Predicted dolutegravir resistance in people living with HIV in South Africa during 2020–35: a modelling study

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Summary

Background In response to increasing resistance to non-nucleoside reverse transcriptase inhibitors, millions of people living with HIV have switched to dolutegravir-based antiretroviral therapy, so understanding the possible emergence of dolutegravir resistance is essential. We aimed to predict how dolutegravir resistance in South Africa will change over time.

Methods For this modelling study, we used the Modelling Antiretroviral Drug Resistance in South Africa (MARISA) model, a deterministic compartmental model calibrated to reproduce the HIV-1 epidemic in South Africa from 2005 to 2035 using data from the International Epidemiology Databases to Evaluate AIDS collaboration and the literature. Key parameters for modelling dolutegravir-resistance evolution were acquisition rates of dolutegravir-resistance mutations, reversion rates of dolutegravir-resistance mutations, the effect of resistance to nucleoside reverse transcriptase inhibitors on dolutegravir-resistance acquisition, the effect of dolutegravir resistance on dolutegravir-treatment efficacy, the probability of transmitting dolutegravir drug-resistance mutations compared with the probability of transmitting wild-type HIV, and the proportion of people with virologic failure on dolutegravir-based antiretroviral therapy with detectable drug levels. Model outcomes were estimated transmitted dolutegravir resistance and estimated acquired dolutegravir resistance.

Findings We estimated a substantial increase in the number of individuals on dolutegravir-based antiretroviral therapy after its introduction in 2020, increasing from 0 to approximately 7 million people (7·08–7·15) living with HIV on dolutegravir in 2035. We estimated the proportion of people living with HIV with viral suppression (ie, viral load <1000 copies per mL) on dolutegravir-based antiretroviral therapy to be 93% (uncertainty range 92·2–94·3) in 2035. We estimated that acquired dolutegravir resistance in people living with HIV on failing dolutegravir-based antiretroviral therapy would increase rapidly, from 18·5% (uncertainty range 12·5–25·4) in 2023 to 41·7% (29·0–54·0) in 2035. For transmitted dolutegravir resistance, we estimated an increase from 0·1% (0·0–0·2) in 2023 to 5·0% (1·9–11·9) in 2035. We estimated that resistance-mitigation strategies involving rapid switching to protease-inhibitor-based antiretroviral therapy could effectively reduce the increase in acquired dolutegravir resistance and slow the increase in transmitted dolutegravir resistance.

Interpretation Although dolutegravir-based antiretroviral therapy maintains high virological suppression, acquired and transmitted dolutegravir resistance are likely to increase. This increase will likely be greater in settings where HIV RNA monitoring, genotypic-resistance testing, and options to switch antiretroviral therapy regimens are scarce.

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Introduction

In response to the increasing prevalence of drug resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs), WHO has recommended the integrase strand transfer inhibitor (INSTI) dolutegravir as a first-line and second-line antiretroviral therapy for all people living with HIV since 2018.[1] By July 2023, dolutegravir was the preferred first-line antiretroviral therapy in 116 countries,[1] including South Africa, where more than 7·5 million people live with HIV.[2] Dolutegravir-based antiretroviral therapy has a higher genetic barrier to resistance than previously recommended, NNRTI-based first-line regimens.[3] Dolutegravir-resistant HIV is currently rare in people living with HIV on first-line antiretroviral therapy, but is observed more frequently in treatment-experienced people in trials,[4] observational cohorts,[5,6] and national surveys.[1,7] The DTG RESIST study combined data from 599 individuals living with HIV, primarily from Europe, who had viraemia on dolutegravir-based antiretroviral therapy and underwent genotypic-resistance testing.[5] At least one major or accessory INSTI drug-resistance mutation was found in

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Research in context

Evidence before this study

We searched Scopus from database inception to April 15, 2024, using the search terms "dolutegravir" and "resistance" without language restrictions, with modelling studies identified via the search term "model*". We did not identify any modelling studies attempting to estimate dolutegravir-resistance trends in the coming years. A collaborative analysis of eight cohort studies combined data from 599 individuals living with HIV, primarily from Europe, who underwent genotypic-resistance testing at detection of being on failing dolutegravir-based treatment showed that risk of dolutegravir resistance increased in the presence of nucleoside reverse transcriptase inhibitor resistance. This finding is particularly concerning in settings such as South Africa, where a high proportion of individuals already exhibit NRTI resistance. Moreover, surveys in South Africa have indicated rapidly increasing acquired dolutegravir resistance.

Added value of this study

Our study is the first to model the dynamics of dolutegravir resistance in South Africa. Including the years 2020–35, our model expands on a previous model of the evolution of drug resistance to dolutegravir-based antiretroviral therapy in South Africa. Our results indicate that although dolutegravir resistance is currently low in South Africa, it could increase at the population level, and transmitted dolutegravir resistance could exceed 10% by 2035, depending on the duration for which people living with HIV are on failing dolutegravir-based antiretroviral therapy but continue treatment.

