Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study

Andrew N Phillips, Francois Venter, Diane Havlir, Anton Pozniak, Daniel Kuritzkes, Annemarie Wensing, Jens D Lundgren, Andrea De Luca, Deenan Pillay, John Mellors, Valentina Cambiano, Loveleen Bansi-Matharu, Fumiyo Nakagawa, Thokozani Kalua, Andreas Jahn, Tsitsi Apollo, Owen Mugurungi, Polly Clayden, Ravindra K Gupta, Ruanne Barnabas, Paul Revill, Jennifer Cohn, Silvia Bertagnolio, Alexandra Calmy

Summary

Background The integrase inhibitor dolutegravir could have a major role in future antiretroviral therapy (ART) regimens in sub-Saharan Africa because of its high potency and barrier to resistance, good tolerability, and low cost, but there is uncertainty over appropriate policies for use relating to the potential for drug resistance spread and a possible increased risk of neural tube defects in infants if used in women at the time of conception. We used an existing individual-based model of HIV transmission, progression, and the effect of ART with the aim of informing policy makers on approaches to the use of dolutegravir that are likely to lead to the highest population health gains.

Methods We used an existing individual-based model of HIV transmission and progression in adults, which takes into account the effects of drug resistance and differential drug potency in determining viral suppression and clinical outcomes to compare predicted outcomes of alternative ART regimen policies. We calculated disability adjusted life-years (DALYs) for each policy, assuming that a woman having a child with a neural tube defect incurs an extra DALY per year for the remainder of the time horizon and accounting for mother-to-child transmission. We used a 20 year time horizon, a 3% discount rate, and a cost-effectiveness threshold of US$500 per DALY averted.

Findings The greatest number of DALYs is predicted to be averted with use of a policy in which tenofovir, lamivudine, and dolutegravir is used in all people on ART, including switching to tenofovir, lamivudine, and dolutegravir in those currently on ART, regardless of current viral load suppression and intention to have (more) children. This result was consistent in several sensitivity analyses. We predict that this policy would be cost-saving.

Interpretation Using a standard DALY framework to compare health outcomes from a public health perspective, the benefits of transition to tenofovir, lamivudine, and dolutegravir for all substantially outweighed the risks.

Funding Bill & Melinda Gates Foundation.

Copyright © 2018 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

Scaling up antiretroviral therapy (ART) in sub-Saharan Africa presents a major achievement, but there are ongoing challenges, including increasing transmitted drug resistance, poor coverage of viral load monitoring, and low numbers of people who have fulfilled the criteria for failure of first-line ART switching to second-line regimens. Until recently, WHO recommended a sequence of first-line tenofovir, lamivudine (or emtricitabine), and efavirenz and second-line zidovudine, lamivudine, and a protease inhibitor in people with first-line failure. However, WHO now recommends use of the integrase inhibitor dolutegravir with tenofovir and lamivudine in people initiating ART and, potentially, in those currently on first-line ART if they have a recent viral load measurement less than 1000 copies per mL. In people with virological failure on tenofovir, lamivudine, and efavirenz, dolutegravir in the context of an optimised nucleoside reverse transcriptase inhibitor background is recommended as a second-line regimen, which most often will be zidovudine, lamivudine, and dolutegravir. Dolutegravir-based regimens are associated with less need to switch to other antiretroviral drugs and there is a lower risk of development of major drug resistance mutations compared with efavirenz-based regimens. Dolutegravir therapy also has superior outcomes compared with a boosted protease inhibitor-based regimen in people starting second-line therapy with at least one active nucleoside reverse transcriptase inhibitor. An alternative to this approach to dolutegravir use would be to transition all people on ART to tenofovir, lamivudine, and dolutegravir, and use dolutegravir, unless or until there is sustained virological failure, at which point zidovudine, lamivudine, and a protease inhibitor would be used. Since access to viral load testing is difficult in many countries, this approach has the potential to bring greater public health benefits. However, these benefits should be balanced against concerns over a possible risk of increased resistance to dolutegravir and other drugs. Modelling can help policy makers think through the balance of these considerations in the context of a public health approach.
Research in context

Evidence before this study
The integrase inhibitor dolutegravir is expected to have a role in future antiretroviral therapy (ART) regimens in sub-Saharan Africa because of its high potency and barriers to resistance, good tolerability, and low cost. However, which policy for use of dolutegravir will produce the greatest population health benefits is unclear because of considerations over the potential for virological failure and drug resistance spread if used with nucleoside reverse transcriptase inhibitors to which HIV is resistant, and a possible association between dolutegravir and an increased risk of neural tube defects in infants if used at conception in women. We searched Web of Knowledge using the terms “dolutegravir” and “model*” on Aug 14, 2018, with no date or language restrictions, and identified 74 papers. When we reviewed these papers we did not identify any that used modelling to quantify the risks and benefits of different policies for introduction of dolutegravir in sub-Saharan Africa.

Added value of this study
We used an existing individual-based model of HIV transmission and progression in adults to compare predicted outcomes of alternative regimen policies. The model takes into account the effects of drug resistance and potency in determining viral load and clinical treatment outcomes, and the effect of a potentially increased risk of neural tube defects in infants if dolutegravir is taken by women at conception. We considered policies of using a regimen containing tenofovir, lamivudine, and dolutegravir for all individuals on ART, or of making tenofovir, lamivudine, and dolutegravir dependent on viral load suppression (whether on first-line or second-line ART) or, for women, intention to have (more) children.

Implications of all the available evidence
Using a standard disability adjusted life-year framework for comparing health outcomes from a public health perspective, we found that the benefits of transition to a regimen of tenofovir, lamivudine, and dolutegravir for all people on ART, without dependence on viral suppression or intention to have (more) children, substantially outweighed the risks. Our evaluation provides quantitative assessment to guide policy formulation by ministries of health on the use of dolutegravir.

Furthermore, dolutegravir could be a cause of neural tube defects in the children of a small proportion of women taking dolutegravir at the time of conception—in a 2018 report, four incidences of neural tube defects occurred in 596 pregnancies, which is above the background expected for efavirenz-based therapy regimens. This finding has raised questions over the use of dolutegravir in women of child bearing age. However, restriction of dolutegravir use in women of child bearing age has a public health cost that policy makers should weigh against the possible neural tube defect risk.

In this study, we used an existing individual-based model of HIV transmission, progression, and the effect of ART to help inform policy makers on approaches to the use of dolutegravir that are likely to lead to the highest population health gains. We aimed to provide quantitative assessment of the risks and benefits of alternative policies for use of dolutegravir to inform ministries of health in their policy decision making in consultation with the communities they serve.

Methods

Model description
In this modelling study, we used the HIV Synthesis Model (for full details see appendix). Briefly, this model (programmed in SAS version 9.4) generates a population who are individually tracked, with updates every 3 months, for risk of HIV acquisition. Those who acquire HIV are tracked in terms of their viral load, CD4 cell count, occurrence of WHO stage 3 and 4 conditions, use of specific drugs, presence of resistance mutations, adherence, and drug toxicities. The ongoing effects of a drug regimen (on viral load, drug resistance, and CD4 count, and hence risk of AIDS and death) are dependent on the sum of the activity of each drug in the regimen, accounting for presence of drug resistance mutations, drug potency, and level of adherence. This study was not submitted for ethics committee review as it does not involve research on human subjects.

