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

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Word count: 3477

**Summary**

**Background:** The integrase inhibitor dolutegravir is expected to have a role in future ART regimens in sub-Saharan Africa due to its high potency and barrier to resistance, good tolerability, and low cost but there is uncertainty over appropriate policies for its use relating to potential for drug resistance spread and a possible increased risk of neural tube defects (NTD) if used in women at time of conception. We aimed to synthesize data with use of a model in order to assess the effectiveness and cost effectiveness of alternative policies.

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

**Findings:**  The greatest number of DALYs is predicted to be averted with use of a policy in which TLD is used in all people on ART, including switching to TLD in those currently on ART, regardless of current viral load suppression and of intention to have (more) children. This result held in a range of sensitivity analyses. The policy is predicted to be cost-saving.

**Interpretation:** Using a standard DALY framework for comparing health outcomes from a public health perspective the benefits of transition to TLD for all substantially outweigh the risks.

**Funding:** Bill & Melinda Gates Foundation.

**Research in Context**

**Evidence before this study**

The integrase inhibitor dolutegravir is expected to have a role in future ART regimens in sub-Saharan Africa due to its high potency and barrier to resistance, good tolerability, and low cost. However, it is uncertain which policy for use of the drug will produce the greatest population health benefits. This is due to considerations over potential for virologic failure and drug resistance spread if it is used with nucleoside reverse transcriptase inhibitors to which the virus is resistant, and that a possible association between dolutegravir and an increased risk of neural tube defects if used in women at conception has recently been identified. We searched Web of Knowledge using the search terms “dolutegravir” and model\* on 14 August 2018 and identified 74 papers. Review of these papers did not reveal any that have 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 account of the effects of drug resistance and drug potency in determining viral load and clinical treatment outcomes, as well as the effect of a potential raised risk of neural tube defects if dolutegravir is taken at conception. We considered policies of using a regimen containing tenofovir-lamivudine-dolutegravir (TLD) for all people on ART, or of making TLD dependent on viral load suppression (whether on 1st or second-line ART) and / or, for women, intention to have (more) children.

**Implications of all the available evidence**

Using a standard disability adjusted life year (DALY) framework for comparing health outcomes from a public health perspective we found that the benefits of transition to a regimen of TLD for all people on ART, without dependence on viral suppression or intention to have (more) children, substantially outweigh the risks. This evaluation provides quantitative assessment to guide policy formulation by Ministries of Health on the use of dolutegravir .

**Introduction**

The scaling up of ART in sub-Saharan Africa represents a major achievement, but there are ongoing challenges, including growing levels of transmitted drug resistance1, low coverage of viral load monitoring2, and low rates of switching to second-line regimens in those who have fulfilled criteria for failure of first-line ART3.

Until recently, the WHO has recommended a sequence of first and second-line regimens of tenofovir disoproxil fumarate(tenofovir)-lamivudine (or emtricitabine)-efavirenz (TLE) first-line and zidovudine-lamivudine-protease inhibitor (ZL-PI) as second-line in people with first-line failure based on elevated viral load4. However, in recently issued guidance there is now a recommendation for use of the integrase inhibitor dolutegravir with tenofovir-lamivudine (TLD) in people initiating ART and, potentially, in those currently on first-line ART if they have a recent viral load measurement below 1000 copies/mL5. In people virologically failing TLE, the recommendation is for dolutegravir in the context of an optimized nucleoside reverse transcriptase inhibitor background as second-line regimen, which most often will mean zidovudine-lamivudine-dolutegravir (ZLD). Dolutegravir has been shown to lead to lower rates of switching and to be much less susceptible to the development of significant drug resistance mutations compared with efavirenz-based regimens6,7 . . It has also been shown to lead to 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 8. An alternative to this approach to dolutegravir use is simply to transition all people on ART to TLD, unless and until there is sustained virological failure identified on TLD, at which point ZL-PI would be used. Since access to viral load testing remains limited in many countries this approach has the potential to bring a greater public health benefit. However, these benefits must be balanced against concerns over possible increased risk of drug 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.

Further, a recent report suggested that dolutegravir could be a cause of neural tube defects (NTD) in children of a small proportion of women who are taking dolutegravir at the time of conception; there have been 4 incidences of NTDs in 596 pregnancies, which is significantly above the background rate for efavirenz-based regimens9. This report has raised questions over the use of dolutegravir in women of child-bearing age. Restriction of use of dolutegravir in women of child-bearing age has a public health cost which policy makers must weigh against the possible NTD risk with the drug.

Here we use an existing individual-based model of HIV transmission, progression and the effect of ART to help inform policymakers on approaches to use of dolutegravir which are likely to lead to the highest population health gain. The intent is that this evaluation provides 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 servce

**Methods**

*Model Description*

We use the HIV Synthesis Model, 10. Full details of the model can be accessed in the Appendix. In brief, the model (programmed in SAS 9.4) generates a population of individuals who are individually tracked, with updates 3 monthly, for risk of HIV acquisition. Those who acquire HIV are tracked in terms of their viral load, CD4 count, occurrence of WHO stage 3 and 4 conditions, use of specific drugs, presence of resistance mutations, adherence and drug toxicities. The on-going effects of a drug regimen (on viral load, drug resistance and CD4 count, and hence risk of AIDS/death) are dependent on the sum of the current activity levels of each drug in the regimen, accounting for presence of drug resistance mutations, drug potency and the current level of adherence.

*Ethical Considerations*

This work was not submitted for Ethics Committee review as it does not involve research on human subjects.

*Setting-scenarios*

The model is based on southern Africa with 1000 potential *setting-scenarios* generated through simulation. Parameters such as the rate of HIV testing, the distribution of ART adherence across individuals, the ART interruption, the rate of switch after first-line failure, and the ability to measure viral load (VL) as indicated11 were varied randomly within plausible bounds for settings in the region.

For each setting-scenario, we consider the situation in 2018 and compare outcomes of potential regimen policies over a 20 year time horizon (50 year in sensitivity analysis). The regimen policies considered and the short names we use for them are described in Table 1. Our reference regimen policy is continuation of the current approach of use of TLE in first-line regimens. We also consider four further policies, involving of use of TLD. These policies consider TLD use with and without dependence on the intention to have (more) children and/or on current viral load suppression being documented. The rationale for restriction of TLD’s use to those with viral suppression is concern that in those with virologic failure resistance to tenofovir as well as lamivudine is likely to have developed, making dolutegravir the only fully active drug, under which conditions the risk of resistance to dolutegravir arising is increased. The extent of any residual effects on viral replication due to continued taking of lamivudine and tenofovir in these circumstances is uncertain12,13. The policies involving TLD *dependent 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 guidance5. We refer throughout to use of lamivudine (3TC) in regimens, but it is recognised that it may be that emtricitabine (FTC) is used. The dependence on women’s intention to have (more) children relates to concern over risk of a child with NTD if dolutegravir is used at the time of conception. Policies with this dependence are envisaged as offering dolutegravir to women only upon reaching the point of intending to have no more children. We assume a rate of reaching a point of intending to have no more children to be 0.005 per three months from age 25. This results in 16% of women age 15-55 not intending to have (more) children, which is broadly consistent with data from Demographic and Health Surveys14,15. We assume that women who intend to have no more children are able to have access to and use contraception, and that the contraception efficacy is 80% (50% in sensitivity analysis). The policy for which TLD use is dependent on neither on viral suppression or intention to have more children is referred to as *TLD for all*.

