WHO
Considering programmatic implications of rising levels of HIV drug resistance: finalizing the Global Action Plan
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Modelling the impact of HIVDR : the cost of inaction

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Questions to be addressed with modelling

- What is the impact that HIV drug resistance is having, and projected to have, on key outcomes of HIV deaths, HIV incidence and programme costs in sub-Saharan Africa ?

- What is the most cost effective programme policy in the presence of a given level of pre-ART NNRTI resistance ?

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Modelling approach

- Individual-based simulation model of HIV transmission, effect of ART, considering specific drugs and resistance mutations (HIV Synthesis model) *
- Acquisition and transmission of drug resistance mutations and their consequences for virological suppression are explicitly modelled.
- Model based around southern Africa with multiple potential epidemics/ART programs generated through simulation
    - Each run of the model program generates an epidemic/ART program
- Parameters for which plausible values are randomly sampled each time the program is run include:
    - ART adherence profile and interruption rate
    - ART monitoring strategy (whether viral load used)
    - Switch rate after first line failure

**Phillips et al 2011, 2014; Cambiano et al 2013, 2014*

Modelling approach

- For each epidemic/ART program generated we look at the projected outcomes from 2016 to 2030 under the following two scenarios:

  (i) no change in the rates of resistance acquisition and transmission (with HIVDR)

  (ii) a hypothetical 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).

- Comparison of outcomes in these two scenarios gives us an estimate of the **causal impact of HIVDR**

Modelling approach

- Assume from 2016 viral load monitoring is introduced

- 1st line: efavirenz + tenofovir + FTC/3TC
  2nd line: atazanavir/r + zdv + FTC/3TC
  3rd line: darunavir + dolutegravir + tenofovir + FTC/3TC

- 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.

Results

- Characteristics of HIV epidemic/ART programs in 2015 (n=2500; median; 5%, 95%):

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%)

Projected impact of HIVDR

In the context of adult population size 10 million and with current level of pre-treatment HIVDR ≥ 10% (mean 15%)

	% of those on ART who have viral load < 1000 cps/mL	**AIDS deaths**	**HIV incidence (adults 15-49) / 100 person years**
(i) With HIVDR	85%	26,074 per year	0.479
(ii) Without further HIVDR	93%	21,989 per year	0.434
Impact of HIVDR	7.71% lower viral suppression rate in those on ART Median 7.5% (5.9% - 10.2%)*	15.97% attributable to HIVDR Median 16.09% (6.73% - 25.23%)*	8.74% HIV incidence attributable to HIVDR Median 9.33% (0.00% - 25.91%)*

Mean unless stated; *Median (5%, 95%) over model runs

Projected impact of HIVDR

In the context of adult population size 10 million and with current level of pre-treatment HIVDR ≥ 10% (mean 15%)

	Cost of 1st line ART	**Cost of 2nd line**	**Cost of 3rd line**	**Overall ART cost**
(i) With HIVDR	$71m	$38m	$2.0m	$111m
(ii) Without further HIVDR	$79m	$22m	$1.4m	$102m
Impact of HIVDR	Greater cost of 1st line drugs	Lower cost of 2nd line drugs	Lower cost of 3rd line drugs	7.71% Median 7.83% (4.01% - 11.38%) of ART costs attributable to HIVDR

Mean unless stated; *Median (5%, 95%) over model runs

UNAIDS Fast-track projections
Sub-Saharan Africa 2016-2030

Stover J, Bollinger L, Izazola JA, Loures L, DeLay P, Ghys PD, et al. What Is Required to End the AIDS Epidemic as a Public Health Threat by 2030? The Cost and Impact of the Fast-Track Approach. PLoS ONE 2016

	AIDS deaths	New infections	ART costs
Fast-track projections (with HIVDR)	5.6 million	5.1 million	$ 83 billion

Projected absolute impact of HIVDR in sub-Saharan Africa 2016-2030

In the context of current level of pre-treatment HIVDR ≥ 10%

	AIDS deaths	New infections	ART costs
Fast-track projections (with HIVDR)	5.6 million	5.1 million	$ 83 billion
Percentage attributable to HIVDR	15.97%	8.74%	7.71%
Amount attributable to HIVDR	890,000	450,000	$6.5 billion

Projected absolute impact of HIVDR in sub-Saharan Africa 2016-2030

In the context of current level of pre-treatment HIVDR < 10%

	AIDS deaths	New infections	ART costs
Fast-track projections (with HIVDR)	5.6 million	5.1 million	$ 83 billion
Percentage attributable to HIVDR	12.68%	7.40%	5.93%
Amount attributable to HIVDR	710,000	380,000	$5.0 biillion

Comments

- Even in settings where pre-treatment HIVDR levels are lower (<10%), resistant virus is responsible for a significant burden of new AIDS deaths and additional costs.

- Note that comparisons across the < 10% and ≥ 10% pre-treatment HIVDR situations should be interpreted with caution as they not only reflect the effect of HIVDR but also the presence of confounding by population adherence.

- Estimates are based on adults only.

Conclusions and Implications

- 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.

- 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.

Questions to be addressed with modelling

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- What is the most cost effective programme policy in the presence of a given level of pre-ART NNRTI resistance ?

Potential Policies in response to high levels of PDR

1	No change
2	ART initiators with prior ARV exposure: dolutegravir first line regimen
3	ART initiators with prior ARV exposure: if viral load > 1000 at 6 months (without confirmation) switch to atz 2nd line
4	ART initiators with prior ARV exposure: if viral load > 1000 at 6 months (without confirmation) switch to dolutegravir 2nd line
5	ART initiators with prior ARV: resistance test at treatment initiation - dolutegravir if NNRTI resistance detected.
6	All ART initiators: dolutegravir first line regimen
7	All ART initiators: if viral load > 1000 at 6 months (without confirmation) switch to atz 2nd line
8	All ART initiators: if viral load > 1000 at 6 months (without confirmation) switch to dolutegravir 2nd line
9	All ART initiators: resistance test at treatment initiation - dolutegravir if NNRTI resistance detected.
10	All on first line ART: move from efavirenz to dolutegravir.
11	All on ART: Increase the rate of switching to second line in people with 1st line failure (to 0.5 per 3 mths)
12	All on ART: Increase population adherence profile

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Working Group on Modelling Potential Responses to High Levels of pre-ART Drug Resistance in Sub-Saharan Africa

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