Setting scenarios
The model is based on sub-Saharan Africa, with 1000 potential setting scenarios generated through simulation. We randomly varied parameters, including the rate of HIV testing, distribution of ART adherence across individuals, the rate of ART interruption, number of switches to a second-line regimen after failure of a first-line regimen (detected by confirmed viral load above 1000 copies per mL), and the ability to measure viral load as indicated, within plausible bounds for settings in the region. For a complete list of parameters see the appendix (p 27).

For each setting scenario, we considered the situation in 2018 and compared outcomes of potential regimen policies over a 20 year time horizon (50 years in sensitivity analysis). The regimen policies considered are described in table 1. Our reference regimen policy was a continuation of the approach of use of tenofovir, lamivudine, and efavirenz in first-line regimens. We also considered four further policies, involving use of tenofovir, lamivudine, and dolutegravir. These policies consider tenofovir, lamivudine, and dolutegravir use with or without dependence on intention to have (more) children

Elizabeth Glaser Paediatric AIDS Foundation, Geneva, Switzerland (J Cohn PhD); World Health Organization, Geneva, Switzerland (S Bertagnolio PhD); and University of Geneva, Geneva, Switzerland (Prof A Calmy PhD)
Correspondence to: Prof Andrew N Phillips, University College London, London NW3 2PF, UK andrew.phillips@ucl.ac.uk
or current viral load suppression being documented. The rationale for restriction of use of tenofovir, lamivudine, and dolutegravir to those with viral suppression is due to concern that resistance to tenofovir and lamivudine is likely to have developed in those with virological failure, making dolutegravir the only fully active drug and likely to have developed in those with virological failure, meaning the risk of resistance to dolutegravir is increased. The extent of any residual effects on viral replication due to continued exposure to lamivudine and tenofovir in these circumstances is uncertain.\(^\text{111}\) Policies involving tenofovir, lamivudine, and dolutegravir depending on viral suppression also involve use of zidovudine rather than tenofovir in newly initiated second-line regimens. This approach is broadly consistent with current WHO interim guidance.\(^\text{7} \) We refer throughout this Article to use of lamivudine in regimens, but emtricitabine might be used instead. Dependence on a woman’s intention to have (more) children relates to concern over the risk of neural tube defects if dolutegravir is used at the time of conception. Policies with this dependence are envisaged to offer dolutegravir to women only upon reaching the point of intention to have no more children. We assume a rate of reaching a point of intention to have no more children to be 0·005 per 3 months from age 25 years. This rate results in 16% of women aged 15–55 years not intending to have (more) children, which is consistent with data from Demographic and Health Surveys.\(^\text{14,15}\) We assume that women who intend to have no more children are able to access and use contraception, and that contraceptive efficacy is 80% (50% in sensitivity analysis). We refer to the policy for which tenofovir, lamivudine, and dolutegravir use is dependent on neither viral suppression nor intention to have more children as tenofovir, lamivudine, and dolutegravir for all.

### Table 1: Description of regimen policies considered

| Men and women not intending to have (more) children | Women intending to have (more) children |
|---------------------------------------------------|----------------------------------------|
| **New initiators**                                | **New initiators**                     |
| Currently on first-line tenofovir, lamivudine, and efavirenz | Currently on first-line tenofovir, lamivudine, and efavirenz |
| Currently on second-line zidovudine, lamivudine, and protease inhibitor (atazanavir) | Currently on second-line zidovudine, lamivudine, and protease inhibitor (atazanavir) |
| At future tenofovir, lamivudine, and efavirenz failure | At future tenofovir, lamivudine, and efavirenz failure |
| At future tenofovir, lamivudine, and efavirenz failure | At future tenofovir, lamivudine, and efavirenz failure |

| Tenofovir, lamivudine, and efavirenz for all | Tenofovir, lamivudine, and efavirenz |
|---------------------------------------------|------------------------------------|
| Tenofovir, lamivudine, and efavirenz | Zidovudine, lamivudine, and protease inhibitor (atazanavir) |
| Zidovudine, lamivudine, and protease inhibitor (atazanavir) | Zidovudine, lamivudine, and protease inhibitor (atazanavir) |

| Tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children only | Tenofovir, lamivudine, and efavirenz |
|----------------------------------------------------------------------------------------------------------------|------------------------------------|
| Tenofovir, lamivudine, and dolutegravir if viral load <1000 copies per mL | Switch to tenofovir, lamivudine, and dolutegravir |
| Switch to tenofovir, lamivudine, and dolutegravir | Zidovudine, lamivudine, and protease inhibitor (atazanavir) |
| Zidovudine, lamivudine, and protease inhibitor (atazanavir) | Zidovudine, lamivudine, and protease inhibitor (atazanavir) |

| Tenofovir, lamivudine, and dolutegravir dependent on intention to have (more) children only | Tenofovir, lamivudine, and efavirenz |
|----------------------------------------------------------------------------------------------------------------|------------------------------------|
| Tenofovir, lamivudine, and dolutegravir | Switch to tenofovir, lamivudine, and dolutegravir |
| Switch to tenofovir, lamivudine, and dolutegravir | Zidovudine, lamivudine, and protease inhibitor (atazanavir) |
| Zidovudine, lamivudine, and protease inhibitor (atazanavir) | Zidovudine, lamivudine, and protease inhibitor (atazanavir) |

| Tenofovir, lamivudine, and dolutegravir dependent on viral suppression only | Tenofovir, lamivudine, and efavirenz |
|----------------------------------------------------------------------------------------------------------------|------------------------------------|
| Tenofovir, lamivudine, and dolutegravir if viral load <1000 copies per mL | Switch to tenofovir, lamivudine, and dolutegravir |
| Switch to tenofovir, lamivudine, and dolutegravir | Zidovudine, lamivudine, and protease inhibitor (atazanavir) |
| Zidovudine, lamivudine, and protease inhibitor (atazanavir) | Zidovudine, lamivudine, and protease inhibitor (atazanavir) |

| Tenofovir, lamivudine, and dolutegravir for all | Tenofovir, lamivudine, and efavirenz |
|----------------------------------------------------------------------------------------------------------------|------------------------------------|
| Tenofovir, lamivudine, and dolutegravir | Switch to tenofovir, lamivudine, and dolutegravir |
| Switch to tenofovir, lamivudine, and dolutegravir | Zidovudine, lamivudine, and protease inhibitor (atazanavir) |
| Zidovudine, lamivudine, and protease inhibitor (atazanavir) | Zidovudine, lamivudine, and protease inhibitor (atazanavir) |
resistance to dolutegravir than to efavirenz. Dolutegravir is generally associated with a lower risk of toxicity than are efavirenz and protease inhibitors, resulting in reduced discontinuation.\textsuperscript{2,5,21} We assumed that the risk of neurological toxicity with dolutegravir was half that for efavirenz, and assumed that dolutegravir has 1·5 times higher potency than does efavirenz (lower than boosted protease inhibitors, which were assumed to have potency of 2), consistent with its effect as a monotherapy\textsuperscript{17} (although insufficient for its clinical use to have potency of 2), consistent with its effect as a monotherapy.\textsuperscript{17} We assumed that the residual effects of tenofovir in the presence of the Lys65Arg mutation and lamivudine in the presence of the Met184Val mutation mean that they each have 0·25 times full drug activity in this situation.\textsuperscript{25,27} We present our main results as the mean and mean difference compared with the policy of tenofovir, lamivudine, and efavirenz for all, with a 90% range reflecting variation across setting scenarios and 95% CI reflecting stochastic simulation variability.