Assumptions for resistance acquisition with dolutegravir-containing regimens are informed by data on the risk of resistance mutations existing at virologic failure, and studies of monotherapy, which were mainly conducted in people with existing viral suppression but include a small study of dolutegravir monotherapy in ART naïve people with viral load < 100,000 copies/mL 6,7,16-22. We infer a 13 times lower rate of dolutegravir resistance than for efavirenz. Dolutegravir has also been generally found to be associated with lower risk of toxicity than both efavirenzand protease inhibitors which results in a lower rate of discontinuation6,16, 19, 23. We assume that the risk of neurologic toxicity with dolutegravir is half that of efavirenz. We made the assumption that dolutegravir has 1.5-fold higher potency than efavirenz (lower than boosted PIs, which are assumed to have potency of 2), consistent with its effect as monotherapy, albeit that this is insufficient for its clinical use as monotherapy. We assume that the residual effects of tenofovir and lamivudine in the presence of the K65R and M184V mutations, respectively, mean that they each have 0.25 times full drug activity in this situation12,13. Our main results are presented as the mean and mean difference compared with policy of *TLE for all,* with a 90% range reflecting variation across setting-scenarios and 95% confidence interval reflecting stochastic simulation variability

Although these formed our base assumptions, we considered the possibility of different assumptions for dolutegravir in a proportion of our 1000 setting-scenarios, i.e. that potency of dolutegravir could be instead 1-fold, 1.25-fold or 2- fold (20%, 20% and 5% of setting-scenarios respectively, 55% 1.5 fold); that the rate of resistance development to dolutegravir could be only 4 times lower than for efavirenz (20% of setting-scenarios), that the risk of neurologic toxicity using dolutegravir could be equal to that of efavirenz (20% of setting-scenarios), the residual effects of tenofovir and lamivudine in the presence of the K65R and M184V mutations is 0.0 rather than 0.25 active drugs (20% of setting-scenarios in each case). These probabilities for alternative assumptions were selected based on the perceived probability that they hold. We also considered different degrees to which viral load monitoring is 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 recommended monitoring strategy) and that switching in regimen is done after viral failure has been determined (probabilities of 0.05, 0.20 and 0.50 per 3 months, in 30%, 50% and 20% of setting-scenarios, respectively). These alternative assumptions were determined by random independent sampling for each setting-scenario. Full details of the distribution of all sampled parameters used in deriving our 1000 setting-scenarios is shown in Table S10 of the Appendix (page 29). Excess risk of NTD in women on dolutegravir at the time of pregnancy is assumed to be 0.58% (4/596 = 0.67% minus the background rate in HIV negative women, 0.09%); a sensitivity analyses was conducted using a value of 1.0%.

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

*Outcomes*

Our primary measure of health outcome is the disability adjusted life year (DALY). While we explicitly model the individual life courses of adults only, we consider the DALY effects of NTDs and of mother to child transmission. We estimate the aggregate effects alternative policies have on population burden of disease by calculating net DALYs; which is the DALYs averted by a policy less the health opportunity costs imposed as a result of costs incurred. The health opportunity costs are calculated using a cost-effectiveness threshold (CET) for a country representing the health gains that could be generated by alternative uses of resources24. The threshold for a country is not readily apparent, but $500 per DALY averted is likely to be at the upper end based upon evidence of how resources would otherwise be employed25 and we adopt this value. Net DALYs are calculated as DALYs + Costs/CET. Absolute numbers of health-related events, costs, DALYs and net DALYs that we report are relevant for a country of population size of approximately 10 million adults in 2018. The analysis is conducted from a healthcare perspective. Future costs and health outcomes are both discounted to present $ values at 3% per annum. The cost of TLD and TLE are assumed $75 per year, ZL-PI (atazanavir) $26526. Full details of unit costs and disability weights are provided in the Appendix.

For a woman having a baby with an NTD, and since the baby is assumed to die, an extra DALY is incurred for each subsequent year of the time horizon (i.e. years lost to a child’s life are valued the same as years lost to an adult’s life). No additional costs are assumed (except in a sensitivity analysis). Also, dependent on an HIV positive woman's viral load at birth, birth of an infected child can occur. It is assumed that an HIV infected child will access ART and we include an additional 0.1 DALYs and a cost of $160 per year are incurred for each subsequent year of the time horizon .

*Role of the Funding Source*

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

The consequences of the various regimen policies for the use of each drug is shown in Table 3 indicating, for example, that 98% of people on average over 20 years would be expected to be on dolutegravir with the policy of *TLD for all,* compared with only 43% if its use is dependent on viral load suppression and being male or a woman not intending to have (more) children.

The impact on viral load suppression levels in people on ART is shown over a mean of 1, 5 and 20 years (Table 3). Restriction of TLD use in women who intend to have (more) children is predicted to lead to poorer overall viral suppression levels over 1, 5 and 20 year time periods. Dependence of use of TLD on viral load suppression is predicted to lead to lower overall levels of viral suppression over a 1 and 5 year time period, although there is little difference over a 20 year time period. Restricting attention to the group with viral load above 1000 copies/mL and presence of drug mutations to tenofovir and lamivudine at baseline, there is a markedly higher predicted proportion with viral load suppression over 1 year with the policy of *TLD for all* compared with the other policies. This is because with this policy a switch is made to TLD while with the dependence on viral suppression it is not. This difference persists with longer follow-up but is less marked as identification of virologic failure and switching to ZLD or ZL-PI occurs with the policy of TLD dependent on viral suppression. Since this is a selected group with a tendency for poorer adherence, and with our assumptions around the rate of resistance to dolutegravir and the residual activity of tenofovir and lamivudine, the percent with viral suppression in this group is predicted to remain below 60% with all policies, including *TLD for all*. Use of *TLD for all* leads to higher predicted future levels of dolutegravir resistance compared with TLD dependent on viral suppression (mean of 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 intending to have more children). 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%).

Rates of AIDS death in people on ART follow a similar pattern to the overall viral suppression over 1 and 5 years, with AIDS death rates declining with increasing use of TLD, and lowest for the policy of *TLD for all*. Differences between policies in the proportion of people on ART with viral load suppression translate into substantial differences in AIDS death rate in people on ART, due to the relatively high death rate in those without viral suppression at any point in time. The lower death rate in those without viral suppression in the *TLD for all* policy is likely due to there being a lower CD4 count, even within the CD4 count < 200 cells per µL range.

The predicted proportion of HIV positive women for which mother to child transmission occurs also follows this pattern. The reduction in risk of MTCT with the TLD policy is greater in absolute terms than the increased risk of neural tube defect with the TLD policy.

