Evaluation of antiretroviral regimen switching options in adults with HIV with sustained viral load non-suppression on dolutegravir, lamivudine, and tenofovir in eastern, central, southern, and western Africa: a modelling study

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Summary

Background In Africa, for people with HIV on a dolutegravir-based regimen with a viral load of more than 1000 copies per mL despite enhanced adherence counselling, the appropriate course of action is uncertain. We aimed to evaluate the predicted effects of alternative antiretroviral regimen switching options in this population, including consideration of cost-effectiveness.

Methods We used an existing individual-based model to simulate risk and experience of HIV in 100 000 adults alive between 1989 and 2076. Using sampling of parameter values, we created 1000 setting-scenarios, reflecting the uncertainty in assumptions and a range of settings similar to those seen in eastern, central, southern, and western Africa. For each setting-scenario, we predicted the outcomes from the three alternative policies for people with sustained viral load non-suppression on a dolutegravir-containing regimen from 2026: a switch to a protease inhibitor-based regimen (switch policy), a switch to a protease inhibitor-based regimen only if HIV drug resistance testing beforehand shows integrase inhibitor resistance (resistance test policy), and no switch with no HIV drug resistance test (no switch policy). We considered predicted outcomes over 10-year and 50-year periods from 2026, used a 3% discount rate, and a cost-effectiveness threshold of US$500 per disability-adjusted life-year (DALY) averted. Ritonavir-boosted darunavir costs $210 per year, and dolutegravir less than $20. We assumed a cost of HIV drug resistance testing of $200 and considered variations around this. For comparing policies, we calculated net DALYs, which account for the health consequences of differences in costs and provide a measure of the impact of a policy on overall population burden of disease.

Findings Across setting-scenarios, there was a mean of 14 480 deaths per year (95% CI 13 750–15 210) over 50 years with a mean annual discounted cost of $103·2 million (95·8–106·5) with the switch policy in the context of having scaled to a setting with an adult population of 10 million in 2024. Compared with the switch policy, the no switch policy was predicted to lead to an overall increased number of DALYs incurred (mean 4400 per year, 95% CI 3200–5500), although it resulted in the lowest overall cost, with a difference in annual discounted costs of $5·1 million (95% CI 4·6–5·6) lower than the switch policy. The resistance test policy led to a similar risk of death and DALYs to the switch policy at a lower overall cost (difference in annual discounted costs $3·5 million per year, 95% CI 3·1–3·9), leading to 6900 (95% CI 5500–8200) fewer net DALYs per year. Net DALYs for the resistance test versus no switch policies were similar (–1000 net DALYs, 95% CI 400 to –2300). The incremental cost-effectiveness ratio when comparing the resistance test policy with the no switch policy was $376 per DALY averted; the switch policy was dominated.

Interpretation Introduction of HIV drug resistance testing for people with sustained viral load non-suppression on dolutegravir-based antiretroviral therapy is likely to be cost-effective. We suggest that exploratory planning for increased access and scale-up of high-quality, low-cost drug resistance testing for the region is undertaken.

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Introduction

More than 10 million people living with HIV in eastern, central, southern, and western Africa are receiving a regimen of tenofovir–lamivudine–dolutegravir.[1] Data from several countries, including Population-based Health Impact Assessments by ICAP at Columbia

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See Online for appendix

Research in context

Evidence before this study

We searched Web of Science on July 5, 2024, using the terms "dolutegravir AND resistance AND cost-effect*" without language restriction. 31 articles were identified. None of these articles evaluated the cost-effectiveness of policy options for people with sustained viral load non-suppression in an African context.

Added value of this study

We found that introduction of drug resistance testing for people with sustained viral load non-suppression on dolutegravir-based antiretroviral therapy probably provides the most cost-effective means to ensure that those with dolutegravir resistance can have their regimen switched, and exploratory planning for increased access and scale-up of high-quality, low cost, drug resistance testing needs to be undertaken for the region. A test which only looks for dolutegravir mutations and not mutations for other drugs is likely to be sufficient. However, uncertainty remains, including over the cost for which resistance testing could be delivered, and we propose that this analysis is repeated as further data accrue on this and from planned and ongoing trials, observational studies, and surveillance activities on the incidence of dolutegravir-associated drug resistance mutations and their clinical implications and outcomes from the various alternative policies.

Implications of all the available evidence

We suggest that consideration is given to introducing access to HIV drug resistance testing in African countries to allow careful selection of who needs to be given a darunavir-based second-line regimen.