Although these assumptions formed our base assumptions, we considered the possibility of different assumptions for dolutegravir in a proportion of our 1000 setting scenarios. These proportions for alternative assumptions were selected on the basis of the perceived probability that they hold. Thus, we considered that potency of dolutegravir could be 1 (20% of setting scenarios), 1·25 (20% of setting scenarios), or 2 times (5% of setting scenarios) that of efavirenz, instead of 1·5 times (55% of setting scenarios); that development of resistance to dolutegravir could be only 3 times lower than for efavirenz (20% of setting scenarios); that the risk of neurological toxicity using dolutegravir could be equal to that of efavirenz (20% of setting scenarios); and that the residual effects of tenofovir and lamivudine in the presence of the Lys65Arg and Met184Val mutations was 0·0 rather than the 0·25 of a fully active drug (20% of setting scenarios in each case). We also considered different degrees to which viral load monitoring was implemented (25% of setting scenarios each for probabilities of 0·0, 0·10, 0·25, and 0·85 of a viral load test being done, and the result delivered in accordance with the recommended monitoring strategy) and ART regimen was switched after viral failure was determined (probabilities of 0·05 in 30% of setting scenarios, 0·20 in 50% of setting scenarios, and 0·50 in 20% of setting scenarios per 3 months). We determined these alternative assumptions by random independent sampling for each setting scenario. Full details of the distribution of all sampled parameters used in deriving our 1000 setting scenarios are shown in the appendix (p 27). Excess risk of neural tube defects in babies of women on dolutegravir at the time of conception was assumed to be 0·58% (4 in 596 = 0·67% minus the 0·09% background rate in HIV-negative women); we did sensitivity analyses using values of 1% and 3%.

The range of HIV epidemic and programmatic characteristics in 2018 for our 1000 setting scenarios are shown in table 2 with comparable observed data.

Model outcomes

Our primary measure of health outcome was disability adjusted life-years (DALYs). Although we explicitly modelled the individual life courses of adults only, we considered DALY effects of neural tube defects and of mother-to-child HIV transmission. We estimated the aggregate effects that alternative policies have on population burden of disease by calculating net DALYs, which are the DALYs averted by a policy minus the health opportunity costs imposed as a result of costs incurred. Health opportunity costs are calculated using country cost-effectiveness thresholds, which represent the health gains that could be generated by alternative uses of resources.\textsuperscript{29} Country-specific thresholds are uncertain but US$500 averted per DALY is likely to be at the upper end on the basis of evidence concerning how resources would otherwise be used,\textsuperscript{29} and we used this value. We calculated net DALYs as DALYs plus costs divided by the cost-effectiveness threshold. Absolute numbers of health-related events, costs, DALYs, and net DALYs that we report are relevant for a country with a population size of around 10 million adults in 2018. We did our analysis from

![Table 2: HIV epidemic and programmatic characteristics of setting scenarios in 2018](https://ipha.icap.columbia.edu/)
Table 3: Predicted effect of regimen policies on intermediate outcomes, DALYs, and net DALYs

| Policy Description | Proportion on efavirenz | Proportion on tenofovir, lamivudine, and dolutegravir on viral suppression only | Proportion on tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children | Proportion on tenofovir, lamivudine, and dolutegravir dependent on intention to have (more) children only | Proportion on tenofovir, lamivudine, and dolutegravir dependent on viral suppression only | Proportion on tenofovir, lamivudine, and dolutegravir for all medications |
|--------------------|------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|
| Mean over 1 year   | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines |
| Mean over 5 years   | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines |
| Mean over 20 years  | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines |

Of people with baseline viral load >1000 copies per mL and L90M/Arg and Met184Val mutations at baseline, percentage of people on ART with viral load <1000 copies per mL.

| Policy Description | Proportion on efavirenz | Proportion on tenofovir, lamivudine, and dolutegravir on viral suppression only | Proportion on tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children | Proportion on tenofovir, lamivudine, and dolutegravir dependent on intention to have (more) children only | Proportion on tenofovir, lamivudine, and dolutegravir dependent on viral suppression only | Proportion on tenofovir, lamivudine, and dolutegravir for all medications |
|--------------------|------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|
| Mean over 1 year   | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines |
| Mean over 5 years   | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines |
| Mean over 20 years  | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines |

Adverse birth outcomes among women with HIV (percentage of pregnancies)

| Policy Description | Proportion on efavirenz | Proportion on tenofovir, lamivudine, and dolutegravir on viral suppression only | Proportion on tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children | Proportion on tenofovir, lamivudine, and dolutegravir dependent on intention to have (more) children only | Proportion on tenofovir, lamivudine, and dolutegravir dependent on viral suppression only | Proportion on tenofovir, lamivudine, and dolutegravir for all medications |
|--------------------|------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|
| Mean over 1 year   | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines |
| Mean over 5 years   | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines |
| Mean over 20 years  | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines | Proportion on medicines |

Data are mean proportion and mean difference (95% CI; 90% range reflecting variation across setting scenarios) compared with the policy of tenofovir, lamivudine, and efavirenz, unless otherwise indicated. DALYs and net DALYs were measured over 20 years (2018–38) and represent the mean over 3 month periods, unless otherwise stated. Costs are in US$. ART=antiretroviral therapy. DALY=disability adjusted life-year. As opposed to tenofovir disoproxil fumarate, all are on lamivudine. Neural tube defects potentially caused by dolutegravir if possible signal is confirmed. In the context of an adult population of 10 million people with HIV prevalence as in table 2. Costs and DALYs are discounted at 3% per annum. | Values are mean and mean difference (95% CI; 90% range reflecting variation across setting scenarios). | Values are p value (95% CI; 90% range reflecting variation across setting scenarios). | Policies are dominated if there is another policy with both lower cost and more DALYs averted. The reference policy is selected among non-dominated policies. | Table 3: Predicted effect of regimen policies on intermediate outcomes, DALYs, and net DALYs
a health-care perspective. We discounted future costs and health outcomes to present values of 3% per annum. We assumed the costs of tenofovir, lamivudine, and dolutegravir and tenofovir, lamivudine, and efavirenz to be US$75 per year, and the cost of zidovudine, lamivudine, and a protease inhibitor (atazanavir) to be $265. Full details of unit costs and disability weights are provided in the appendix (p 33).

For a woman having a baby with a neural tube defect, an extra DALY was incurred for each subsequent year of the 20 year time horizon since the baby is assumed to die (ie, years lost from a child’s life were valued the same as years lost from an adult’s life). We assumed no monetary costs as a result of neural tube defects, except in a sensitivity analysis. Depending on an HIV-positive woman’s viral load, birth of an HIV-infected child can occur. We assumed that an HIV-infected child will access ART and that an additional 0·1 DALYs, and cost of $160 per year are incurred for each subsequent year of the 20 year time horizon.

Role of the funding source
The funder of the study had no role in study design, modelling approach, interpretation, or writing of the report. The corresponding author had full access to all model programs and outputs in the study and had final responsibility for the decision to submit for publication.