There are substantially more DALYs averted with the policy of *TLD for all* than any of the policies in which TLD use is dependent on viral suppression and / or not intending to have (more) children. The lowest cost is with the policies of *TLD for all* or *TLD dependent on viral suppression only* ( illustrated in Figure 1). In terms of net DALYs, the benefit of the *TLD for all* policy is greater still, reflecting the health gains elsewhere resulting from the lower costs, mainly as a result of lower use of protease inhibitors which are over seven times the cost of dolutegravir. The policy of *TLD for all* was the most cost effective policy in 83% of setting-scenarios, with *TLD dependent on viral suppression only* being the most cost effective in 16% settings scenarios, *TLD dependent on intention to have (more) children only* was cost effective in 0.8% and *TLD dependent on viral suppression and intention to have (more) children* in 0.2%. The policy of *TLE for all* was not cost effective in any setting-scenario.

The *TLD for all* policy remained the most effective and cost effective in a range of sensitivity analyses (Table 4).

**Discussion**

Building on earlier work32, we found that the benefits of a policy of using TLD in people currently on first or second-line regimens, without any dependence on viral load or consideration of use of zidovudine rather than tenofovir, outweigh the risks. We also found that, in terms of DALYs incurred in the whole population, including consideration of DALYs incurred as a result of birth of a child with an NTD, there are substantial net public health benefits of use of TLD, including in women of child-bearing age.

The benefits of the policy of *TLD for all* compared with TLD *dependent on viral suppression* are due to pro-active use of dolutegravir without requiring a viral load measure or a switch algorithm to have been fulfilled. Even in the sub-group of people with viral load above 1000 copies/mL and presence of drug mutations to tenofovir and lamivudine at baseline, switching to TLD is predicted to bring benefits compared with the policies with TLD *dependent on viral suppression*, under which this group continue to await fulfilment of the viral load failure criteria and subsequent switch to ZLD. This is despite that, with the *TLD for all* policy, the proportion of this group on ART with viral suppression over 1, 5 and 20 years is predicted to be relatively low (55% on average over 5 years), due both to the higher tendency for poor adherence in this group and the potential for dolutegravir resistance to emerge. Overall, dolutegravir resistance (transmitted or acquired) is predicted to be present in 6.7% of people over 20 years under the policy of *TLD for all* compared with 4.4% under the policy of *TLD dependent on viral suppression only*. Our findings held in a range of sensitivity analyses, including one in which we assume that lamivudine and tenofovir have zero effect on viral replication in the presence of the M184V and K65R mutations, respectively, and one which takes a 50 year time horizon.

More children are predicted to be prevented from acquiring HIV than are born with NTDs with a *TLD for all* policy. In calculating DALYs we assume lesser consequences of an HIV infection in a child (0.1 DALY per year) than a child born with an NTD (1 DALY per year), which assumes availability of good HIV diagnosis and treatment in infants; without such good availability of diagnosis and treatment the DALY consequences of a child birth with HIV would be greater and the benefits of *TLD for all* greater.

Our work has limitations. As for any cost-effectiveness analyses which takes a suitably long time horizon we rely on a model to give predictions of the long term impact of the alternative policies. We make assumptions about the benefits and harms associated with different ART regimens based on available data, which includes different levels of uncertainty. In particular, the recent reports on NTDs in infants born to women using dolutegravir are the first indication of this risk and planned further follow up of women similarly exposed should reduce uncertainty over this risk . This situation emphasizes that to support future decision making, including through modelling approaches, studies of novel drugs through the development phase and beyond, including in women periconception, during pregnancy and postpartum, are critical. Current evidence on the antiretroviral effects of dolutegravir are more extensive. Our results are robust to modifications in assumptions within plausible levels of uncertainty, supporting our main conclusions. We recognise that our assumption that women can access contraception from the time of wanting no more children does not reflect reality in many settings, and partially 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 as we considered that this would be unrealistic to implement.

We consider that our results should be used to inform relevant constituencies about the risks and benefits of the alternative policy options and for an informed representative view from people living with HIV to be ascertained when developing Ministry of Health policy. Without such consultation there is the risk that future ART uptake and retention is undermined if it proves to be that the signal for dolutegravir risk is real; the extent to which this could occur is difficult to quantify and account for at this point. However, we recognise the substantial challenges with achieving such an effective consultation.

In conclusion, using a standard DALY framework for comparing health outcomes from a public health perspective the benefits of transition to TLD for all substantially outweigh any risks.

**Contributors**

Conceptualisation of the analysis, substantive input into the modelling plan and advice on relevant data, interpretation of results, critical comment on manuscript drafts: all authors. Writing and execution of modelling program: AP, VC, FN, LB-M. Overall study lead: ANP. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the authors’ institutions.

*Acknowledgements*

We acknowledge helpful advice from: Elliot Raizes, Nathan Ford, Meg Doherty, George Siberry, David Ripin, Juliana da Silva, Carolyn Amole, Geoff Garnett, Peter Ehrenkranz. Computing resource: legion@ucl. JDL receives funding from the Danish National Research Foundation [Grant no 126].

**Declarations of interest**

None for APh, LBM, FN, VC, RB, DP, PC, JC, TK, TA, OM, PR, SB; AJ, RG, JDL -; DK - consultant to ViiV, Gilead and Merck, and have received research funding from all three companies, as well as from Janssen and Abbvie; JWM – grants from BMGF, USAID, Brigham Women's Hospital / AIDS Clinical Trials Group (ACTG) to the University of Pittsburgh Virology Support Laboratory, Janssen Pharmaceuticals, Gilead Sciences, personal fees from University of Pittsburgh and Gilead Sciences, share options in Co-Crystal Pharma, Inc. ; FV - honoraria for talks and advisory boards from multiple ART manufacturers, and received drug donations for studies from Viiv and Gilead, study support from USAID, UNITAID and the BMGF; DH - funding from NIH and non-financial support from Gilead Sciences (ART donation for NIH funded clinical study); APo - member of advisory boards for Gilead, ViiV, Merck and Jannsen and spoken at non-commercial symposia funded by  Gilead, ViiV, Merck and Jannsen, chair of the ARV section of the EACS guidelines; AdL - research grants from ViiV, Merck Sharp and Dome and Gilead (Fellowship Program), paid consultancies with ViiV, Merck Sharp and Dome, Janssen-Cilag, Abbvie and Gilead; AW - advisoryboards/grants from Janssen, Merck, Gilead, Viiv Healthcare and CLJI; AC – institutional unrestricted educational grants from ViiV, AbbVie, BMS, MSD, Gilead.