University, show that more than 90% of people receiving tenofovir–lamivudine–dolutegravir have a viral load suppressed to below 1000 copies per mL.[2] People with viral loads of greater than 1000 copies per mL often receive enhanced adherence counselling, because low adherence is a leading cause of viral non-suppression. This counselling often results in viral loads of less than 1000 copies per mL within 3 months due to improved adherence.[3,4] However, the appropriate course of action is uncertain for people whose viral loads remain at more than 1000 copies per mL (referred to as sustained viral load non-suppression). Dolutegravir-containing regimens have a high barrier to resistance, but dolutegravir-associated resistance mutations have been identified in a minority of people with sustained viral load non-suppression for whom drug resistance testing has been performed.[5–11] WHO guidance recommends that people with sustained viral load non-suppression have their regimen switched to a protease inhibitor-based regimen,[12] with tenofovir–lamivudine–ritonavir-boosted darunavir widely seen as the preferred option.[13] Due to the relatively low but variable prevalence of integrase inhibitor-resistance mutations detected in studies of people with sustained viral load non-suppression,[5–11] whether this remains the optimal approach for people with sustained viral load non-suppression on a dolutegravir-containing regimen is unclear. Aside from switching to a protease inhibitor-based regimen, the other options for people with sustained viral load non-suppression include continuing the current regimen or performing a drug resistance test so that a regimen switch occurs only for people with certain integrase mutations detected. Until now, resistance testing has not been available for use in routine care in most countries in eastern, central, southern, and western Africa due to the high cost, limitations in laboratory capacity, and challenges with equipment requirements and supply chains for reagents.

While we await results of clinical trials (NCT05373758) and observational studies and surveillance data, we aimed to use an existing individual-based model of HIV for the context of eastern, central, southern, and western Africa to evaluate predicted effects of these alternative policies, including consideration of cost-effectiveness.

Methods

Model design

HIV Synthesis is an ongoing, individual-based, dynamic model of HIV parameterised to reflect a generalised epidemic setting in all countries in eastern, central, southern, and western Africa.[14] For this study, each model run generated a simulated population of 100 000 people aged 15 years at some point between 1989 (the start of the HIV epidemic) and 2075. Variables updated every 3 months included age, sex, primary and non-primary condomless sex partners, whether currently a female sex worker, HIV testing, male circumcision status, presence of sexually transmitted infections other than HIV, and use of oral or (from 2027) injectable pre-exposure prophylaxis. Projected population growth was accounted for, and only heterosexual sex is modelled. In people living with HIV, viral load, CD4 cell count, use of specific antiretroviral drugs, and drug resistance were modelled. Risk of AIDS-related death in the model depended on CD4 cell count, viral load, age, and antiretroviral therapy (ART) status. For a person on treatment, the true underlying (not known to the clinic unless a measure is done) viral load, CD4 cell count, and risk of resistance were primarily determined by the modelled person's adherence (on a scale of 0 to 1) and the number of active drugs being taken, where the activity level of each drug depended on its underlying potency (activity against HIV when resistance not present) and which, if any, drug resistance mutations were present (appendix p 50). A person's adherence in a given 3-month period depended on various factors, including their lifetime tendency to

adhere, age, sex, and whether they have drug toxicity. Informed by short-term viral suppressive capacity as monotherapy, we assume that nucleoside reverse transcriptase inhibitors lamivudine and tenofovir have a potency of 1 and dolutegravir (in 90% of setting-scenarios, 1·5 in the remainder) and ritonavir-boosted darunavir each have a potency of 2 (appendix p 64). Thus, for a person receiving tenofovir–lamivudine–dolutegravir with no drug resistance mutations present, the number of active drugs was 1+,1, 2=4 (appendix p 50). Whether a viral load test was done for the person as indicated in a given 3-month period depended on a probability selected at random at the start of each model run from a distribution (*prob_vl_meas_done*; 5% chance for probablity of 0·3, 5% for 0·5, 5% for 0·7, and 85% for 1·0). The underlying rate of full interruption of ART, for a period of a whole 3 months or more, was determined by a parameter (*rate_int_ch;* 10% chance for probability of 0·0020, 30% for 0·0040, 30% for 0·0080, 25% for 0·02, and 5% for 0·05) and is modified by whether a drug toxicity was being experienced.

For dolutegravir, consistent with information from the Stanford HIV Drug Resistance Database, we considered the most significant major mutations, at codon positions 118 (Gly to Arg), 148 (Gln to His, Arg, or Lys), and 263 (Arg to Lys) as well as two other major mutations (position 140 [Gly to Ser, Ala, or Cys] and 155 [Asn to His]) from among the five other codon positions with major mutations. Mutations at codons 148 and 263 were each assumed to lead to a resistance level of 0·5, 0·75, and 1·00 (for each run there is a third chance of each parameter value being selected). HIV drug resistance level was modelled on a scale of 0 to 1 and is sampled at random for each model run or setting-scenario. For example, if the resistance level for dolutegravir was 0·5, dolutegravir (with potency 2) had an activity level of $2\times0\cdot5=1$, the same as a fully active nucleoside reverse transcriptase inhibitor. Mutation at codon 118 was assumed to lead to a 0·25 higher level of resistance than those at codons 148 and 263. Mutations at codon positions 140 and 155 were not assumed to lead to any resistance on their own, but any two of the five mutations together were assumed to lead to a resistance level of 1·00. For context, the Met184Val mutation was assumed to lead to a resistance level or loss of activity of lamivudine of 0·75, and the same was assumed for the tenofovir-associated Lys65Arg mutation. For newly HIV-positive people, if the infecting virus included a dolutegravir-associated mutation, this resistance was transmitted with a probability sampled with the same probability (0·25) among the values 0·2, 0·4, 0·6, and 0·8, reflecting high uncertainty over transmissibility.[15] We assumed resistance testing had sensitivity of 90%, 95%, and 99% to detect resistance if present (each value has the same probability of being sampled).