Results
Consequences of the various regimen policies for the use of each drug are shown in table 3. A mean of 98% of people receiving ART over 20 years would be expected of each drug are shown in table 3. A mean of 98% of people receiving ART over 20 years (table 3). Restriction of tenofovir, lamivudine, and dolutegravir use in women who intend to have (more) children was predicted to lead to poorer overall viral suppression and being male or a woman not intending to have (more) children.

The predicted effect on viral load suppression is shown in people on ART over a mean of 1 year, 5 years, and 20 years (table 3). Restriction of tenofovir, lamivudine, and dolutegravir use in women who intend to have (more) children was predicted to lead to poorer overall viral suppression over 1 year, 5 year, and 20 year time periods. Dependence of use of tenofovir, lamivudine, and dolutegravir on viral load suppression was predicted to lead to reduced overall viral suppression over 1 year and 5 year time periods, although we found little difference in viral suppression over the 20 year time period. Restriction of analysis to the subgroup of people with viral loads greater than 1000 copies per mL and presence of drug mutations to tenofovir and lamivudine at baseline revealed a markedly higher predicted proportion of people with viral load suppression over the 1 year time period for the policy of tenofovir, lamivudine, and dolutegravir for all compared with the other policies, because with this policy a switch was made to tenofovir, lamivudine, and dolutegravir and with the dependence on viral suppression policies no switch was made. This difference persisted with longer follow-up durations but was less marked because of identification of virological failure and switching to zidovudine, lamivudine, and dolutegravir or zidovudine, lamivudine, and a protease inhibitor occurs with the policy of tenofovir, lamivudine, and dolutegravir dependent on viral suppression. Since this subgroup has a tendency for poorer adherence, and with our assumptions about resistance to dolutegravir and the residual activity of tenofovir and lamivudine, the percentage of patients with viral suppression was predicted to remain at less than 60% with all policies, including tenofovir, lamivudine, and dolutegravir for all. Use of tenofovir, lamivudine, and dolutegravir was predicted to lead to more future dolutegravir resistance compared with tenofovir, lamivudine, and dolutegravir dependent on viral suppression (mean 6·7%, 90% range across setting scenarios 1·2–18·5 vs 4·4%, 0·7–12·9% in the context of no dependence on intention to have more children; table 3). In the final year of the 20 year time horizon, the corresponding figures were 9·4% (1·6–26·3) and 7·6% (1·4–21·3; data not shown).

The number of deaths due to AIDS in people on ART showed a similar pattern to overall viral suppression over the 1 year and 5 year time horizons, with AIDS deaths declining with increasing use of tenofovir, lamivudine, and dolutegravir, and at their lowest for the policy of tenofovir, lamivudine, and dolutegravir for all (table 3). Differences between policies in people on ART with viral load suppression translate into substantial differences in AIDS deaths because of the high death rate in those without viral suppression at any point in time. The lower death rate in those without viral suppression in the tenofovir, lamivudine, and dolutegravir for all policy is due to a lower CD4 count, even within the CD4 count less than 200 cells per µL range.
### DALYs averted

|                               | Tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children | Tenofovir, lamivudine, and dolutegravir dependent on intention to have (more) children only | Tenofovir, lamivudine, and dolutegravir dependent on viral suppression only | Tenofovir, lamivudine, and dolutegravir for all |
|-------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|---------------------------------------------|
| **No restriction (base case)** | 22,300 (21,300 to 23,300; 1400 to 53,000)                                                           | 32,800 (31,300 to 34,300; 3900 to 78,200)                             | 39,500 (37,000 to 42,000; 7900 to 87,900)                           | 58,200 (55,700 to 61,300; 11,500 to 138,300) |
|                               | 32,900 (<1%) (31,400 to 34,400; 2700 to 84,200)                                                     | 43,500 (1%) (41,700 to 45,300; 88,000 to 103,100)                    | 60,600 (16%) (58,000 to 63,200; 11,800 to 143,400)                 | 77,700 (83%) (74,700 to 80,700; 20,800 to 177,600) |

### Restrictions to setting scenarios

#### Development of resistance to dolutegravir is 3 times higher

|                               | Tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children |
|-------------------------------|----------------------------------------------------------------------------------------------------------|
| **Toxicity to dolutegravir the same as efavirenz** | 21,800 (19,600 to 24,000; 2800 to 52,300)                                                            |
|                               | 31,600 (28,400 to 34,800; 3200 to 73,500)                                                              |
|                               | 38,800 (35,200 to 42,400; 3600 to 89,700)                                                              |
|                               | 58,400 (52,800 to 64,000; 11,800 to 131,110)                                                           |

#### Potency of dolutegravir

|                               | Tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children |
|-------------------------------|----------------------------------------------------------------------------------------------------------|
| **Potency of dolutegravir 1.0 (equal to efavirenz)** | 16,900 (15,200 to 18,600; -1000 to 40,600)                                                            |
|                               | 23,700 (21,100 to 26,300; -100 to 53,900)                                                              |
|                               | 30,200 (27,500 to 32,900; 4400 to 62,900)                                                              |
|                               | 41,900 (37,800 to 46,000; 2200 to 93,900)                                                              |

#### Pre-ART non-nucleoside reverse transcriptase inhibitor resistance in 2018 >10%

|                               | Tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children |
|-------------------------------|----------------------------------------------------------------------------------------------------------|
| **Pre-ART non-nucleoside reverse transcriptase inhibitor resistance** | 27,900 (26,40 to 29,40; 5100 to 61,400)                                                                |
|                               | 40,400 (38,100 to 42,700; 8600 to 93,800)                                                              |
|                               | 48,800 (46,300 to 51,300; 12,800 to 104,700)                                                            |
|                               | 71,100 (67,700 to 75,100; 19,300 to 157,200)                                                            |
|                               | 41,500 (39,100 to 43,900; 7900 to 97,200)                                                              |
|                               | 54,200 (<1%) (51,500 to 56,900; 14,200 to 118,800)                                                     |
|                               | 76,100 (14%) (72,100 to 80,100; 21,900 to 172,000)                                                     |
|                               | 96,400 (86%) (92,000 to 100,800; 34,500 to 20,300)                                                     |

#### Zero residual activity of tenofovir and lamivudine in the presence of Lys65Arg or Met184Val mutations

|                               | Tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children |
|-------------------------------|----------------------------------------------------------------------------------------------------------|
| **Rate of switch after virological failure 0.05 per 3 months** | 26,600 (20,900 to 32,300; 2500 to 67,900)                                                              |
|                               | 35,300 (32,700 to 38,300; 5300 to 94,800)                                                              |
|                               | 46,700 (43,700 to 50,600; 6300 to 109,500)                                                              |
|                               | 62,700 (59,400 to 66,000; 10,500 to 168,200)                                                            |
|                               | 37,600 (32,600 to 42,800; 2500 to 98,500)                                                              |
|                               | 45,000 (38,500 to 54,200; 108,500 to 172,300)                                                           |
|                               | 68,300 (26%) (54,300 to 82,300; 18,400 to 172,200)                                                     |
|                               | 80,500 (74%) (64,800 to 96,200; 20,290 to 198,394)                                                     |