Implications of all the available evidence

Dolutegravir resistance could undermine the success of integrase strand transfer inhibitor-based antiretroviral therapy in South Africa, where guidelines limit drug-resistance testing to people living with HIV with repeated viral load measurements more than 1000 copies per mL and with evidence of good adherence. Monitoring the evolution of dolutegravir resistance at the population level is crucial to inform future changes in guidelines on drug-resistance testing and switching to protease-inhibitor-based antiretroviral therapy. Such resistance-mitigation strategies could substantially reduce the emergence of dolutegravir resistance at the population level.

86 (14%) of 599 study participants, and 23 (4%) had high or intermediate estimated resistance to dolutegravir.[5]

In South Africa, current treatment guidelines only recommend genotypic-resistance testing for people who have two or more viral load measurements of more than 1000 copies per mL and have been on dolutegravir-based or protease-inhibitor-based antiretroviral therapy for more than 2 years with good adherence.[8] Consequently, individuals often remain viraemic for extended periods.[9] Furthermore, switching to alternative regimens, such as protease-inhibitor-based regimens, is relatively uncommon among people on failing dolutegravir-based antiretroviral therapy.[10] Together, these factors might be facilitating the emergence and spread of resistance to antiretroviral drugs. We therefore aimed to predict how dolutegravir resistance in South Africa will change over time.

Methods

Model design and data sources

For this modelling study, we used the Modelling Antiretroviral Drug Resistance in South Africa (MARISA) model, a deterministic compartmental model calibrated to reproduce the HIV-1 epidemic in South Africa with monthly timesteps from 2005 to 2035 using data from the International Epidemiology Databases to Evaluate AIDS (IeDEA) collaboration[11] and the literature (appendix p 6), allowing for a decade of estimated trends[12,13] by fitting MARISA to estimates of the demographic and epidemiological Thembisa model[12,14] and assuming the introduction of dolutegravir-based treatment started in 2020 (appendix pp 4–5). Briefly, it consists of four dimensions: the continuum of care from HIV infection through to diagnosis and initiation of antiretroviral therapy, suppressive antiretroviral therapy (ie, viral load <1000 copies per mL) or being on failing antiretroviral therapy (ie, viral load ≥1000 copies per mL), and possible transfer to protease-inhibitor-based anti-retroviral therapy; disease progression, with four CD4 count groups (ie, >500 cells per µL, 350–500 cells per µL, 200–349 cells per µL, and <200 cells per µL); sex; and binary resistance to nucleoside reverse transcriptase inhibitor (NRTI)-class and NNRTI-class antiretrovirals (appendix p 3). IeDEA ensures data quality through standardised data collection, site assessments, data linkages, and tracing of participants who are lost to care.[11]

The original implementation of MARISA treated resistance as two states (ie, susceptible or resistant), which is appropriate for antiretroviral drugs with a low genetic barrier, such as NRTIs and NNRTIs. However, this approach is unsuitable for dolutegravir, which has a higher genetic barrier.[3] We included the drug-resistance mutations observed in the DTG RESIST study (ie, Gly118Arg, Glu138Ala, Glu138Lys, Glu138Thr, Gly140Ala, Gly140Cys, Gly140Ser, Gln148His, Gln148Lys, Gln148Asn, Gln148Arg, Asn155His, and Arg263Lys).[5] The drug-resistance mutations on these six positions include all mutations identified as signature drug-resistance mutations for dolutegravir resistance; we assumed Arg263Lys occurred in isolation, whereas we assumed Gly140Ala, Gly140Cys, Gly140Ser and Gln148His, Gln148Lys, Gln148Asn, Gln148Arg occurred

For the **IeDEA collaboration** see https://www.iedea.org/

See **Online** for appendix

in combination, as we did with Gly118Arg and Glu138Ala, Glu138Lys, Glu138Thr.[15] We classified the resulting genotypes as susceptible, potential low, low, intermediate, and high dolutegravir resistance according to the Stanford resistance algorithm (figure 1).[16] As in Hauser and colleagues,[12,13] we included resistance for NRTI and NNRTI (ie, susceptible or resistant), resulting in 48 drug-resistance compartments. We expanded the treatment cascade, stratifying the compartments relevant to being on failing treatment according to the mean duration on failing antiretroviral therapy (ie, <6 months, 6 months to 1·5 years, and >1·5 years). Finally, we modified the model to include out-of-care dynamics, whereby individuals on failing dolutegravir-based antiretroviral therapy could leave and re-enter care (figure 1). We retained rates and parameters for the HIV epidemic in South Africa from the previous model version (appendix pp 5–6).[13]

This modelling study did not require additional ethical approval. The retrospective cohort analysis in the DTG RESIST study was approved by the Human Research Ethics Committee of the University of Cape Town and the Cantonal Ethics Committee of the Canton of Bern (2021–01504). Ethical approval for data used in the initial model calibration by Hauser and colleagues[12,13] was provided by the Canton of Bern, the University of Cape Town, and local ethics committees or institutional review boards within the IeDEA collaboration, which approved the use of routine clinical data for research.