**Data sharing**

Model programs and simulations are accessible in Figshare (<https://figshare.com/s/2365d0eb9edd1e04294f>)

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**Table 1.** Description of regimen policies considered.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Men, and women not intending to have (more) children** | | | | | **Women intending to have (more) children** | | | | |
| **Regimen policy** | **New initiators** | **Currently on first-line TLE** | **Currently on second-line ZL-PI** | **At future TLE failure** | **At future TLD failure** | **New initiators** | **Currently on 1st**  **line TLE** | **Currently on second-line ZL-PI** | **At future TLE**  **failure** | **At future TLD failure** |
| **TLE for all** | TLE | TLE | ZL-PI | ZL-PI | --- | TLE | TLE | ZL-PI | ZL-PI | --- |
| **TLD dependent on viral suppression and intention to have (more) children** | TLD | --> TLD if VL < 1000 | --> TLD if VL < 1000 | ZLD | ZL-PI | TLE | TLE | ZL-PI | ZL-PI | --- |
| **TLD dependent on intention to have (more) children only** | TLD | --> TLD | --> TLD | --- | ZL-PI | TLE | TLE | ZL-PI | ZL-PI | --- |
| **TLD dependent on viral suppression only** | TLD | --> TLD if VL < 1000 | --> TLD if VL < 1000 | ZLD | ZL-PI | TLD | --> TLD if VL < 1000 | --> TLD if VL < 1000 | ZLD | ZL-PI |
| **TLD for all** | TLD | --> TLD | --> TLD | --- | ZL-PI | TLD | --> TLD | --> TLD | --- | ZL-PI |

VL viral load (in HIV RNA copies / mL); TLE tenofovir disoproxil fumarate (TDF) – lamivudine – efavirenz; TLD TDF – lamivudine – dolutegravir; ZLD zidovudine – lamivudine – dolutegravir; ZL-PI zidovudine – lamivudine – protease inhibitor (atazanavir); --> means switch

**Table 2.** HIV epidemic and programmatic characteristics of setting-scenarios in 2018

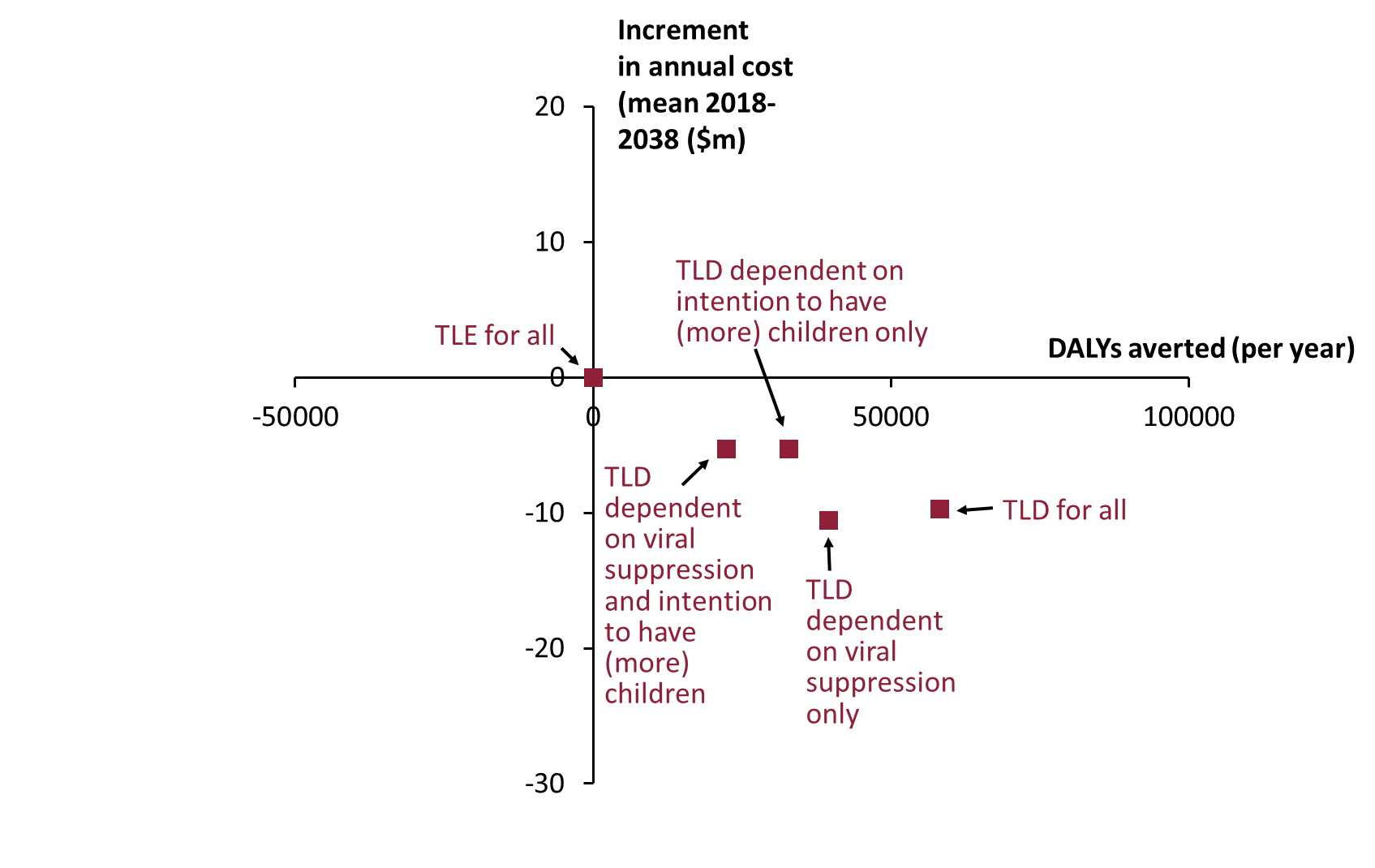
|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Model (2018)**  **(Median, 90% range)** | **Examples of observed data** |
| HIV prevalence (age 15-49) | 10% (5% - 19%) | Zimbabwe 2016 14%, Tanzania 2017 5%, Uganda 2017 6%, Lesotho 2017 24%, Swaziland 2017 27%, Malawi 2016 10%27 |
| HIV incidence age 15-49 (/100 person years) | 0.8 (0.3 – 1.6) | Malawi 2016 0.37, Zambia 2016 0.66, Zimbabwe 2016 0.45, Lesotho 2017 1.55, Namibia 2016 0.40, Swaziland 2017 1.48, Tanzania 2017 0.2727 |
| Proportion of HIV positive people diagnosed | 83% (69% - 93%) | Malawi 2016 73%, Zambia 2016 67%, Zimbabwe 2016 74%, Namibia 2017 86%, Tanzania 2017 52% 27 (see also Kim et al, which suggests undisclosed diagnosed HIV 28) |
| Proportion of all HIV positive people with VL < 1000 | 57% (31% - 71%) | Zambia 2016 60%, Malawi 2016 68%, Zimbabwe 2016 60%, Swaziland 2017 73%, Lesotho 2017 68%, Tanzania 2017 52%, Uganda 2017 60%, Cameroon 2017 45%, Namibia 2017 77% 27 |
| Proportion of ART experienced people who have started second-line (boosted PI) ART | 2.4% (0.5% - 9.4%) | Malawi 1.5% 29 |
| Of people on ART, proportion with VL < 1000 | 85% (74% - 91%) | Zambia 2016 89%, Malawi 2016 91%, Zimbabwe 2016 87%, Cameroon 2017 80%, Namibia 2017 91%, Tanzania 2017 88%, Uganda 2017 84% 27 |
| Of ART naïve ART initiators % with NNRTI resistance | 11% (2% - 29%) | Angola 2012 14% , Botswana 2016 8% , South Africa 2017 14% , Zimbabwe 2015 10%, Namibia 9%, Cameroon 2015 8%, Uganda 2016 16% 30 |
| Mother to child transmission rate | 3.7% (1.9% - 6.7%) | All 2014: Botswana 2% within 6 weeks / 4% final, South Africa 1% / 4%, Namibia 1% / 7%, Uganda 2%, 8%, Zimbabwe 5% / 12%, Malawi 7% / 17%, Angola 10% / 25% 31 |

N=1000 setting-scenarios. People age 15-64 unless stated.