#### Rate of switch after virological failure 0.05 per 3 months

|                               | Tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children |
|-------------------------------|----------------------------------------------------------------------------------------------------------|
| **Proportion of women giving birth per 3 month period >4%** | 24,700 (22,000 to 27,400; 2580 to 47,300)                                                              |
|                               | 36,600 (32,000 to 40,700; 2200 to 95,600)                                                              |
|                               | 43,500 (41,400 to 47,700; 12,700 to 191,200)                                                            |
|                               | 65,800 (59,000 to 72,600; 11,900 to 160,700)                                                            |
|                               | 35,000 (1%) (31,000 to 39,000; 4900 to 97,500)                                                          |
|                               | 47,000 (0%) (42,000 to 51,600; 11,500 to 106,400)                                                       |
|                               | 64,800 (11%) (58,400 to 71,200; 18,000 to 144,200)                                                      |

#### Proportion of women giving birth per 3 month period >4%

|                               | Tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children |
|-------------------------------|----------------------------------------------------------------------------------------------------------|
| **Proportion of women giving birth per 3 month period >4%** | 21,900 (20,800 to 23,000; 1400 to 52,600)                                                              |
|                               | 32,100 (30,400 to 33,800; 1900 to 79,500)                                                              |
|                               | 38,800 (37,000 to 40,600; 7000 to 87,800)                                                              |
|                               | 56,700 (54,000 to 59,400; 11,308 to 131,110)                                                            |
|                               | 32,500 (<1%) (31,700 to 34,300; 2200 to 84,100)                                                         |
|                               | 42,800 (40,800 to 44,800; 7800 to 97,100)                                                              |
|                               | 59,800 (12%) (56,900 to 63,700; 10,800 to 142,600)                                                     |

#### Net DALYs averted (% of setting scenarios in which policy is the most cost-effective)

|                               | Tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children |
|-------------------------------|----------------------------------------------------------------------------------------------------------|
| **Net DALYs averted** | 32,900 (-1%) (31,400 to 34,400; 2700 to 84,200)                                                         |
|                               | 43,500 (1%) (41,700 to 45,300; 88,000 to 103,100)                                                        |
|                               | 60,600 (16%) (58,000 to 63,200; 11,800 to 143,400)                                                       |
|                               | 77,700 (83%) (74,700 to 80,700; 20,800 to 177,600)                                                      |

*Table 4 continues on next page*
### DALYs averted

|               | Tenovox, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children |
|-------------------------------|--------------------------------------------------------------------------------|
| Risk of neural tube defects with dolutegravir 1% | 22,300 (21,300 to 23,600; 19,200 to 24,900) |
| Risk of neural tube defects with dolutegravir 3% | 22,100 (21,100 to 23,400; 19,000 to 24,700) |
| Viral load testing fully implemented | 19,100 (17,300 to 20,900; 800 to 43,000) |
| Viral load testing not implemented | 19,100 (17,200 to 21,000; 800 to 44,000) |
| Higher background treatment interruption | 20,900 (18,900 to 22,900; 100 to 51,300) |
| HIV prevalence (age 15–49 years) in 2018 | 12,700 (11,500 to 13,900; 19,700 to 27,000) |
| HIV prevalence (age 15–49 years) in 2018 >1% | 3,220 (3,000 to 3,440; 7,800 to 68,400) |
| HIV incidence (age 15–49 years) in 2018 (per 100 person-years) <6 | 12,800 (11,600 to 14,000; 16,600 to 26,800) |
| HIV incidence (age 15–49 years) in 2018 (per 100 person-years) >1 | 3,800 (2,880 to 4,880; 5100 to 68,400) |
| Proportion of HIV-positive people diagnosed in 2018 <75% | 17,700 (15,500 to 19,900; 200 to 41,500) |
| Proportion of HIV-positive people diagnosed in 2018 >80% | 25,400 (23,300 to 27,500; 2000 to 59,900) |
| Proportion of ART-experienced people who started second-line (boosted protease inhibitor) ART in 2018 <1.5% | 19,900 (17,900 to 21,900; 300 to 47,000) |
| Proportion of ART-experienced people who started second-line (boosted protease inhibitor) ART in 2018 >4% | 20,600 (18,800 to 22,400; 1200 to 47,000) |

### Net DALYs averted (% of setting scenarios in which policy is the most cost-effective)

|               | Tenovox, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children |
|-------------------------------|--------------------------------------------------------------------------------|
| Risk of neural tube defects with dolutegravir 1% | 32,900 (<1% (31,300 to 34,500; 2700 to 84,200) |
| Risk of neural tube defects with dolutegravir 3% | 32,700 (<1% (31,200 to 34,700; 2700 to 84,200) |
| Viral load testing fully implemented | 40,700 (0% (27,200 to 44,200; 8400 to 92,300) |
| Viral load testing not implemented | 18,300 (0% (16,300 to 20,600; 2800 to 44,600) |
| Higher background treatment interruption | 27,700 (0% (24,300 to 30,900; 500 to 27,900) |
| HIV prevalence (age 15–49 years) in 2018 | 27,000 (0% (24,300 to 30,900; 500 to 27,900) |
| HIV prevalence (age 15–49 years) in 2018 >1% | 48,400 (0% (45,400 to 51,400; 12,000 to 103,000) |
| HIV incidence (age 15–49 years) in 2018 (per 100 person-years) <6 | 19,400 (0% (17,600 to 21,200; 21,600 to 24,700) |
| HIV incidence (age 15–49 years) in 2018 (per 100 person-years) >1 | 45,000 (0% (42,400 to 48,800; 19,100 to 22,100) |
| Proportion of HIV-positive people diagnosed in 2018 <75% | 22,900 (0% (20,000 to 25,800; 300 to 35,800) |
| Proportion of HIV-positive people diagnosed in 2018 >80% | 39,700 (0% (36,100 to 43,300; 100 to 58,400) |
| Proportion of ART-experienced people who started second-line (boosted protease inhibitor) ART in 2018 <1.5% | 21,300 (<1% (19,100 to 23,500; 16,000 to 23,700) |
| Proportion of ART-experienced people who started second-line (boosted protease inhibitor) ART in 2018 >4% | 44,900 (0% (41,700 to 48,100; 12,100 to 98,800) |