Ritonavir-boosted darunavir was assumed to lead to a small increased risk of lower adherence or ART interruption compared to dolutegravir, because it is a less convenient regimen (multi-pill regimen) with risk of drug interactions and adverse events, including gastrointestinal adverse events;[16] although we note that, in a randomised controlled trial setting, little difference in toxicity or discontinuation rates has been shown.[17,18]

After an initial measured viral load of above 1000 copies per mL in a person, we assumed that an enhanced adherence intervention is delivered, resulting in a substantially higher lifetime adherence in 20%, 35%, 50%, and 80% of people (each value sampled with the same probability). Reports on percentages of people with re-suppression tend to show values above 50%;[3–8] however, the long-term durability of the effect remains uncertain.

Analysis approach

Through sampling of parameter values (appendix p 82) at the start of each model run, we created 1000 setting-scenarios reflecting uncertainty in assumptions and a range of characteristics similar to those currently seen in eastern, central, southern, and western Africa (ie, in 2024; table 1). We assumed that from initial introduction of tenofovir–lamivudine–dolutegravir in mid-2019 this was used only in those starting ART for the first time. However, reflecting the fact that switching to tenofovir–lamivudine–dolutegravir is common we considered that, from 2021, all people on ART, regardless of their virological failure history, had their regimen transitioned to a dolutegravir-containing regimen (tenofovir–lamivudine–dolutegravir, unless the person has experienced toxicity to tenofovir, in which case they are given zidovudine). For each setting-scenario, we simulated predicted outcomes resulting from each of three potential policies in people with sustained viral load non-suppression on tenofovir–lamivudine–dolutegravir from 2026 onwards: a switch to a protease inhibitor-based regimen (switch policy), a switch to a protease inhibitor-based regimen only if HIV drug resistance testing shows integrase inhibitor resistance (resistance test policy), and no switch with no HIV drug resistance test (no switch policy). Before 2026, we assumed that the no switch policy was the de-facto policy. These policies are evaluated in the context of the WHO HIV treatment guidelines that recommend viral load testing annually in people on ART. We assumed that, after the policy is introduced, people with previous sustained viral load non-suppression are assessed when it is time for their annual viral load measure rather than immediately at the time of introduction of the policy.

We show results for the effects of these policies over 10 years and 50 years from 2026, showing the median and 90% range across setting-scenarios as well as the mean and 95% CI for the mean. Absolute numbers of health-related events, costs, and disability-adjusted life-years (DALYs) that we provide are scaled to be relevant for a setting of population size of 10 million adults in 2024 (with the characteristics shown in table 1).

For **Population Health Impact Assessments** see https://phia.icap.columbia.edu/

For the **Stanford University Drug Resistance Database** see https://hivdb.stanford.edu