Definitions, parameters, and calibration

We defined transmitted dolutegravir resistance as the proportion of people with intermediate or high dolutegravir resistance among those newly diagnosed with HIV. We defined acquired dolutegravir resistance as the proportion of people with intermediate or high dolutegravir resistance among people on failing dolutegravir-based therapy.

Key parameters for modelling dolutegravir-resistance evolution were acquisition rates of dolutegravir-resistance mutations, reversion rates of dolutegravir-resistance mutations, the effect of NRTI resistance on dolutegravir-resistance acquisition, the effect of dolutegravir resistance on dolutegravir-treatment efficacy, the probability of transmitting dolutegravir drug-resistance mutations compared with the probability of transmitting wild-type HIV, and the proportion of people on failing dolutegravir-based antiretroviral therapy with detectable drug levels (appendix pp 3–12).

On the basis of the DTG RESIST study,[5] we assumed that NRTI resistance increased the risk of acquiring dolutegravir drug-resistance mutations on failing treatment (appendix p 11). We estimated mutation-specific acquisition rates on the basis of an estimated duration of 3 months of viraemia on dolutegravir-based antiretroviral therapy in the DTG RESIST study.[5] The reversal of dolutegravir-resistance mutations is not well documented but might occur rapidly.[17] We assumed a mean duration to reversion of 2 years for each mutation

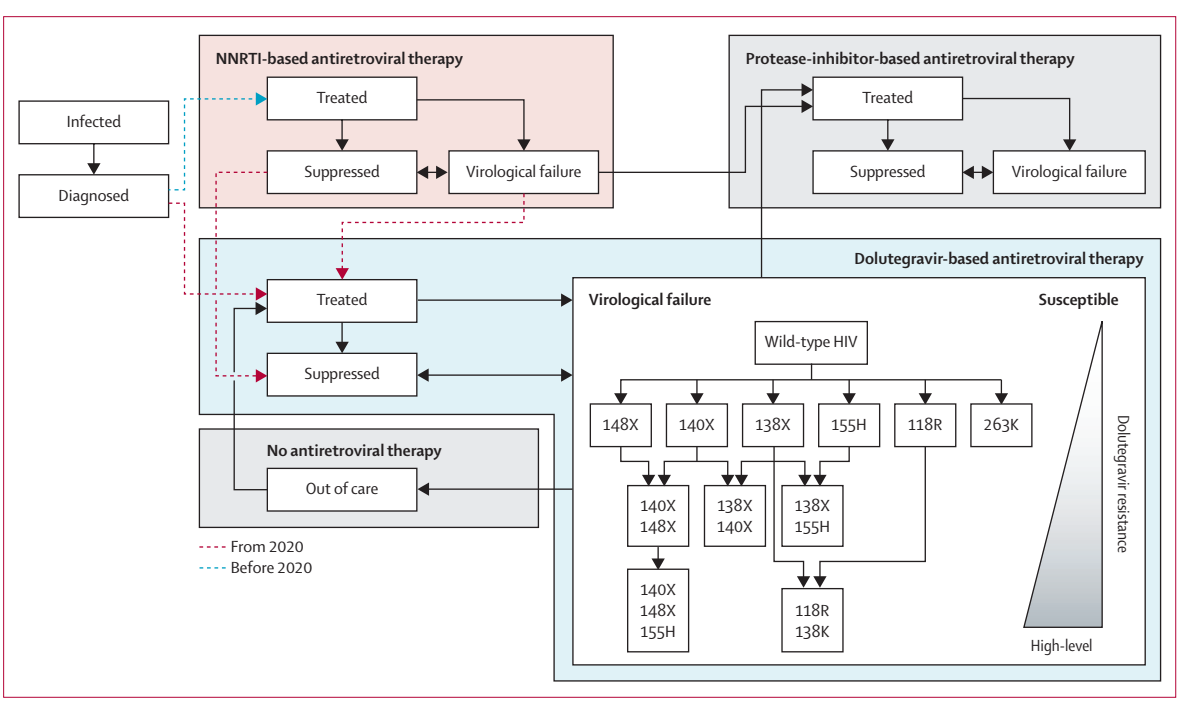

Figure 1: **Overview of the adapted MARISA model**

Not shown in this figure are dimensions for sex, CD4 count, NNRTI resistance acquisition, NRTI resistance acquisition, and mortality (appendix pp 3–11). 140X=drug-resistance mutations at integrase position 140 (ie, Gly140Ala, Gly140Cys, and Gly140Ser). 148X=drug-resistance mutations at integrase position 148 (ie, Gln148His, Gln148Lys, Gln148Asn, and Gln148Arg). MARISA=Modelling Antiretroviral Drug Resistance in South Africa. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleoside reverse transcriptase inhibitor.