(Continued from previous page)
### DALYs averted

| Tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children | Tenofovir, lamivudine, and dolutegravir dependent on intention to have (more) children only | Tenofovir, lamivudine, and dolutegravir dependent on viral suppression only | Tenofovir, lamivudine, and dolutegravir for all | Tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children | Tenofovir, lamivudine, and dolutegravir dependent on intention to have (more) children only | Tenofovir, lamivudine, and dolutegravir dependent on viral suppression only | Tenofovir, lamivudine, and dolutegravir for all |
|---|---|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | | | |
| Of people on ART, proportion with viral load <1000 copies per ml in 2018 <80% | 32 800 (29 600 to 36 000; 10 400 to 74 000) | 48 400 (43 600 to 53 200; 10 700 to 109 500) | 59 000 (54 000 to 64 000; 17 400 to 129 500) | 87 300 (84 800 to 90 800; 24 300 to 185 900) | 40 900 (39 400; 38 000 to 98 500) | 55 400 (50 000 to 60 800; 72 200 to 122 900) | 77 500 (70 900 to 87 100; 18 200 to 185 700) | 101 400 (98 400 to 104 400; 31 000 to 218 800) |
| Of people on ART, proportion with viral load <1000 copies per ml in 2018 >88% | 13 700 (12 400 to 15 000; 1600 to 30 900) | 17 600 (15 800 to 19 400; 1800 to 40 600) | 23 600 (21 600 to 25 600; 1900 to 51 100) | 30 000 (27 200 to 32 800; 13 000 to 67 800) | 27 300 (24 700 to 29 900; 22 000 to 61 300) | 32 200 (29 500 to 34 900; 68 000 to 69 100) | 48 900 (44 800 to 53 000; 11 000 to 211 200) | 56 100 (51 800 to 60 400; 14 500 to 120 100) |
| Cost-effectiveness threshold US$200 | 22 300 (21 300 to 23 300; 1400 to $3 000) | 32 800 (31 300 to 34 300; 3900 to 78 200) | 39 500 (37 000 to 42 000; 7900 to 87 900) | 58 200 (55 700 to 61 300; 11 500 to 138 300) | 48 700 (<1%; 45 900 to $5 100; 100 to 107 200) | 59 400 (56 500 to 62 600; 84 000 to 156 900) | 92 200 (21%; 87 300 to 97 300; 12 600 to 252 200) | 106 900 (78%; 101 900 to 111 900; 20 700 to 270 100) |
| Cost-effectiveness threshold US$1000 | 22 300 (21 300 to 23 300; 1400 to $3 000) | 32 800 (31 300 to 34 300; 3900 to 78 200) | 39 500 (37 000 to 42 000; 7900 to 87 900) | 58 200 (55 700 to 61 300; 11 500 to 138 300) | 27 600 (<1%; 26 300 to 28 900; 3100 to 66 000) | 38 200 (1%; 36 800 to 39 800; 7 200 to 87 300) | 50 100 (14%; 48 100 to $5 200; 12 600 to 211 600) | 67 900 (85%; 64 300 to 70 200; 18 800 to 152 200) |
| Additional sensitivity analyses | | | | | | | | |
| Tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children | 21 700 (18 700 to 24 700; 4800 to 49 700) | 31 300 (26 300 to 36 300; 2600 to 69 000) | 38 600 (33 800 to 43 400; 6 700 to 73 700) | 55 300 (47 100 to 63 500; 13 500 to 222 600) | 31 800 (0%; 27 500 to 36 100; 5 000 to 72 400) | 41 500 (0%; 36 300 to 46 700; 15 200 to 85 700) | 58 700 (0%; 53 800 to 61 600; 16 200 to 134 900) | 74 900 (0%; 68 300 to 83 500; 23 500 to 158 700) |
| Tenofovir, lamivudine, and dolutegravir dependent on intention to have (more) children only | 32 800 (31 300 to 34 300; 3900 to 78 200) | 39 500 (37 000 to 42 000; 7900 to 87 900) | 58 200 (55 700 to 61 300; 11 500 to 138 300) | 33 900 (0%; 30 500 to 37 300; 3900 to 81 200) | 43 700 (0%; 39 900 to 47 500; 11 400 to 90 000) | 62 300 (20%; 66 600 to 68 000; 14 400 to 128 900) | 76 900 (80%; 70 400 to 83 400; 22 500 to 159 100) |
| Tenofovir, lamivudine, and dolutegravir dependent on viral suppression only | 36 400 (33 400 to 39 400; 8800 to 79 600) | 54 000 (49 200 to 54 800; 9 100 to 123 900) | 30 800 (0%; 27 900 to 33 700; 4500 to 68 900) | 40 700 (0%; 37 400 to 44 000; 9 050 to 88 500) | 58 300 (15%; 53 600 to 65 000; 14 300 to 219 800) | 75 600 (85%; 70 100 to 81 100; 23 600 to 260 800) | (Table 4 continues on next page) |
The predicted proportion of HIV-positive women for whom mother-to-child transmission occurs also followed this pattern. The reduction in risk of mother-to-child transmission with the tenofovir, lamivudine, and dolutegravir for all policy was greater in absolute terms than the increased risk of neural tube defects with the same policy (table 3).

There were substantially more DALYs averted with the tenofovir, lamivudine, and dolutegravir for all policy than for any of the policies in which tenofovir, lamivudine, and dolutegravir use was dependent on viral suppression or intention to have no (more) children. The lowest cost was for the tenofovir, lamivudine, and dolutegravir for all and tenofovir, lamivudine, and dolutegravir dependent on viral suppression only policies (figure). For net DALYs, the benefit of the tenofovir, lamivudine, and dolutegravir for all policy was greater still, reflecting the health gains elsewhere due to the lower costs, mainly because of reduced use of protease inhibitors, which are more than 7 times the cost of dolutegravir. The policy of tenofovir, lamivudine, and dolutegravir for all was the most cost-effective in 83% of setting scenarios, with tenofovir, lamivudine, and dolutegravir dependent on viral suppression only and tenofovir, lamivudine, and dolutegravir dependent on intention to have (more) children only being cost-effective in 16% of setting scenarios. Tenofovir, lamivudine, and dolutegravir dependent on intention to have (more) children only was cost-effective in less than 1% of setting scenarios (table 4). Tenofovir, lamivudine, and efavirenz were not cost-effective in any setting scenario.

**Table 4: Sensitivity analyses**

| Atazanavir resistance rate 3 times lower | 50 year time horizon |
|-----------------------------------------|----------------------|
| Tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children only | 50 year time horizon |
| 22 600 (18 600 to 26 600; 4200 to 60 800) | 49 000 (41 800 to 56 200; 700 to 136 000) |
| 37 500 (26 600 to 39 600; 7500 to 85 700) | 60 000 (50 800 to 69 200; 15 800 to 17 800) |
| 27 500 (19 900 to 43 300; 7300 to 86 400) | 84 200 (72 800 to 95 600; 9800 to 218 700) |
| 56 600 (46 400 to 66 800; 17 000 to 128 000) | 92 200 (79 500 to 106 900; 8800 to 269 300) |
| 34 600 (28 200 to 41 000; 6600 to 78 900) | 57 800 (50 400 to 65 200; 1800 to 127 900) |
| 45 700 (38 100 to 53 300; 12 200 to 107 300) | 69 100 (60 600 to 77 600; 4200 to 161 500) |
| 60 400 (49 800 to 71 000; 13 100 to 130 300) | 99 800 (88 600 to 111 000; 15 500 to 211 200) |
| 78 200 (66 200 to 90 200; 23 900 to 150 000) | 107 200 (94 600 to 119 800; 12 600 to 242 200) |

Table 4: Sensitivity analyses

Values are DALYs and net DALYs averted compared with the policy of tenofovir, lamivudine, and efavirenz for all (95% CI; 90% range, reflecting variation across setting scenarios), unless otherwise indicated. DALY=disability adjusted life-year. ART=antiretroviral therapy. *Tenofovir, lamivudine, and efavirenz for all policy was the most cost-effective policy in 0% of all setting scenarios. †Disability weight for child living with neural tube defect is 0.5, cost is US$5000 in the first year (cost of surgery) and $1000 per year (cost of ongoing care and support) thereafter.