	Model output, median (90% range)	Examples of observed data
HIV prevalence in people aged 15–49 years		
Women	12·7% (4·6–30·9)	Zimbabwe 2016 16%, 2020 15%; Tanzania 2017 6%; Uganda 2017 8%, 2020 7·1%; Lesotho 2017 30%, 2020 28%; Eswatini 2017 34%, 2021 32%; Malawi 2016 12%, 2020 10%; Namibia 2017 15%; Zambia 2016 14%; Cameroon 2017 5%, 2018 3%; Côte d'Ivoire 2017–18 4%; Rwanda 2019 3·3%; Kenya 2018 (age 15–64 years) 6·6%
Men	6·3% (2·4–16·7)	Zimbabwe 2016 11%%, 2020 9%; Tanzania 2017 3%; Uganda 2017 4%, 2020 3·8%; Lesotho 2017 19%, 2020 16%; Eswatini 2017 19%, 2021 16%; Malawi 2016 8%, 2020 6%; Namibia 2017 8%; Zambia 2016 8%; Cameroon 2017 2%, 2018 2%; Côte d'Ivoire 2017–18 1%; Rwanda 2019 1·8%; Kenya 2018 (age 15–64 years) 3·1%
HIV incidence per 100 person-years (age 15–49 years)	0·36 (0·08–1·28)	Malawi 2016 (women/men) 0·44/0·22, 2020 0·31/0·15; Zambia 2016 1·00/0·28; Zimbabwe 2016 0·57/0·30, 2020 0·67/0·23; Lesotho 2017 1·31/1·05, 2020 0·81/0·33; Namibia 2016 0·66/0·15; Eswatini 2017 1·73/0·85, 2021 1·45/0·20; Tanzania 2017 0·34/0·14; Cameroon 2017 0·40/0·08; Rwanda 2019 0·08; Uganda 2020 0·32; Kenya 2018 (age 15–64 years) 0·14
Proportion of people living with HIV aged ≥15 years diagnosed	91% (85–96)	Malawi (women/men) 2016 80%/72%, 2020 90%/85%; Zambia 2016 73%/69%, 2021 90%/87%; Zimbabwe 2016 80%/72%, 2020 88%/84%; Namibia 2017 (age 15–64 years) 90%/80%; Tanzania 2017 55%/45%, 2023 85%/78%; Ethiopia (age 15–64 years) 2018 83%/70%; Côte d'Ivoire 2017–18 (age 15–64 years) 43%/24%; Cameroon 2017 (age 15–64 years) 58%/51%; Mozambique 2021 73%/69%; Uganda 2021 84%/76%; Rwanda 2019 86%/80%; Eswatini 2017 91%/80%, 2021 95%/92%; Lesotho 2020 91%/88%; Kenya 2018 (age 15–64 years) 83%/73%
Proportion of people diagnosed with HIV on antiretroviral therapy*	94% (81–98)	Lesotho (women/men) 2016–17 92%/92%, 2020 98%/96%; South Africa 2017 71%; Eswatini 2016–17 88%/90%, 2021 98%/96%; Namibia 2017 97%/95% (age 15–64 years); Zambia 2016 87%/88%, 2021 98%/98%; Tanzania 2016–17 93%/86%, 2023 98%/97%; Ethiopia (age 15–64 years) 96%/99%; Malawi 2016 93%/89%, 2020 98%/97%; Uganda 2016/17 90%/85%, 2021 97%/95%; Cameroon 2017 (age 15–64 years) 93%/94%; Zimbabwe 2016 89%/88%, 2020 98%/96%; Côte d'Ivoire 2017/18 (age 15–64 years) 93%/71%; Mozambique 98%/94%; Rwanda 98%/97%; Kenya 2018 97%/95%
Proportion of people on antiretroviral therapy with viral load <1000 copies per mL*	94% (84–98)	Zambia 2016 (women/men) 90%/88%, 2021 96%/97%; Malawi 2016 92%/90%, 2020 97%/97%; Zimbabwe 2016 88%/84%, 2020 91%/89%; Namibia 2017 92%/90%; Tanzania 2017 83%/89%, 2023 95%/93%; Ethiopia 2018 (age 16–64 years) 86%/91%; Côte d'Ivoire 2017–18 (age 15–64 years) 78%/65%; Cameroon 2017 80%/81%; Mozambique 2021 90%/88%; Uganda 2021 93%/91%; Rwanda 2018 92%/85%; Eswatini 2021 96%/98%; Lesotho 2020 92%/90%; Kenya 2018 90%/91%
Proportion of all people living with HIV with viral load <1000 copies per mL	78% (63–88)	Zambia 2016 59%; Malawi 2016 68%, 2020 87%; Zimbabwe 2016 60%, 2020 76%; Eswatini 2017 73%, 2021 87%; Lesotho 2017 68%, 2020 81%; Tanzania 2017 52%, 2023 78%; Uganda 2017 60%, 2020 75%; Namibia 2017 (age 15–64 years) 77%; Ethiopia 2018 (age 15–64 years) 70%; Côte d'Ivoire 2017/18 (age 15–64 years) 40%; Cameroon 2017 (age 15–64 years) 47%; Rwanda 2019 76%; Kenya 2018 72%
Proportion of people on antiretroviral therapy who had SVLNS on a dolutegravir-containing regimen	1·8% (0·5–6·2)	ADVANCE trial (South Africa) <1%,[19] Uganda 1·8%,[2] Lesotho 1%[6]
Proportion of all adults (HIV-positive and HIV-negative) with viral load >1000 copies per mL	2·4% (0·8–6·4)	Zambia 2016 (age 15–59 years) 4·8%; Namibia 2017 (age 15–64 years) 2·8%; Malawi 2015–16 (age 15–64 years) 3·4%, 2020 1·2%; Zimbabwe 2016 (age 15–64 years) 5·7%, 2020 (age ≥15 years) 3·1%; Côte d'Ivoire 2018 (age 15–64 years) 1·7%; Eswatini 2017 (age ≥15 years) 7·3%, 2021 3·1%; Lesotho 2018 (age 15–59 years) 8·3%, 2020 4·4%; Rwanda 2019 0·4; Uganda 2020 1·45%; Kenya 2018 1·4%
Proportion of people with SVLNS on a dolutegravir-containing regimen that have dolutegravir resistance	7% (1–23)	Malawi 27%;[7] Malawi 14%;[8] WHO Drug Resistance Report 4–20%;[9] Togo 9%;[20] Lesotho 9%;[6] multi-country 14%[11] †
Proportion of people receiving dolutegravir with dolutegravir resistance		
People with 0·50 or fewer active NRTIs	1·5% (0·1–7·0)	..
People with 0·75–1·75 active NRTIs	0·9% (0·0–3·1)	..
People with 2·00 active NRTIs	0·2% (0·0–0·8)	..

All observed data are from Population-Based HIV Impact Assessment surveys unless otherwise stated. Please note that we show national data from countries, but setting-scenarios are considered to reflect sub-settings within countries as well as countries as a whole. NRTI=nucleoside reverse transcriptase inhibitor. SVLNS=sustained viral load non-suppression. *Adjusted for having a detectable antiretroviral in blood or having interrupted antiretroviral therapy but still attending clinics and reporting being on antiretroviral therapy. †Studies range in size from 68 to 750 with drug resistance testing.