**Table 3**. Predicted effect of regimen policies on intermediate outcomes, DALYs and net DALYS over 20 years unless stated (2018-2038)\*. Mean and mean difference (95% confidence interval for mean difference; 90% range reflecting variation across setting-scenarios) compared with policy of *TLE for all*. 95% confidence intervals added (not tracked)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcome** (mean over 20 years unless stated) | **Regimen Policy** | | | | |
|  | **TLE for all** | **TLD dependent on viral suppression and intention to have (more) children** | **TLD dependent on intention to have (more) children only** | **TLD dependent on viral suppression only** | **TLD for all** |
| **Proportion on efavirenz** | 92% | 52%  -40%  (-41% - -39%)  (-52% - -22%) | 42%  -50%  (-51% - - 49%)  (-61% - -39%) | 15%  -77%  (-78% - -76%)  (-92% - -47%) | 0%  -92%  (-93% - -91%)  (-100% - -78%) |
| **Proportion on dolutegravir** | 0% | 43%  +43%  (+42% - +44%)  (+22% - +57%) | 54%  +54%  (+53% - +55%)  (+42% - +63%) | 83%  +83%  (+82% - +85%)  (+47% - +97%) | 98%  +98%  (+97% - +99%)  (+94% - +100%) |
| **Proportion on atazanavir** | 8% | 5%  -3%  (-4% - -2%)  (-9% - -0%) | 4%  -3%  (-4% - -2%)  (-9% - -1%) | 2%  -6%  (-7% - -5%)  (-16% - -0%) | 2%  -6%  (-7% - -5%)  (-16% - -0%) |
| **Proportion on zidovudine**\*\* | 8% | 5%  -2%  (-3% - -1%)  (-8% - +0%) | 4%  -4%  (-5% - -3%)  (-10% - -2%) | 4%  -4%  (-5% - -3%)  (-13% - -0%) | 2%  -6%  (-7% - -5%)  (-16% - -0%) |
| **Percentage of people**  mean over 1 year  **on ART with VL < 1000:**  mean over 5 years      mean over 20 years | 84%  84%  82% | 85%  +0%  (+0% - +0%)  (-0% - +2%)  86%  +2%  (+2% - +2%)  (+0% - +4%)  87%  +5%  (+5% - +5%)  (+1% - +9%) | 87%  +2%  (+2% - +2%)  (-0% - +5%)  87%  +3%  (+3% - +3%)  (+0% - +7%)  87%  +5%  (+5% - +5%)  (+1% - +11%) | 85%  +1%  (+1% - +1%)  (-1% - +3%)  88%  +4%  (+4% - +4%)  (+1% - +8%)  91%  +9%  (+9% - +9%)  (+3% - +16%) | 90%  +6%  (+6% - +6%)  (+1% - +11%)  91%  +7%  (+7% - +7%)  (+1% - +14%)  91%  +10%  (+10% - +10%)  (+2% - +18%) |
| **Of people with K65R**  mean over 1 year  **and M184V mutation**  **at baseline~, percentage**  **of people on ART with**  **VL < 1000:**  mean over 5 years      mean over 20 years | 7%  22%  50% | 9%  +3%  (+2% - +4%)  (-1% - +8%)  26%  +4%  (+3% - +5%)  (-1% - +10%)  50%  -0%  (-1% - +1%)  (-9% - +8%) | 23%  +16%  (+15% - +17%)  (+4% - +28%)  35%  +13%  (+12% - +14%)  (-3% - +32%)  52%  +2%  (-1% - +5%)  (-16% - +46%) | 14%  +7%  (+6% - +8%  (-1% - +21%)  33%  +11%  (+9% - +13%)  (-1% - +25%)  53%  +3%  (+1% - +5%)  (-15% - +18%) | 49%  +42%  (+40% - +44%)  (+15% - +64%)  55%  +32%  (+29% - +35%)  (-3% - +72%)  57%  +7%  (+3% - +11%)  (-22% - +64%) |
| **AIDS death rate in people on ART** (per 100 person years) | 1.70 | 1.25  -0.46  (-0.48 - -0.44)  (-0.94 - -0.12) | 1.08  -0.63  (-0.66 - -0.60)  (-1.34 - -0.14) | 0.94  -0.76  (-0.79 - -0.73)  (-1.51 - -0.24) | 0.72  -0.98  (-1.02 - -0.94)  (-2.02 - -0.24) |
| **AIDS death rate in people on ART with VL > 1000** (per 100 person years) | 7.05 | 6.29  -0.76  (-0.82 - -0.70)  (-1.41 - -0.12) | 5.71  -1.34  (-1.44 - -1.24)  (-2.54 - -0.45) | 5.92  -1.12  (-1.22 - -1.02)  (-2.22 - -0.14) | 4.77  -2.28  (-2.08 - -2.48)  (-4.36 - -0.48) |
| **AIDS death rate in people on ART with VL > 1000 and CD4 count < 200 cells per µL** (per 100 person years) | 18.07 | 17.22  -0.85  (-1.24 - -0.66)  (-2.01 - +0.91) | 16.05  -2.02  (-2.26 – 1.78)  (-4.15 - -0.11) | 17.05  -1.03  (-1.34 - -0.72)  (-3.41 - +1.45) | 14.77  -3.30  (-3.78 - -2.82)  (-8.43 - +0.03) |
| **Proportion of all HIV positive people with a dolutegravir resistance mutation** | 0% | 2.6%  +2.5%  (+2.3% - +2.7%)  (+0.4% - +7.7%) | 4.0%  +4.0%  (+3.8% - +4.2%)  (+0.6% - +11.0%) | 4.4%  +4.4%  (+4.1% - +4.7%)  (+0.7% - +12.9%) | 6.7%  +6.6%  (+6.2% - 7.0%)  (+1.2% - +18.5%) |
| **Proportion of all HIV positive people with an efavirenz resistance mutation** | 28% | 22%  -6%  (-6% - -6%)  (-12% - -1%) | 20%  -8%  (-8% - -8%)  (-14% - -3%) | 15%  -13%  (-13% - -13%)  (-22% - -6%) | 13%  -15%  -15%  (-24% - -8%) |
| **Adverse birth outcomes amongst women with HIV** (percent of pregnancies):  **MTCT**      **NTD due to dolutegravir+** | 4.2%  0% | 3.9%  -0.2%  (-0.2% - -0.2%)  (-0.8% - +0.3%)  0.02%  +0.02%  (+0.02% - +0.02%)  (-0.0% - +0.08%) | 3.8%  -0.3%  (-0.3% - -0.3%)  (-1.1% - +0.3%)  0.03%  +0.03%  (+0.03% - +0.03%)  (-0.0% - +0.09%) | 2.9%  -1.2%  (-1.2% - -1.2%  (-2.5% - -0.3%)  0.52%  +0.52%  (+0.49% - +0.55%)  (-0.12%-+1.38%) | 2.8%  -1.4%  (-1.4% - -1.4%)  (-2.9% - -0.3%)  0.60%  +0.60%  (+0.58% - +0.62%)  (+0.15%-+1.51%) |
| **Costs**^ (annual, difference compared with TLE) | ---- | -$5.3m  (-$5.8 - - $4.8m)  (-$19.6m - +$2.0m) | -$5.3m  (-$4.8m - -$5.8m)  (-$20.4m - +$3.1m) | -$10.5m  (-$11.3m - $9.7m)  (-$37.4m - +$1.4m) | -$9.7m  (-$10.6m - -$8.8m)  (-$38.0m - +$3.9m) |
| **DALYs averted**^ (per year, compared with TLE) | ---- | 22,300  (21,300-23,300)  (1,400 – 53,000) | 32,800  (31,300-34,300)  (3,900 – 78,200) | 39,500  (37,000-42,000)  (7,900 – 87,900) | 58,200  (55,700-61,300)  (11,500 – 138,300) |
| **Incremental cost effectiveness ratio** | dominated | dominated | dominated | reference | $44 |
| **Net DALYs** ( per year, compared with TLE) | ---- | 32,900  (31,400-34,400)  (2,700 – 84,200) | 43,500  (41,700-45,300)  (8,600 – 103,100) | 60,600  (58,000-63,200)  (11,800 – 143,400) | 77,700  (74,700-80,700)  (20,800 – 177,600) |