**Discussion**

Supporting earlier work,31 we found that the benefits of a policy using tenofovir, lamivudine, and dolutegravir in people currently on first-line or second-line regimens, without any dependence on viral load or consideration of use of zidovudine rather than tenofovir, outweighed the risks. We also found that there were substantial net public health benefits of use of tenofovir, lamivudine, and dolutegravir, including in women of child-bearing age, in terms of DALYs incurred in the whole population, and considering DALYs incurred as a result of birth of a child with a neural tube defect.

The benefits of the policy of tenofovir, lamivudine, and dolutegravir for all compared with tenofovir, lamivudine, and dolutegravir dependent on viral suppression are due to proactive use of dolutegravir without requiring a viral load measure or a switch algorithm to have been fulfilled. Even in the subgroup of people with viral load greater than 1000 copies per mL and presence of drug mutations to tenofovir and lamivudine at baseline, switching to tenofovir, lamivudine, and dolutegravir was predicted to bring benefits compared with the policies of tenofovir, lamivudine, and dolutegravir dependent on viral suppression, as members of this subgroup must await fulfilment of the viral load failure criteria and subsequent switch to zidovudine, lamivudine, and dolutegravir. These benefits occur despite the fact that with the tenofovir, lamivudine, and dolutegravir for all policy than for any of the policies in which tenofovir, lamivudine, and dolutegravir use was dependent on viral suppression or intention to have no (more) children. The lowest cost was for the tenofovir, lamivudine, and dolutegravir for all and tenofovir, lamivudine, and dolutegravir dependent on viral suppression only policies (figure). For net DALYs, the benefit of the tenofovir, lamivudine, and dolutegravir for all policy was greater still, reflecting the health gains elsewhere due to the lower costs, mainly because of reduced use of protease inhibitors, which are more than 7 times the cost of dolutegravir. The policy of tenofovir, lamivudine, and dolutegravir for all was the most cost-effective in 83% of setting scenarios, with tenofovir, lamivudine, and dolutegravir dependent on viral suppression only and tenofovir, lamivudine, and dolutegravir dependent on intention to have (more) children only being cost-effective in 16% of setting scenarios. Tenofovir, lamivudine, and dolutegravir dependent on intention to have (more) children only was cost-effective in 1% of setting scenarios and tenofovir, lamivudine, and dolutegravir dependent on viral suppression and intention to have (more) children was cost-effective in less than 1% of setting scenarios (table 4). Tenofovir, lamivudine, and efavirenz were not cost-effective in any setting scenario.

Tenofovir, lamivudine, and dolutegravir for all remained the most effective and cost-effective policy in several sensitivity analyses (table 4).
period under the policy of tenofovir, lamivudine, and dolutegravir for all compared with 4·4% under the policy of tenofovir, lamivudine, and dolutegravir dependent on viral suppression only. Our findings were consistent in several sensitivity analyses, including one in which we assumed that lamivudine and tenofovir had no effect on viral replication in the presence of the Met184Val and Lys65Arg mutations, and one over a 50 year time horizon.

More children are predicted to be prevented from acquiring HIV through mother-to-child transmission than are born with neural tube defects with a tenofovir, lamivudine, and dolutegravir for all policy. When calculating DALYs in children born with HIV, we assumed availability of good HIV diagnosis and treatment services in infants meaning less poor consequences for an HIV infection in a child (0·1 DALYs per year) than for a child born with a neural tube defect (1 DALY per year). Without such good availability of diagnosis and treatment services, the DALY consequences of a child born with HIV would be worse and the benefits of a policy of tenofovir, lamivudine, and dolutegravir for all greater.

Our study has limitations. As for any cost-effectiveness analysis over a long time horizon, we relied on a model for predictions of the long-term effect of the alternative policies. We made assumptions about the benefits and harms associated with different ART regimens on the basis of available data, which included different levels of uncertainty. The reports of neural tube defects in infants born to women using dolutegravir are the first indication of this risk and planned further follow-up of women who have been similarly exposed could reduce uncertainty over this risk. This situation emphasises that studies of novel drugs during the development phase and beyond—including in women before conception, during pregnancy, and postpartum—are crucial to support future decision making. Evidence of the antiretroviral effects of dolutegravir is more extensive, including recent data from a randomised trial in Cameroon.17 Our results are robust to modifications in assumptions within plausible levels of uncertainty, which supports our main conclusions. We recognise that our assumption that women can access contraception from the time of intention to have no (more) children does not reflect reality in many settings, and partly accounted for this by considering both an 80% and 50% effectiveness of contraception. We did not consider a policy option in which women could move between efavirenz and dolutegravir between pregnancies because we considered that this would be unrealistic to implement.

Our results could be used to inform relevant constituencies about the risks and benefits of alternative dolutegravir-containing ART regimen policy options, and to help gain an informed representative view from people with HIV that can be considered during development of ministry of health policies. If ministries of health decide to give dolutegravir to women who might become pregnant without adequate consultation and it then becomes clear that there is a real risk of neural tube defects, this could undermine confidence in treatment and in the ministry of health, although the extent to which ART uptake could be affected is difficult to quantify. However, we recognise that there will be substantial challenges in achieving such effective consultation.

In conclusion, the benefits of transition to tenofovir, lamivudine, and dolutegravir for all substantially outweighed any risks when using a standard DALY framework to compare health outcomes from a public health perspective.

Contributors
All authors conceptualised the analysis, had substantial input into the modelling plan and advised on relevant data, interpreted the results, and made comments on the manuscript drafts. AP, VC, FN, and LB-M wrote and executed the modelling program. ANP was the overall study lead.

Declaration of interests
DK is a consultant to ViIV Healthcare, Gilead Sciences, and Merck, and reports research funding from all three companies, and Janssen and AbbVie. JM reports grant support from the Bill & Melinda Gates Foundation, USAID, Brigham Women’s Hospital/AIDS Clinical Trials Group (ACTG) to the University of Pittsburgh Virology Support Laboratory, Janssen Pharmaceuticals, and Gilead Sciences, personal fees from University of Pittsburgh and Gilead Sciences, and share options in Co-Crystal Pharma, Inc. FV reports grants, personal fees and non-financial support from Viiv Healthcare and Gilead Sciences, personal fees and non-financial support from Mylan and Roche, personal fees from Adcock Ingram, Aspen Healthcare, J&J, and Merck, and grants from the Bill and Melinda Gates Foundation, Unitaid, USAID, and South African MRC, outside the submitted work. AP is a member of advisory boards for Gilead Sciences, Viiv Healthcare, Merck, and Janssen, has spoken at non-commercial symposia funded by Gilead Sciences, Viiv Healthcare, Merck, and Janssen, and is chair of the antiretrovirals section of the European AIDS Clinical Society guidelines. ADL reports research grants from Viiv Healthcare, Merck, and Gilead Sciences (Fellowship programme), and paid consultancies with Viiv Healthcare, Merck, Janssen, and AbbVie, and Gilead Sciences. AW reports being on advisory boards for and grants from Janssen, Merck, Gilead Sciences, Viiv Healthcare, and CJI; AC reports institutional unrestricted educational grants from Viiv Healthcare, AbbVie, BMS, MSD, and Gilead Sciences. All other authors declare no competing interests.

Data sharing
Model programs and simulations are accessible in Figshare.