Table 1: **Description of characteristics of 1000 setting-scenarios representing eastern, central, southern, and western Africa in 2024**

For **Population-Based HIV Impact Assessment** see https://phia.icap.columbia.edu/

Cost-effectiveness analysis

Cost-effectiveness analysis was conducted from a health-care perspective using a time horizon of 50 years. Costs and health outcomes were both discounted to present US$ values at 3% per annum, and a cost-effectiveness threshold of US$500 per DALY averted was used. We used this threshold to calculate net DALYs averted.[21] Net DALYs account for the health consequences of the difference in costs and the difference in health and reflect the impact of a policy on overall population burden of disease: net DALYs averted=DALYs averted+difference in costs÷cost effectiveness threshold. Including supply chain costs, tenofovir–lamivudine–dolutegravir was assumed to cost $50 per year and tenofovir–lamivudine–ritonavir-boosted darunavir $292 per year.[22] Drug resistance testing was assumed to cost $200 in our primary analysis, which would include initial costs to set up infrastructure, the fact that a proportion of tests fail and need to be re-run, and all that would be required to make the testing feasible to carry out within routine care. We recognise that there is uncertainty regarding this cost and explored alternative

values. Other costs and disability weights are shown in the appendix (p 104).

We fitted a logistic regression model across the setting-scenarios to evaluate the baseline characteristics of a setting scenario in 2024 as predictors of whether the resistance test policy would be cost-effective. Furthermore, we conducted sensitivity analyses around the costs of ritonavir-boosted darunavir, the cost of resistance testing, and the cost-effectiveness threshold.

In a scenario analysis, we repeated the main analysis, but we adapted the resistance test policy so that a point-of-care, urine-based test for presence of tenofovir was done before the resistance test as an objective check on adherence, with a resistance test conducted only for those with adequate adherence.[23] It is uncertain, when used in eastern, central, southern, and western Africa, what the measurement error for the tenofovir test of adherence will be, so we sampled error from a normal distribution with standard deviation ranging from 0·00 (test 100% accurate) to 0·15. A urine tenofovir test is assumed to cost $15 (including time for interpretation of the result and decision on whether to perform a resistance test).

The model was coded in SAS 9.4.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Predicted outcomes of the three policies over 10 years are shown in table 2. The median number of resistance tests needed per year in the resistance test policy was 5 per 1000 people on ART. The generally low viral suppression rates are due to this being a group susceptible to lower adherence regardless of regimen and presence of drug resistance. The rate of HIV-related death (per 100 person years) in people who had sustained viral load non-suppression on a dolutegravir-containing regimen was lower with the switch policy, and the resistance test policy than with the no switch policy, by 0·7–0·9 per 100 person years. The rate of HIV-related death in the subset of people with dolutegravir resistance followed a similar pattern but with a more marked elevated rate under the no switch policy. The slightly higher rate under the resistance test policy compared with the switch policy is likely due to the fact that the resistance test does not have 100% sensitivity. Further results to provide context are shown in the appendix (p 2).

Across setting-scenarios, compared with the policy of switch, the resistance test policy did not result in increased number of deaths or DALYs over 50 years, whereas the policy of no switch resulted in an increase by a mean of 500 HIV deaths per year (95% CI 410 to 590) and 4400 DALYs per year (3200 to 5500) for a setting of population size of 10 million adults in 2024 (table 3). Mean annual costs were lowest with the policy of no switch, at $5·1 m lower (4·6 to 5·6) than the switch policy, and intermediate for the resistance test policy, at $3·5 m lower (3·1 to 3·9) than the switch policy. For context, the annual discounted cost of ritonavir-boosted darunavir with the switch policy was $6·3 million (table 4). The switch policy resulted in a higher mean number of net DALYs than the other two policies (by 6900 per year [95% CI 5500 to 8200] for the resistance test policy and by 5900 per year [4500 to 7300] for the no switch policy). There was uncertainty over which of the resistance test and no switch policies led to the lowest number of net DALYs, with the resistance test policy leading to a slightly lower number than the no switch policy (–1000 net DALYs [95% CI –2300 to 400]), although the 95% CI overlapped 0. The cost-effectiveness plane for the overall outcomes (based on the means) is shown