with HIV replicating in the absence of dolutegravir. We assumed that high and intermediate dolutegravir resistance increased the rate of being on failing treatment for people on dolutegravir-based antiretroviral therapy. For high resistance, we assumed that the effect was equal to that of high NNRTI resistance on NNRTI-based antiretroviral therapy and for intermediate resistance, we assumed that the effect was halved. The probability of transmitting dolutegravir-resistance mutations in an HIV-transmission event is unknown; however, transmission is possible.[18,19] We assumed a reduced transmission rate for dolutegravir-resistant strains compared with wild-type HIV (appendix p 9) and explored decreased rates in sensitivity analyses (ie, allowing for up to 20 times decreased transmission rates in resistant strains).

To construct plausible ranges of model outcomes (ie, predicted transmitted dolutegravir resistance and predicted acquired dolutegravir resistance) that reflected uncertainty in the choice of parameter values, we defined an uncertainty range using pessimistic (ie, favouring the emergence of resistance) or optimistic (ie, impeding the emergence of resistance) parameter values in addition to our baseline parameterisation (table; appendix p 13).

Counterfactual scenarios

In counterfactual scenarios, we investigated the effect of drug-resistance mitigation strategies, such as those proposed in the RESOLVE trial (NCT05373758), on acquired and transmitted dolutegravir resistance. Specifically, we compared our baseline scenario, in which we modelled current treatment guidelines in South Africa, with two alternative scenarios: immediate switching to protease-inhibitor-based treatment and treatment adjustment based on genotypic-resistance testing. In immediate switching, we assumed switching to protease-inhibitor-based treatment after a mean duration of viraemia on dolutegravir-based treatment of 6 months or 12 months. In treatment adjustment informed by genotypic-resistance testing, we assumed that resistance status was ascertained after a mean duration of viraemia on dolutegravir-based treatment of 6 months and 12 months. People with intermediate or high dolutegravir resistance were then switched to protease-inhibitor-based treatment after an additional mean delay of 6 months after genotypic resistance testing, accounting for time for drug-level and resistance testing, receiving results, and implementing treatment adjustments or continuing on dolutegravir-based treatment otherwise.

These two modelled scenarios corresponded closely to interventions the ongoing RESOLVE trial is assessing. In this trial, individuals with virological failure on dolutegravir-based treatment are either immediately switched to protease-inhibitor-based antiretroviral therapy or have drug-level and resistance testing, followed by switching to protease-inhibitor-based antiretroviral therapy in case of resistance or continuing on dolutegravir-based antiretroviral therapy otherwise (appendix p 15).

	Description	Baseline	Uncertainty range	
			Pessimistic choice in parameter values	Optimistic choice in parameter values
$1/r_{DRM}$	Mean time for dolutegravir drug-resistance mutations to revert in years	2	3	2
$\alpha_{NRTI \rightarrow DTG}$	Effect of NRTI resistance on acquisition rates of dolutegravir drug-resistance mutations (ie, hazard ratio *vs* susceptible)	4	5	3
$\alpha_{impact\ DTG}$	Effect of high-level dolutegravir resistance on dolutegravir efficacy (ie, hazard ratio *vs* susceptible)	3·24	2·00	4·00
$\phi_{transmission\ DTG}$	Probability of dolutegravir-resistance transmission compared with wild-type HIV transmission	81·3%	94·3%	68·5%
$\rho_{drug\ detect}$	Proportion of people with detectable drugs on failing dolutegravir-based antiretroviral therapy	0·626	0·814	0·482

Modelled prospective scenarios included baseline parameter values and ranges with pre-defined increased and decreased resistance parameters to derive an uncertainty interval (appendix pp 3–12). For all scenarios, we calculated mutation rates on the basis of an assumed time of 3 months on failing dolutegravir-based antiretroviral therapy (appendix pp 7–8). DTG=dolutegravir. MARISA=Modelling Antiretroviral Drug Resistance in South Africa. NRTI=nucleoside reverse transcriptase inhibitor.

Table: **Dolutegravir-resistance parameters of the MARISA model**

Statistical analysis

We investigated the effects of mutation acquisition and reversion rates by varying viraemia duration on dolutegravir-based antiretroviral therapy from 2 months to 6 months (appendix pp 7–8) and varying time for dolutegravir drug-resistance mutations to revert to wild-type HIV from 6 months to 20 years. Furthermore, we varied the hazard ratio for acquiring dolutegravir-resistance mutations, comparing NRTI susceptible with resistant, from 1 (ie, no effect) to 10. Similarly, we varied the hazard ratio for being on failing dolutegravir-based antiretroviral therapy associated with high resistance from 2 to 4 (appendix p 21). We varied the probability of transmitting resistant strains from 100% (ie, as likely as wild-type HIV transmission) to 5% (ie, 20 times less likely than wild-type HIV transmission). Finally, we varied the proportion of people living with HIV with detectable drugs who were on failing dolutegravir-based antiretroviral therapy from 0·3 to 1·0.