\*Mean over 3 month periods; \*\* as opposed to TDF, all are on 3TC. + NTDs potentially caused by dolutegravir if possible signal is confirmed. ~ and viral load > 1000 ^ In context of adult population of size 10 million with HIV prevalence range as in Table 2. Costs and DALYs are discounted at 3% per annum.

**Figure 1.** Overall health benefit (DALYs averted) and increment in cost compared with *TLE for all*. (Mean over 3 month periods of 1000 setting-scenarios over 20 years, expressed per year.)

**Table 4.** Sensitivity analyses. DALYs and net DALYs averted compared with policy of *TLE for all*. 95% confidence interval; 90% range, reflecting variation across setting-scenarios.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **DALYs averted** | | | | **Net DALYS averted** (% of setting-scenarios in which policy is the most cost effective&) | | | |
|  | **TLD dependent on viral suppression and intention to have (more) children** | **TLD dependent on intention to have (more) children only** | **TLD dependent on viral suppression only** | **TLD for all** | **TLD**  **dependent**  **on viral suppression and**  **intention to have (more) children** | **TLD**  **dependent**  **on intention**  **to have**  **(more) children only** | **TLD**  **dependent**  **on viral suppression only** | **TLD for all** |
| **No restriction (base case)** | 22,300  21,300-23,300  1,400-53,000 | 32,800  31,300-34,300  3,900-78,200 | 39,500  37,000-42,000  7,900-87,900 | 58,200  55,700-61,300  11,500-138,300 | 32,900 (0.2%)  31,400-34,400  2,700-84,200 | 43,500 (0.8%)  41,700-45,300  8,600-103,100 | 60,600 (16%)  58,000-63,200  11,800-143,400 | 77,700 (83%)  74,700-80,700  20,800-177,600 |
| **Restricting to setting-scenarios in which:** |  |  |  |  |  |  |  |  |
| Rate of development of resistance to dolutegravir 3 times higher | 20,300  18,100-22,500  -0 - 50,400 | 29,100  25,800-32,400  3,000-72,800 | 35,800  32,400-39,200  8,900-81,400 | 50,100  44,700-55,500  4,800-124,500 | 29,700 (0.0%)  26,700-32,700  3,400-72,800 | 38,300 (1.0%)  34,700-41,900  9,200-88,800 | 54,400 (24%)  49,400-59,400  11,900-127,200 | 66,600 (75%)  50,900-72,300  21,000-149,100 |
| Rate of toxicity to dolutegravir the same as efavirenz | 21,800  19,600-24,000  2,800-52,300 | 31,600  28,400-34,800  3,200-73,500 | 38,800  35,200-42,400  6,600-87,900 | 58,400  52,800-64,000  11,800-131,100 | 32,100 (0.5%)  28,600-35,600  3,000-84,100 | 41,800 (1.0%)  37,800-45,800  9,300-91,700 | 59,100 (16%)  53,300-64,900  9,800-141,900 | 76,600 (82%)  69,900-83,300  19,500-167,400 |
| Potency of dolutegravir 1.0 (equal to efavirenz) | 16,900  15,200-18,600  -1000 - 40,600 | 23,700  21,100-26,300  -100 - 53,900 | 30,200  27,500-32,900  4,400-62,900 | 41,900  37,800-46,000  2,200-93,900 | 24,000 (1.0%)  21,500-26,500  900 - 52,500 | 30,900 (0.5%)  28,100-33,700  6,500-63,600 | 45,400 (31%)  41,300-49,500  9,600-95,000 | 54,600 (68%)  50,200-59,000  17,700-108,800 |
| Potency of dolutegravir 1.0 (equal to efavirenz) + Rate of development of resistance to dolutegravir 3 times higher | 13,700  10,300-17,100  -2,600-33,500 | 18,600  13,700-23,500  -1,300-53,800 | 25,300  19,800-30,800  4,000-57,100 | 32,000  23,600-40,400  1000 - 91,000 | 19,100 (0.0%)  15,100-23,100  -1,300-41,000 | 23,100 (3.0%)  18,700-27,500  3,300-47,700 | 35,600 (49%)  29,800-41,400  9,200-72,000 | 39,100 (49%)  31,900-46,300  4,900-84,500 |
| Pre-ART NNRTI resistance 2018 > 10% | 27,900  26,400-29,400  5,100-61,400 | 40,400  38,100-42,700  8,600-93,800 | 48,800  46,300-51,300  12,800-104,700 | 71,100  67,700-75,100  19,300-157,300 | 41,500 (0.0%)  39,100-43,900  7,300-97,200 | 54,200 (0.2%)  51,500-56,900  14,200-118,000 | 76,100 (14%)  72,100-80,100  21,700-172,000 | 96,400 (86%)  92,000-100,800  34,500-20,300 |
| Pre-ART NNRTI resistance in 2018 < 5% | 12,700  11,200-14,200  -2,500-34,400 | 20,100  17,900-22,300  -300 - 51,900 | 23,400  21,300-23,500  1,500-51,100 | 36,100  32,400-39,800  3,800-87,000 | 18,200 (1.0%)  16,200-20,200  300 - 42,700 | 25,600 (2.1%)  23,100-28,100  2,800-59,400 | 34,600 (21%)  31,500-37,700  6,000-72,200 | 46,400 (76%)  42,500-50,300  13,700-106,700 |
| Zero residual activity of tenofovir and lamivudine in presence of K65R / M184V mutations | 26,600  20,900-32,300  2,500-67,900 | 35,300  27,300-43,300  5,300-94,800 | 46,700  37,500-55,900  6,300-109,500 | 62,700  49,400-76,000  10,500-168,200 | 37,600 (0.0%)  29,400-45,800  2,500-98,500 | 45,000 (0.0%)  35,800-54,200  5,800-108,500 | 68,300 (26%)  54,300-82,300  18,400-172,100 | 80,500 (74%)  64,800-96,200  20,290-198,394 |