	Switch	Resistance test	No switch
Number of drug resistance tests done per year per 1000 people on antiretroviral therapy			
Median (90% range)	..	5 (1 to 18)	..
Mean (95% CI)	..	7 (6 to 7)	..
Proportion of people with previous SVLNS on a dolutegravir-containing regimen who received ritonavir-boosted darunavir*			
Median (90% range)	72% (56 to 82)	13% (3 to 34)	0% (0–2)
Mean (95% CI)	71% (71 to 72)	15% (14 to 16)	0% (0–0)
Proportion of people with previous SVLNS on a dolutegravir-containing regimen with current adherence <80%			
Median (90% range)	47% (26 to 64)	43% (22 to 61)	41% (20–60)
Mean (95% CI)	47% (46 to 48)	42% (42 to 43)	41% (40–41)
Proportion of people with previous SVLNS on a dolutegravir-containing regimen with viral load <1000 copies per mL			
Median (90% range)	53% (37 to 71)	57% (41 to 75)	49% (32–67)
Mean (95% CI)	53% (52 to 54)	57% (57 to 58)	50% (49–50)
HIV-related mortality (per 100 person-years) in people with previous SVLNS on a dolutegravir-containing regimen			
Median (90% range)	5·2 (2·5 to 9·5)	5·2 (2·5 to 8·7)	6·0 (3·4–10·0)
Mean (95% CI)	5·5 (5·4 to 5·6)	5·3 (5·3 to 5·4)	6·2 (6·1–6·4)
HIV-related mortality (per 100 person-years) in people with previous SVLNS on a dolutegravir-containing regimen with dolutegravir resistance mutation(s)			
Median (90% range)	5·3 (0·0 to 13·3)	6·6 (1·4 to 15·4)	12·2 (4·8–24·6)
Mean (95% CI)	6·4 (5·8 to 6·9)	7·5 (7·1 to 7·9)	13·5 (12·9–14·1)
Relative risk compared with the no switch policy			
Median (90% range)	0·42 (0·05 to 1·18)	0·53 (0·13 to 1·35)	..
Mean (95% CI)	0·53 (0·48 to 0·58)	0·62 (0·59 to 0·65)	..
Difference compared with the no switch policy			
Median (90% range)	6·8 (–1·8 to 17·3)	5·5 (–2·8 to 16·0)	..
Mean (95% CI)	7·1 (6·4 to 7·8)	6·0 (5·4 to 6·6)	..

For each setting-scenario we calculate the mean over all 3-month periods in the 10 years then values shown are median (90% range) and mean (95% CI for the mean) over setting-scenarios. SVLNS=sustained viral load non-suppression. *The proportion on ritonavir-boosted darunavir is less than 100% with the switch policy, because we assume that, after the policy is introduced, people with previous SVLNS are assessed when it is time for their annual viral load measure, rather than immediately at the time of introduction of the policy, and because switching does not necessarily occur immediately after a decision to switch has been made (appendix p 84).

Table 2: **Predicted outcomes of the policy options in 1000 setting-scenarios representing eastern, central, southern, and western Africa over 10 years from 2026**

	Switch	Resistance test	No switch
Number of HIV-related deaths per year	14 480 (13 750 to 15 210)	14 440 (13 720 to 15 170)	14 990 (14 230 to 15 740)
Absolute difference in number of HIV related deaths per year			
Compared with the switch policy	..	−40 (−100 to 20)	500 (410 to 590)
Compared with the no switch policy	−500 (−410 to −590)	−550 (−630 to −460)	..
Percentage difference in number of HIV related deaths per year			
Compared with the switch policy	..	0·2% (−0·3 to 0·7)	3·8% (3·1 to 4·4)
Compared with the no switch policy	−3·7% (−3·1 to 4·2)	−2·9% (−2·4 to −3·4)	..
Difference in DALYs per year			
Compared with the switch policy	..	100 (−900 to 1100)	4400 (3200 to 5500)
Compared with the no switch policy	−4400 (−5500 to −3200)	−4300 (−5400 to −3100)	..
Annual cost	$103·2 million (99·8 to 106·5)	$99·7 million (96·5 to 102·8)	$98·0 million (95·0 to 101·1)
Difference in annual cost			
Compared with the switch policy	..	−$3·5 million (−3·9 to −3·1)	−$5·1 million (−5·6 to −4·6)
Compared with the no switch policy	$5·1 million (4·6 to 5·6)	1·6 million (1·4 to 1·9)	..
Difference in net DALYs per year			
Compared with the switch policy	..	−6900 (−8200 to −5500)	−5900 (−7300 to −4500)
Compared with the no switch policy	5900 (4500 to 7300)	1000 (2300 to 400)	..
Incremental cost-effectiveness ratio	Dominated	$376	Comparator
Proportion of setting-scenarios for which policy incurs the lowest DALYs	38%	36%	26%
Proportion of setting-scenarios for which policy has the lowest cost	11%	29%	61%
Proportion of setting-scenarios for which policy has the lowest net DALYs*	23%	39%	38%

For each setting-scenario we calculate the mean over all 3-month periods in the 50 years; values shown are the mean (95% CI) over setting-scenarios. Costs in US$. DALY=disability-adjusted life-year. Calculations are for an adult population of 10 million with a median of 940 000 people (90% range 470 000–2 160 000) on a dolutegravir-containing antiretroviral therapy regimen in 2024. *Net DALYs take into account the health consequences of the difference in costs and the difference in health and reflect the impact of a policy on overall population burden of disease: net DALYs averted=DALYs averted + (difference in costs ÷ cost effectiveness threshold).