As well as varying parameters one by one, we conducted a multidimensional sensitivity analysis by implementing a Monte Carlo estimation of the first-order and total Sobol indices, which are quantitative measures to assess the importance of parameters—and their interactions in the case of total Sobol indices—on the variability of modelled outcomes (appendix pp 21, 23). We also assessed the effect of salvage regimens for people living with HIV who were on failing protease-inhibitor-based antiretroviral therapy (appendix p 16) and explored a scenario in which the INSTI roll-out in 2020 was based on long-acting cabotegravir and rilpivirine treatment

instead of daily oral dolutegravir-based antiretroviral therapy (appendix pp 17–20).

Role of the funding source

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

Results

We estimated a substantial increase in the number of individuals on dolutegravir-based antiretroviral therapy in South Africa after its introduction in 2020, increasing from 0 to approximately 7 million people (7·08–7·15) living with HIV on dolutegravir in 2035. We estimated the proportion of people living with HIV with viral suppression (ie, viral load <1000 copies per mL) on dolutegravir-based antiretroviral therapy to be 93% (uncertainty range 92·2–94·3) in 2035, with an increasing estimated proportion of dolutegravir resistance among people who were not virally suppressed (figure 2; appendix p 14).

We estimated that acquired dolutegravir resistance in people living with HIV on failing dolutegravir-based antiretroviral therapy would increase rapidly, from 18·5% (uncertainty range 12·5–25·4) in 2023 to 41·7% (29·0–54·0) in 2035 (figure 2). There were substantial differences in estimated acquired dolutegravir resistance depending on the duration of viraemia during dolutegravir-based antiretroviral therapy, with a lower prevalence in people who were viraemic for 6 months or less and a higher prevalence among people on failing treatment for more than 1·5 years (figure 2). For transmitted dolutegravir resistance, we estimated an increase from 0·1% (0·0–0·2) in 2023 to 5·0% (1·9–11·9) in 2035. We also estimated that transmitted NNRTI resistance would remain stable from 2025 to 2035 (parameters affecting NNRTI resistance were not varied for deriving uncertainty ranges; figure 2).

We estimated that reducing the duration people living with HIV remained viraemic while on dolutegravir-based antiretroviral therapy would substantially reduce acquired dolutegravir resistance at the population level (figure 2). Immediately switching to protease-inhibitor-based antiretroviral therapy upon detection of being on failing treatment was estimated to reduce acquired dolutegravir resistance from 41·7% (uncertainty range 29·0–54·0) in 2035 to 8·0% (5·5–11·1) when switching after 6 months of viraemia up to 13·8% (9·4–19·2) when switching after 12 months of viraemia (figure 3). In the mitigation strategy with antiretroviral therapy adjustment informed by genotypic-resistance testing

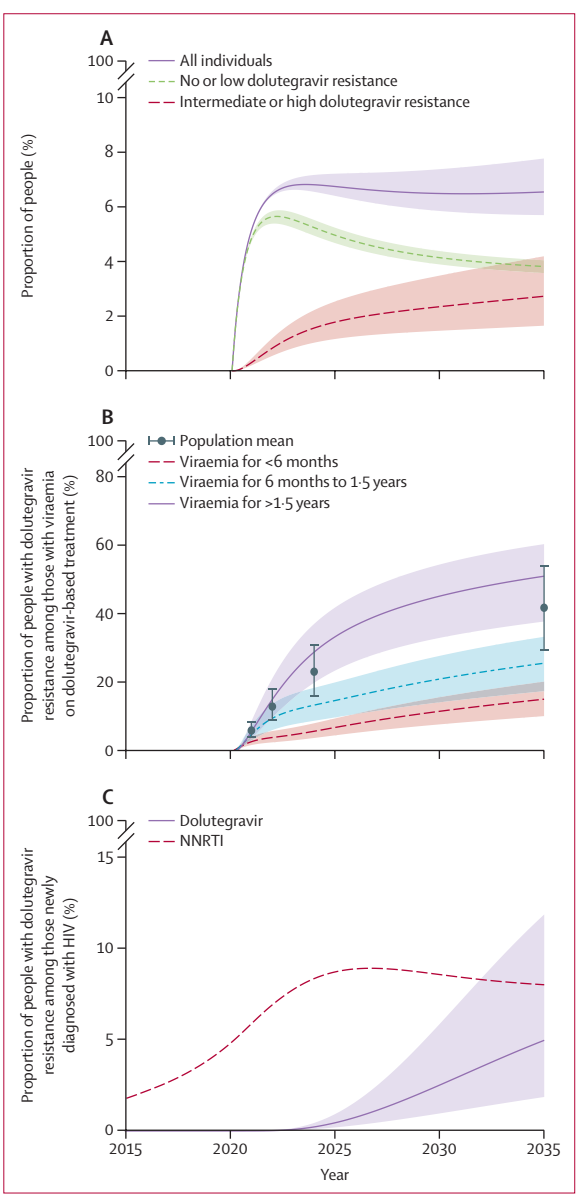

Figure 2: **Modelled viral suppression on dolutegravir-based antiretroviral therapy (A), acquired dolutegravir resistance (B), and transmitted dolutegravir resistance (C)**