Acknowledgments
We thank Elliot Raizes, Marco Vitoria, Nathan Ford, Meg Doherty, George Silberry, David Ripin, Lisa Nelson, Juliana da Silva, Carolyn Amole, Geoff Garnett, and Peter Ehrenkranz for their helpful advice. Our computing resource was legion@ucl. JD1 is supported by Danish National Research Foundation. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the authors’ institutions.

References
1 Gupta RK, Gregson J, Parkin N, et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. Lancet Infect Dis 2018; 18: 346–55.
2 Medicins Sans Frontieres. Making viral load routine. Successes and challenges in the implementation of routine HIV viral load monitoring, 2016. https://www.msf.org/sites/msf.org/files/making_viral_load_routine_part_1_programmatic_strategies.pdf (accessed Nov 1, 2018).
Articles

3 Haas AD, Keiser O, Balestre E, et al. Monitoring and switching of first-line antiretroviral therapy in adult treatment cohorts in sub-Saharan Africa: collaborative analysis. Lancet HIV 2015; 2: e271–78.

4 WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. 2nd edn. Geneva: World Health Organization, 2016.

5 WHO. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV. July, 2018. Geneva: World Health Organization, 2018.

6 Walsmey SL, Antela A, Clameck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med 2013; 369: 1807–18.

7 Wainberg MA, Han YS. Will drug resistance against dolutegravir in adult therapy ever occur? Front Pharmacol 2015; 6: 14.

8 Aboud M, Kaplan R, Lombarda J, et al. Superior efficacy of dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) compared with lopinavir/ritonavir (LPV/RTV) plus 2 NRTIs in second-line treatment: interim data from the DAWNING study. IAS 2017; Paris, France; July 23–16, 2017.

9 Zash R, Holmes L, Makhema J, et al. Surveillance for neural tube defects following antiretroviral exposure from conception. IAS 2018; Amsterdam, Netherlands; July 23–27, 2018.

10 Phillips AN, Cambiano V, Nakagawa F, et al. Cost-effectiveness of public-health policy options in the presence of pretreatment NNRTI drug resistance in sub-Saharan Africa: a modelling study. Lancet HIV 2018; 5: e146–54.

11 Philips A, Shouval A, Vojnov L, et al. Sustainable HIV treatment in Africa through viral-load-informed differentiated care. Nature 2015; 528: 568–76.

12 Xu HT, Martinez-Cajas JL, Ntemgwa ML, et al. Effects of the K65R and K65R/M184V reverse transcriptase mutations in subtype C HIV on enzyme function and drug resistance. Retrovirology 2009; 6: 14.

13 Castagna A, Danise A, Menzo S, et al. Lamivudine monotherapy in HIV-1-infected patients harbouring a lamivudine-resistant virus: a randomized pilot study (E-184V study). AIDS 2006; 20: 795–803.

14 Zimbabwe National Statistics Agency, The DHS Program, ICF International. Zimbabwe Demographic and Health Survey 2015. Key Indicators. May, 2016. Rockville, MD: Zimbabwe National Statistics Agency (ZIMSTAT) and ICF International, 2016.

15 National Statistical Office Malawi, The DHS Program ICF, Malawi Demographic and Health Survey 2015–16. Zomba and Rockville, MD: National Statistical Office Malawi and ICF International, 2017.

16 Walsmey S, Baumgarten A, Berenguer J, et al. Brief report: dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral-therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. J Acquir Immune Defic Syndr 2015; 70: S15–19.

17 Lanzafame M, Gibellini D, Lattuada E, et al. Dolutegravir monotherapy in HIV-infected naive patients with <100 000 copies/mL HIV RNA load. J Antimicrob Chemother 2016; 72: e12–14.

18 van Lunzen J, Maggiolo F, Arribas JR, et al. Once-daily dolutegravir (S/GSK149572) in combination therapy in antiretroviral-naïve adults with HIV: planned interim 48-week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. Lancet Infect Dis 2012; 12: 111–18.

19 Braun DL, Turk T, Hampel B, et al. Simplification to dolutegravir monotherapy is non-inferior compared to continuation of combination antiretroviral therapy during primary HIV infection: a randomized, controlled, non-inferiority trial. IAS 2018; Amsterdam, Netherlands; July 23–27, 2018.

20 Hoqueuleux L, Allavena C, Pranuck T, et al. Dolutegravir monotherapy versus dolutegravir/abacavir/lamivudine for HIV-1-infected virologically suppressed patients: results from the randomized non-inferiority MONCAT trial. IAS 2018; Amsterdam, Netherlands; July 23–27, 2018.

21 Marcellin A, Grude G, Charpentier C, et al. French survey, resistance to integrase inhibitors shows differences of resistance selection in virological failure in care. HIV Glasgow 2016; Glasgow, Scotland; Oct 23–26, 2016. Abstr 332.

22 Bachelet LT, Anton ED, Kudish P, et al. Human immunodeficiency virus type 1 mutations selected in patients failing efavirenz combination therapy. Antimicrob Agents Chemother 2000; 44: 2475–84.

23 Cuzin L. Integrase inhibitors and neuropsychiatric adverse events in a large prospective cohort. IAS 2018; Amsterdam, Netherlands; July 23–27, 2018.

24 Kim AA, Mukui I, Young PW, et al. Undisclosed HIV infection and antiretroviral therapy use in the Kenya AIDS indicator survey 2012: relevance to national targets for HIV diagnosis and treatment. AIDS 2016; 30: 2685–95.

25 Ministry of Health, Malawi, HIV/AIDS Department. Quarterly Reports. https://www.hiv.health.gov.mw/cha_starpository/file. php/186/186.pdf (accessed Nov 23, 2018).

26 WHO, CDC. The Global Fund. HIV drug resistance report 2017. Geneva: World Health Organization, 2017.

27 UNAIDS. 2015 progress report on the Global Plan towards the elimination of new HIV infections among children and keeping their mothers alive. Geneva: Joint United Nations Programme on HIV/AIDS, 2015. http://www.unaids.org/sites/default/files/media_asset/2211ProgressReport_GlobalPlan_en.pdf (accessed Nov 1, 2018).

28 Claxton K, Walker S, Palmer S, Sculpher M. Appropriate perspectives for health care decisions. Centre for Health Economics, University of York. 2010. https://ideas.repec.org/p/chy/respap/54cherp.html (accessed Nov 1, 2018).

29 Woods B, Revill P, Sculpher M, Claxton K. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. March, 2015. https://www.york.ac.uk/media/che/documents/papers/researchpapers/CHERP109_cost-effectiveness_threshold_LMICs.pdf (accessed Nov 1, 2018).

30 The Global Fund. Pooled procurement mechanism reference pricing. July 2, 2018. https://www.theglobalfund.org/media/5813/ppn_arvreferencing_table_en.pdf (accessed Nov 1, 2018).

31 Phillips A, Venter F, Apollo T, et al Cost-effectiveness of the introduction of dolutegravir in first or second-line ART regimens in sub-Saharan Africa. IAS 2017; Paris, France; July 23–16, 2017.

32 Courmi A, Koutanfack C, Eynard-Duverney S, et al. Dolutegravir versus an efavirenz 400 mg-based regimen for the initial treatment of HIV-infected patients in Cameroon: 48-week efficacy results of the NAMSAL ANRS 12313 trial HIV Glasgow 2018; Glasgow, Scotland; Oct 28–31, 2018. Abstr O342.