6.5 billion

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