Please note that scales change between graphs. Solid lines show baseline parameterisation of rates of mutation reversion, effect of NRTI resistance on acquisition of a dolutegravir drug-resistance mutation, effect of dolutegravir resistance on its efficacy, transmission probability of dolutegravir drug-resistance mutations in an HIV-transmission event, and the proportion of people with detectable drug levels on failing dolutegravir-based antiretroviral therapy. Shaded areas show uncertainty intervals (appendix p 13). Dots and error bars correspond to population mean and uncertainty range, respectively. Dolutegravir rollout was started in 2020. Viral suppression (ie, viral load less than 1000 copies per mL) on dolutegravir-based antiretroviral therapy was high depending on model assumptions for dolutegravir resistance; we estimated that up to 6–8% of people on dolutegravir-based antiretroviral therapy could be virally unsuppressed. Acquired dolutegravir resistance was defined as the proportion of people with intermediate or high dolutegravir resistance on failing dolutegravir-based antiretroviral therapy. Transmitted dolutegravir resistance was defined as the proportion of newly diagnosed people with intermediate or high dolutegravir resistance among those newly diagnosed with HIV. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleoside reverse transcriptase inhibitor.

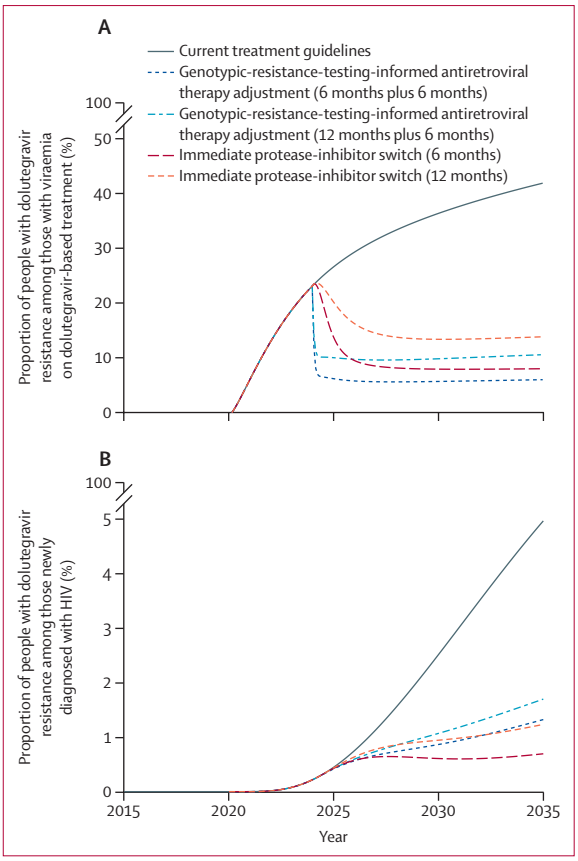

Figure 3: **Effects of the counterfactual scenario and modelled resistance-emergence-mitigation strategies on acquired dolutegravir resistance (A) and transmitted dolutegravir resistance (B)**

Please note that scales change between graphs. Antiretroviral therapy adjustment informed by genotypic-resistance testing was drug-level testing and genotypic-resistance testing upon detection of being on failing treatment, then switching to protease-inhibitor-based antiretroviral therapy in case of intermediate or high dolutegravir resistance. Immediate protease-inhibitor switch was immediately switching people on failing dolutegravir-based antiretroviral therapy to protease-inhibitor-based antiretroviral therapy. In case of drug-level and genotypic-resistance testing, we assumed an additional mean duration of 6 months from detection of virological failure to informed treatment adjustment. Acquired dolutegravir resistance was defined as the proportion of people with intermediate or high dolutegravir resistance on failing dolutegravir-based antiretroviral therapy. Transmitted dolutegravir resistance was defined as the proportion of newly diagnosed people with intermediate or high dolutegravir resistance among those newly diagnosed with HIV.

upon detection of virological failure, estimated acquired dolutegravir resistance could be reduced to 6·0% (4·1–8·3) when resistance testing was done after 6 months of viraemia on dolutegravir-based treatment and up to 10·5% (7·1–14·8) when resistance testing was done after 12 months of viraemia on dolutegravir-based treatment, with treatment switch to protease-inhibitor-based treatment for those with intermediate or high dolutegravir resistance an additional 6 months after genotypic resistance testing (figure 3). Transmitted dolutegravir resistance could be reduced from 5·0% (1·9–11·9) in 2035 to 0·7% (0·2–2·0) when switching after 6 months of viraemia and up to 1·2% (0·4–3·4) when switching after 12 months of viraemia in 2035 in case of immediate switching to protease-inhibitor-based antiretroviral therapy. Resistance could be reduced to 1·3% (0·5–3·4) when resistance testing was done after 6 months of viraemia on dolutegravir-based treatment and up to 1·7% (0·6–4·3) when resistance testing was done after 12 months of viraemia on dolutegravir-based treatment in 2035, with treatment switch to protease-inhibitor-based treatment for those with intermediate or high dolutegravir resistance an additional 6 months after genotypic resistance testing (figure 3; appendix p 15).