| Rate of switch after virologic failure 0.05 per 3 months | 25,000  23,000-27,000  1,700-57,900 | 37,200  34,300-40.100  5,400-85,600 | 44,900  41,700-48,100  10,400-101,700 | 65,700  61,100-70,300  18,300-145,000 | 31,400 (0.3%)  28,600-34,200  300 - 78,500 | 42,800 (1.0%)  39,500-46,100  6,500-103,600 | 58,500 (14%)  54,000-63,000  12,400-135,800 | 76,500 (84%)  71,100-81,900  19,500-178,100 |
| Rate of switch after virologic failure 0.5 per 3 months | 17,100  15,400-19,800  -600 - 38,700 | 26,300  23,700-28,900  300 - 66,200 | 31,500  28,700-34,300  4,400-63,300 | 46,900  41,400-51,400  3,800-111,200 | 28,900 (0.4%)  26,200-31,600  3,100-72,700 | 38,900 (0.9%)  35,800-42,000  8,800-81,800 | 54,400 (18%)  39,500-58,900  11,600-132,400 | 69,200 (81%)  64,100-74,300  22,600-143,500 |
| Proportion of women giving birth per 3 month period > 4% | 24,700  22,000-27,400  2,300-53,400 | 36,600  32,500-40,700  2,200-95,600 | 43,500  41,300-47,700  12,700-91,200 | 65,800  59,000-72,600  11,900-160,700 | 35,000 (0.6%)  31,000-39,000  4,900-89,700 | 47,000 (0.0%)  42,400-51,600  11,500-106,400 | 64,800 (11%)  58,400-71,200  18,000-144,200 | 85,400 (89%)  77,600-93,200  19,800-184,000 |
| proportion of women giving birth per 3 month period < 4% | 21,900  20,800-23,000  1,400-52,600 | 32,100  30,400-33,800  3,900-75,900 | 38,800  37,000-40,600  7,000-87,800 | 56,700  54,000-59,400  11,308-131,100 | 32,500 (0.1%)  30,700-34,300  2,200-84,100 | 42,800 (1.0%)  40,800-44,800  7,800-97,100 | 59,800 (17%)  56,900-63,700  10,800-142,600 | 76,100 (82%)  72,900-79,300  20,900-168,000 |
| Risk of NTD with dolutegravir 1.0% | 22,300  21,300-23,300  1,400-52,800 | 32,800  31,300-34,300  3,900-78,200 | 38,600  37,000-40,200  7,500-86,900 | 57,100  54,600-59,600  10,600-136,100 | 32,900 (0.2%)  31,300-34,500  2,700-84,200 | 43,400 (0.8%)  41,600-45,200  8,600-102,900 | 59,700 (16%)  57,100-62,300  11,600-141-700 | 76,500 (84%)  75,000-78,000  20,300-175,500 |
| Risk of NTD with dolutegravir 3.0% | 22,100  21,100-23,100  1,400 – 52,700 | 32,500  31,000-34,000  3,700 – 78,200 | 34,300  32,800-35,800  4,300 – 81,300 | 51,600  49,100-54,100  5,900-127,900 | 32,700 (0.4%)  31,200-34,200  2,500 - 84,100 | 43,200 (1.3%)  41,400-45,400  8,600 – 102,000 | 55,400 (16%)  52,900-57,900  9,700-132,700 | 71,000 (82%)  68,200-73,800  18,000-166,800 |
| Viral load testing fully implemented | 19,100  17,300-20,900  800 - 43,000 | 21,000  18,900-23,100  -1,700-48,500 | 32,800  30,000-35,600  6,700-66,800 | 36,200  32,800-39,600  2,500-77,500 | 40,700 (0.0%)  37,200-44,200  8,400-92,300 | 44,100 (1.7%)  40,300-47,900  9,600-98,200 | 72,800 (28%)  66,900-78,700  23,600-150,500 | 78,200 (70%)  71,900-84,500  23,900-173,600 |
| Viral load testing not implemented | 19,100  17,200-21,000  -2500-44,400 | 43,800  40,100-47,500  7,700-96,500 | 34,800  31,800-37,800  2,900-76,100 | 79,300  73,400-85,200  21,600-159,100 | 18,300 (0.0%)  16,300-20,300  -2,800-44,600 | 41,400 (0.0%)  37,800-45,000  5,600-88,500 | 35,700 (2.5%)  32,500-37,900  1,200-82,500 | 75,000 (98%)  69,200-80,800  18,300-152,800 |
| Higher background rate of treatment interruption | 20,900  18,900-22,900  -300 - 51,300 | 29,900  27,100-32,700  3,000-76,400 | 39,000  35,900-42,100  10,200-89,100 | 56,100  51,500-60,700  15,700-128,000 | 27,100 (0.0%)  24,300-29,900  500 - 72,900 | 36,100 (1.2%)  32,800-39,400  3,500-86,400 | 52,300 (16%)  47,700-56,900  9,800-127,700 | 67,500 (83%)  62,000-73,000  16,700-151,200 |
| HIV prevalence (age 15-49) in 2018 < 8% | 12,700  11,500-13,900  -1,900-29,100 | 19,200  17,700-20,700  3,000-40,500 | 22,800  21,100-24,500  2,000-50,800 | 33,500  31,200-35,800  7,000-65,400 | 17,900 (0.8%)  16,200-19,600  -1,300-40,100 | 24,400 (1.9%)  22,600-26,200  3,500-52,100 | 32,900 (22%)  30,300-35,500  3,200-69,000 | 42,600 (76%)  40,000-45,200  14,000-81,100 |
| HIV prevalence (age 15-49) in 2018 > 12% | 32,200  30,200-34,200  7,900-68,400 | 47,100  44,100-50,100;  10,800-101,400 | 56,300  53,300-59,300  17,100-114,000 | 83,700  78,800-88,600  23,000-171,900 | 48,400 (0%)  45,400-51,400  12,000-103,000 | 63,400 (0.3%)  60,100-66,700  21,900-121,200 | 89,300 (10%)  84,400-94,200  30,100-184,100 | 114,500 (90%)  109,300-119,700  45,900-209,200 |
| HIV incidence age 15-49 in 2018 (/100 person years) < 0.60 | 12,800  11,600-14,000  -1,600-28,600 | 20,000  18,200-21,800  1,700-43,800 | 22,000  20,300-23,700  2,900-45,700 | 34,400  31,700-37,100  6,900-69,000 | 19,400 (0%)  17,600-21,200  -1,000-42,100 | 26,600 (0.4%)  24,600-28,600  6,400-55,200 | 33,900 (20%)  31,200-36,600  3,200-67,200 | 45,300 (78%)  42,300-48,300  17,600-83,900 |
| HIV incidence age 15-49 in 2018 (/100 person years) > 1.00 | 30,800  28,800-32,800  5,100-68,400 | 44,600  41,600-47,600  8,600-99,500 | 55,400  52,300-58,500  16,600-114,000 | 81,000  76,200-85,800  21,900-167,500 | 45,000 (0%)  42,000-48,000  8,300-100,200 | 58,900 (0%)  55,500-62,300  13,800-121,000 | 84,900 (12%)  79,900-89,900  26,800-181,900 | 108,000 (88%)  102,500-113,500  36,500-208,500 |