Table 3: **Predicted outcomes of the policy options in 1000 setting-scenarios representing eastern, central, southern, and western Africa over 50 years from 2026**

	Switch	Resistance test	No switch
Antiretroviral drug (ritonavir-boosted darunavir)*	31·7 (6·3)	27·7 (2·2)	26·3 (0·8)
Antiretroviral therapy clinic visits	11·6	11·3	11·3
Treatment for HIV-related diseases	9·7	9·7	9·9
Viral load tests	10·3	10·6	10·7
CD4 count tests	0·6	0·6	0·7
Resistance test	0·0	0·6	0·0
Cotrimoxazole	2·5	2·5	2·5
Treatment for children with HIV	3·8	3·6	3·6
Primary prevention	20·7	20·6	20·7
HIV testing	12·3	12·3	12·3
Total	103·2	99·7	98·0

Data are discounted annual costs (US$ million) over 50 years. Calculations are for an adult population of 10 million with a median of 940 000 people (90% range 470 000–2 160 000) on a dolutegravir-containing antiretroviral therapy regimen in 2024. *Use of darunavir in the no switch policy is due to occasional switching due to dolutegravir toxicity.

Table 4: **Breakdown of costs in 1000 setting-scenarios representing eastern, central, southern, and western Africa**

in the appendix (p 14), indicating that the incremental cost-effectiveness ratio for the resistance test policy was $376 per DALY averted (table 3).

We assessed the short-term budget impact by calculating the mean annual undiscounted cost over the first 3 years after the implementation of each policy. The budget was $191·4 million for the switch policy, $190·5 million for the resistance test policy, and $187·7 million for the no switch policy.

In a multivariable linear regression model across the 1000 setting-scenarios, we considered whether any baseline characteristics of a setting scenario in 2024 predicted whether net DALYs were averted and compared the resistance test and no switch policies (appendix p 4), but none emerged as strong predictors. We fitted a similar model for prediction of whether net DALYs were averted in the resistance test and the switch policies, and higher baseline HIV prevalence was strongly associated with higher odds of the resistance test policy being cost-effective in settings with prevalence below 5% compared with those with prevalence above 15% (relative odds 0·42, 95% CI 0·28 to 0·64; p=0·0001; appendix p 5).

We also fitted a multivariable logistic regression of whether net DALYs were averted comparing the resistance

test and no switch policies, in which we considered the various relevant parameters for which values had been sampled as predictors (appendix p 6). There was a marginally statistically significant association for a parameter indicating a possible increased risk of cardiovascular disease due to dolutegravir-induced weight gain (*incr_mort_risk_dol_weightg_*; appendix p 98), although with no clear trend in effect across levels, and a parameter indicating the level of disability weight associated with experiencing drug toxicity (*greater_disability_tox*), with a higher relative risk with a lower disability weight (relative odds 1·35; 95% CI 1·04 to 1·75; p=0·020). In a similar model for prediction of whether net DALYs were averted comparing the resistance test policy to the switch policy (appendix p 9), the only influential parameter was *res_trans_factor_ii* which relates to the transmissibility of integrase inhibitor resistance mutations.

In a sensitivity analysis, in which we restricted to setting-scenarios for which fewer than 5% of people who had had sustained viral load non-suppression on a dolutegravir-containing regimen had dolutegravir resistance in 2024, the incremental cost-effectiveness ratio for the resistance test policy was above the $500 threshold at $537 (although it resulted in over 400 fewer deaths per year than the no switch policy).

In the scenario analysis in which the resistance test policy involved initial screening with a point-of-care tenofovir level test conducted before resistance, the resistance test policy was the cost-effective choice (incremental cost-effectiveness ratio $290). When compared directly with the main resistance test policy (with no point-of-care tenofovir testing), it resulted in 90 fewer DALYs per year at $0·2 million per year lower cost.

The cost-effectiveness of policies according to the cost-effectiveness threshold, the cost of resistance testing, and the cost of darunavir is shown in the appendix (p 13). The resistance test policy was the cost-effective choice throughout with a cost-effectiveness threshold of $500 or more. With a cost-effectiveness threshold of $300, the resistance test policy was not cost-effective unless the cost of ritonavir-boosted darunavir was $150 or below.

Discussion

Our modelling results suggest that, despite the challenges, consideration should be given to the introduction of access to drug resistance testing in eastern, central, southern, and western Africa to decide which people with sustained viral load non-suppression have significant dolutegravir resistance and need to have their drug regimen switched from a dolutegravir-containing regimen. Given the relative inconvenience and high cost of protease inhibitor-based regimens, detection of clinically important dolutegravir-associated drug resistance seems to be a reasonable prerequisite for such switches to be made. Nonetheless, uncertainties remain, including the activity of dolutegravir in the presence of specific drug resistance mutations, the prevalence of mutations, the rate of accumulation of resistance mutations in people with sustained viraemia and partial adherence, whether viral load can be durably re-suppressed in the presence of one or more dolutegravir-associated drug resistance mutations, the relative extent of adverse effects associated with ritonavir-boosted darunavir compared to dolutegravir, and the cost at which HIV drug resistance testing can be delivered in practice. Furthermore, given a cost-effectiveness threshold of $500 per DALY averted, it is not certain whether either of the switch or resistance test policies is cost-effective in comparison with the no switch policy, despite the latter policy leading to a higher number of deaths. Accrual of further data, including from planned and ongoing clinical trials, observational studies, and implementation studies, will allow these analyses to be updated.