Dolutegravir-resistance outcomes were affected when perturbing several key parameters for modelling dolutegravir-resistance evolution, but results from the main analysis were robust (appendix p 22). However, we observed substantial deviations for extreme parameter values (appendix pp 21–23).

The multidimensional sensitivity analysis showed that estimated acquired dolutegravir resistance was strongly influenced by assumptions regarding the proportion of people living with HIV with detectable drug levels among individuals on failing treatment (total Sobol sensitivity index 0·35, 95% CI 0·31–0·39; appendix p 19) and mutation-acquisition rates (0·31, 0·28–0·34). Assumptions for the effect of NRTI resistance on dolutegravir-resistance acquisition (0·20, 0·17–0·22) and for the effect of dolutegravir resistance on efficacy (0·14, 0·13–0·16) also affected estimates of acquired dolutegravir resistance. Assumed probability of dolutegravir drug-resistance mutation transmission compared with wild-type HIV was the most important factor in uncertainty for estimated transmitted dolutegravir resistance (Sobol sensitivity index 0·55, 95% CI 0·47–0·62). Mutation-reversion rates also affected estimates of transmitted dolutegravir resistance (0·25, 0·20–0·29). Both acquired and transmitted dolutegravir-resistance estimates were minimally affected by parameters describing total population size, HIV transmission, HIV diagnosis, initiation of antiretroviral therapy, and mortality rates (appendix pp 24–25). Salvage regimens for individuals on failing protease-inhibitor-based antiretroviral therapy were not estimated to affect population-level estimates of dolutegravir resistance (appendix p 16). Although the effect of long-acting INSTI-based treatment had high uncertainty, we estimated that population-level estimates of resistance were similar to dolutegravir-based antiretroviral therapy (appendix pp 17–20).

Discussion

Our estimated proportion of people living with HIV with viral suppression was in line with empirical data[20] and the 92% estimate reported by UNAIDS.[2] Although virological failure is uncommon on dolutegravir-based antiretroviral therapy, we estimated that the prevalence of acquired and transmitted dolutegravir resistance in

South Africa could substantially increase during 2020–35. The 10% threshold of pre-treatment drug resistance, above which WHO recommends the replacement of a drug,[21] could be reached by 2035, depending on monitoring and switching strategies. The relationship between transmitted and pre-treatment drug resistance for INSTIs is currently not well known. The WHO definition of pre-treatment drug resistance includes people living with HIV who are re-initiating antiretroviral therapy,[1] so our estimates might be conservative. During the same time period, we estimated that the prevalence of transmitted NNRTI resistance would remain stable from 2025 to 2035. Timely switching of people with virological failure to protease-inhibitor-based antiretroviral therapy could substantially reduce acquired and transmitted dolutegravir resistance.

Currently, viral suppression rates in people living with HIV on dolutegravir are high worldwide.[2] Although acquired drug resistance is rare, it can occur, especially in individuals with a compromised NRTI backbone.[5,6] Transmission of dolutegravir resistance has also been documented.[18,19] Programmatic data on dolutegravir resistance in resource-limited settings are scarce, but nationally representative HIV drug-resistance surveys based on remnant routine diagnostic viral load samples in South Africa suggest increasing dolutegravir resistance.[7] Steegen and colleagues[7] found that in samples with viral load more than 1000 copies per mL and detectable dolutegravir, resistance to dolutegravir increased from 2·7% in 2021 to 11·1% in 2022, consistent with our estimates. Similar proportions of people living with HIV with resistance mutations on failing dolutegravir-based antiretroviral therapy have been reported by Tschumi and colleagues[6] in Lesotho and by WHO in other countries in southern Africa.[1]

We estimated that acquired dolutegravir resistance could increase relatively quickly in South Africa during 2020–35. However, the estimated increase in resistance depended on how long people with HIV remained viraemic on a dolutegravir-based regimen. There are often delays in switching regimens, and some people living with HIV might not be switched at all. For example, a study linking medical and laboratory data from people living with HIV on first-line antiretroviral therapy in 52 South African clinics from 2007 to 2018 reported that only about 40% of people living with HIV with confirmed virological failure were switched.[22] Among those who were switched, median time to switch was 16 months (IQR 8–29).[22] Similarly, an analysis of a South African private-sector antiretroviral therapy programme found that median time from detection of virological failure to switching to second-line antiretroviral therapy was 13 months (8–22), with delays in switching associated with increased mortality.[23] Other studies with data from central, east, and west Africa, have found sub-optimal switching in adults living with HIV after virological failure, with delays typically being 4–17 months.[24]