This policy challenge illustrates the importance of effective adherence counselling interventions. Although adherence counselling interventions are in place throughout Africa, the fact that the majority of people with sustained viral non-suppression likely remain poorly adherent suggests that optimisation of these interventions, within budget constraints, is a crucial first step in minimising the number of candidates for drug resistance testing.

We did not consider ritonavir-boosted atazanavir as the protease inhibitor of choice rather than ritonavir-boosted darunavir. The cost of ritonavir-boosted atazanavir is somewhat lower than that of ritonavir-boosted darunavir, although its barrier to resistance is also lower. In a sensitivity analysis in which we changed the annual cost for ritonavir-boosted darunavir to $150 (appendix p 13), close to the cost of ritonavir-boosted atazanavir, the resistance test policy was the cost-effective choice.

Although clinical studies of dolutegravir monotherapy[24] show that the drug is vulnerable to substantial loss of activity, there is some uncertainty about the significance of some dolutegravir mutations, and it has been observed that viral re-suppression can be achieved in people with such mutations.[25] Keeping people with a single integrase resistance mutation on dolutegravir could be considered for some non-major mutations, perhaps with a double dosing of dolutegravir, but in such people, more frequent (eg, every 3 months) monitoring might be needed for a period, which itself incurs extra costs.

Use of urine tenofovir testing to select candidates for drug resistance testing merits further evaluation as new data emerge on its use in practice.[23] We note there may be some pill-taking just before a clinic appointment, resulting in the appearance of high adherence when, in fact, pill-taking is low; we considered the possibility of the existence of such false positive results, as well as of false negative tests.

Introduction of drug resistance testing as part of routine care, albeit in only a small proportion of people under HIV care, presents a major challenge for many countries in

eastern, central, southern, and western Africa, and it is unclear if it is feasible in the majority of countries, for which even measurement of viral load carries major logistical challenges. Use of central national laboratories with transportation of specimens, despite its challenges, could be possible, because the test results are not urgent. There are also promising ongoing efforts to develop point-of-care drug resistance tests,[26–29] although none are available yet. It is worth noting that a test that only detects specific integrase inhibitor mutations is probably sufficient as a target product profile. Although felt to be realistic, whether such a test is feasible at a cost of $200 per test is uncertain.

Other nuances around the policy approaches might be considered. For example, switching or resistance testing could be targeted to people with certain attributes predictive of increased likelihood of drug resistance, such as occurs in South Africa, where people with previous virological failure of a regimen before tenofovir–lamivudine–dolutegravir are targeted.[11] Some countries could be de-facto using a combination of the switch and no switch policies, with a switch being made only after extensive and long-term adherence support. In future work, and particularly if resistance testing proves to be infeasible to implement, we might also consider that an initial no switch policy is transitioned to a switch policy once surveillance data show dolutegravir resistance levels to be above a given threshold, as was done to make the decision on when to move away from use of efavirenz in the initial regimen.

Limitations of this analysis include the relatively few data available to inform incidence of specific dolutegravir mutations and the consequences of each (and in combination), which is a reflection of how rare such mutations are. As more data accrue,[30] including from NCT05373758, we intend to update this analysis, but this early evaluation was crucial, because it points towards an opportunity to consider strategies for wider access to HIV drug resistance testing. Another limitation is that the policy being evaluated relates to a very small proportion of the population with HIV and an even smaller proportion of the overall adult population. We elected to conduct our primary analysis by simulating the entire population, including those at risk of acquiring HIV, rather than focus only on people on ART, because we wished to account for possible effects of the policies on HIV transmission and transmission of drug resistance. The significance of specific resistance mutations remains uncertain, and we elected to consider the three most significant major resistance mutations on the Stanford HIV Drug Resistance Database and two other major mutations, but others, such as at codon 138, could be important.[11] Furthermore, we assumed that dolutegravir resistance is conferred only due to mutations in the integrase gene, although it is possible that other genes are relevant.[31] More generally, there is uncertainty in many parameter values, which we took into account by sampling from distributions reflecting this uncertainty, and by assessing which parameter values were influential on the policy comparison in a logistic regression model. Another limitation on the sensitivity analyses in which urine tenofovir levels were measured is that we do not know how well the urine tenofovir point-of-care test would perform in predicting drug resistance, but studies are ongoing. A final limitation lies in the number of setting-scenarios generated. We consider the 95% CIs for the means to be sufficiently narrow, but we could have narrowed these even further had we generated more than 1000 setting-scenarios.

In conclusion, introduction of HIV drug resistance testing for people with sustained viral load non-suppression on dolutegravir based ART is likely to be cost-effective. We suggest that exploratory planning for increased access and scale-up of high-quality, low cost, drug resistance testing be undertaken for eastern, central, southern, and western Africa.

Contributors

All authors conceived the study, raised issues to consider based on expertise and clinical experience, made suggestions for approaches to take, and made crucial comments on drafts. ANP, LB-M, and JSm coded the model and had full access to the model programs. ANP wrote the draft and subsequent drafts of the manuscript. All authors had responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Model code used for this paper is available at https://doi.org/10.6084/m9.figshare.29225018.v1.

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