Real-world evidence on effective switching strategies could come from the ongoing RESOLVE trial of public-sector HIV clinics in Uganda and South Africa. The trial compares universal switching to protease-inhibitor-based second-line antiretroviral therapy with switching guided by genotypic-resistance tests, urine tenofovir-adherence assays, and standard of care. In line with the association between duration of viraemia and resistance development, we estimated that such resistance-mitigation strategies involving rapid switching to protease-inhibitor-based antiretroviral therapy could effectively reduce the increase in acquired dolutegravir resistance and slow the increase in transmitted dolutegravir resistance. These strategies were estimated to reduce the prevalence of dolutegravir resistance to less than 10% throughout 2020–35. Of note, the total estimated number of people on protease-inhibitor-based antiretroviral therapy differed strongly between the two mitigation strategies. Implementing the immediate protease-inhibitor-switch strategy could result in almost half of all people on antiretroviral therapy in South Africa on protease-inhibitor-based antiretroviral therapy by 2035 (appendix p 15).

A strength of our study is the combination of modelled epidemiology of the HIV epidemic in South Africa with an analysis of INSTI, NNRTI, and NRTI drug resistance. Moreover, our model accounted for interactions between acquired and transmitted drug resistance and considered the differing genetic barriers of these drug classes. Model parameters were informed by data from a collaborative study on dolutegravir resistance, enhancing the robustness of our findings.[5] Furthermore, the model allowed us to assess the effect of public health interventions in counterfactual scenarios.

A limitation of our study is large parameter uncertainty, particularly regarding mutation pathways and acquisition and reversion rates, which we addressed in the sensitivity analyses. The global sensitivity analysis helped us to understand the relative importance of these parameters and identified key knowledge gaps in our understanding of dolutegravir-resistance dynamics. Furthermore, data for being on failing dolutegravir-based therapy are scarce, necessitating the extrapolation of parameters derived from NNRTI-based antiretroviral therapy. Scarce data on drug-resistance mutations and their accumulation is a further limitation that can only be addressed when more data are available and when more research is conducted. Moreover, there is uncertainty about the effect of interactions between drug-resistance mutations and compensatory mutations on viral fitness and transmission. The uncertainty in INSTI-resistance mutation transmission probability required extrapolation from NNRTI-resistance transmission. This uncertainty affects transmitted drug resistance more than acquired drug resistance, as reflected in the broader range of predicted outcomes for transmitted dolutegravir resistance in this study. Furthermore, the assumed treatment cascade was a simplification. We did not model more complex

treatment histories or disengagement and re-engagement in care,[25] which might affect the emergence of resistance. Additionally, the implementation of pre-exposure prophylaxis was not included in our model, which could, particularly if INSTI-based, be another source of resistance.[26]

Our modelling study indicates that dolutegravir resistance could increase considerably in South Africa during 2020–35. Without changes in the management of people on failing dolutegravir-based antiretroviral therapy, the emergence of transmitted dolutegravir resistance appears to be a question of when, not if, and acquired dolutegravir resistance could increase rapidly in the next decade. Drug-resistance mitigation strategies for people living with HIV on failing dolutegravir-based antiretroviral therapy, such as genotypic-resistance testing-informed antiretroviral-therapy adjustment, could strongly reduce acquired and transmitted dolutegravir resistance if being on failing treatment is detected rapidly. Dolutegravir-resistance surveillance, including enhanced viral load monitoring and genotypic-resistance testing, should be strengthened, especially in settings with programmatic use of dolutegravir-based antiretroviral therapy where people might remain on failing antiretroviral therapy for more than 1 year. Increased access to genotypic-resistance testing,[27] low-cost rapid point-of-care tests for antiretroviral drugs,[28] and generic darunavir–ritonavir available for around US$200 per patient per year[29] could increase rates of switching to second-line antiretroviral therapy and reduce delays, thereby reducing the emergence and spread of dolutegravir resistance.

Contributors

RDK, RL, ME, and HFG conceptualised the study. TL, JJ, and RDK curated the data. TL, NH, AH, JJ, and RDK devised the methodology. TL, NH, and JJ conducted the formal analysis and validation, managed the data, and applied and adapted the software. RDK provided project administration. AH contributed code scripts. ME contributed data. HFG, RL, ME, LFJ, AH, and RDK provided supervision. TL created the figures. TL and RDK wrote the original draft of the manuscript. TL, NH, and RDK directly accessed and verified the underlying data. All authors reviewed the manuscript, had full access to all data in the study, and had final responsibility for the decision to submit for publication.

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Data sharing

All code for the MARISA model is available at https://github.com/Kouyos-Group/DTG-resistance-MARISA. Model parameters are reported in the appendix (pp 3–12).

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