| Proportion of HIV positive people diagnosed in 2018 < 75.0% | 17,700  15,600-19,800  200 - 41,500 | 25,200  22,400-28,000  3,000-56,200 | 36,200  32,700-39,700  6,300-74,200 | 49,800  44,800-54,800  11,900-111,900 | 22,900 (0%)  20,000-25,800  500-58,400 | 30,300 (1.1%)  26,900-33,700  3,900-68,300 | 47,900 (21%)  42,400-52,900  8,200-120,000 | 59,900 (78%)  54,100-65,700  17,600-130,200 |
| Proportion of HIV positive people diagnosed in 2018 > 88% | 25,400  23,300-27,500  2,000 - 59,900 | 37,800  34,500-41,100  5,000-93,800 | 42,300  38,900-45,700  8,300-103,700 | 64,700  61,400-70,000  16,000-152,000 | 39,700 (0%)  36,100-43,300  5,300-98,400 | 52,000 (0%)  48,100-55,900  10,400-118,900 | 68,400 (11%)  62,700-74,100  11,100-162,200 | 88,900 (89%)  82,600-95,200  25,900-200,500 |
| Proportion of ART experienced people who have started second-line (boosted PI) ART in 2018 < 1.5% | 19,900  17,900-21,900;  -300 - 47,000 | 34,200  31,300-37,100  5,000-75,900 | 38,200  35,200-41,200  8,200-82,900 | 63,300  58,700-67,900  16,700-134,900 | 21,300 (0.4%)  19,100-23,500  -1,500-55,900 | 34,700 (0.7%)  31,700-37,700  2,600-79,600 | 42,700 (11%)  39,000-46,400  6,200-101,800 | 64,300 (88%)  59,500-70,100  14,900-136,300 |
| Proportion of ART experienced people who have started second-line (boosted PI) ART in 2018 > 4.0% | 20,600  18,800-22,400  1,200-47,000 | 23,900  21,700-26,100  -1,300-54,600 | 34,800  32,100-36,500  6,400-75,500 | 39,600  36,100-43,100  3,200-93,600 | 44,900 (0%)  41,700-48,100  12,100-98,800 | 49,800 (0.7%)  46,300-53,300  11,600-107,700 | 80,100 (27%)  74,800-85,400  26,100-162,700 | 86,500 (72%)  82,600-92,400  26,800-185,500 |
| Of people on ART, proportion with VL < 1000 in 2018 < 80% | 32,800  29,600-36,000  10,400-74,000 | 48,400  43,600-53,200  10,700-109,500 | 59,000  54,000-64,000  17,400-129,500 | 87,300  84,800-89,800  24,300-185,900 | 40,900 (0%)  36,400-45,400  3,800-98,500 | 55,400 (0%)  50,000-60,800  7,400-122,900 | 77,500 (11%)  70,900-87,100  18,200-185,700 | 101,400 (89%)  98,400-104,400  31,000-218,800 |
| Of people on ART, proportion with VL < 1000 in 2018 > 88% | 13,700  12,400-15,000  -1,600-30,900 | 17,600  15,800-19,400  -1,800-40,600 | 23,600  21,600-25,600  1,900-51,100 | 30,000  27,200-32,800  1,300-67,800 | 27,300 (0.9%)  24,700-29,900  2,200-61,300 | 32,200 (2.1%)  29,500-34,900  6,800-69,100 | 48,900 (26%)  44,800-53,000  11,000-111,200 | 56,100 (71%)  51,800-60,400  14,500-120,100 |
| Cost effectiveness threshold $200 | 22,300  21,300-23,300  1,400-53,000 | 32,800  31,300-34,300  3,900-78,200 | 39,500  37,000-42,000  7,900-87,900 | 58,200  55,700-61,300  11,500-138,300 | 48,700 (0.3%)  45,900-51,500  -100 - 107,200 | 59,400 (0.9%)  56,500-62,300  8,400-156,900 | 92,300 (21%)  87,300-97,300  12,600-252,200 | 106,900 (78%)  101,900-111,900  20,700-270,100 |
| Cost effectiveness threshold $1000 | 22,300  21,300-23,300  1,400-53,000 | 32,800  31,300-34,300  3,900-78,200 | 39,500  37,000-42,000  7,900-87,900 | 58,200  55,700-61,300  11,500-138,300 | 27,600 (0.2%)  26,300-28,900  3,100-66,000 | 38,200 (1.0%)  36,600-39,800  7,200-87,300 | 50,100 (14%)  48,100-52,100  12,600-111,600 | 67,900 (85%)  65,300-70,500  18,800-153,100 |
| **Additional sensitivity analyses** |  |  |  |  |  |  |  |  |
| Dolutegravir becomes potency 0.75 during TB treatment | 21,700  18,700-24,700;  4,800-42,900 | 31,300  26,300-36,300  2,700-69,400 | 38,600  33,800-43,400  6,700-73,700 | 55,300  47,100-63,500  13,500-122,600 | 31,800 (0.0%)  27,500-36,100  5,600-72,400 | 41,500 (0.0%)  36,300-46,700  15,200-85,700 | 58,700 (15%)  51,800-65,600  16,200-134,900 | 74,900 (85%)  68,300-83,500  23,500-158,700 |
| For policies with dependence on viral suppression, people on ZL-PI are moved to ZLD rather than TLD. | 23,100  20,800-25,400  1300 – 52,800 | 33,000  29,600-36,400  6,200 – 68,100 | 40,800  37,100-44,500  10,400 – 83,700 | 56,800  53,400-60,200  13,000-131,700 | 33,900 (0%)  30,500-37,300  3,900 - 81,200 | 43,700 (0%)  39,900-47,500  11,400 - 90,000 | 62,300 (20%)  66,600-68,000  14,400-128,900 | 76,900 (80%)  70,400-83,400  22,500-159,100 |
| Higher rate of MTCT | 20,000  18,000-22,000  1,100-46,300 | 29,700  26,700-32,700  2,600-75,800 | 36,400  33,400-39,400  5,900-80,000 | 54,000  49,200-54,800  9,100-123,900 | 30,800 (0%)  27,900-33,700  4,500-68,900 | 40,700 (0%)  37,400-44,000  9,000-85,800 | 58,300 (15%)  53,600-63,000  14,300-119,800 | 75,600 (85%)  70,100-81,100  23,600-160,800 |
| NTDs not fatal in 50% of babies born with NTDs and lifetime disability weight and cost incurred for surviving babies ^ | 21,100  18,900-23,300  1,400-50,200 | 29,900  26,800-33,000  2,000-67,500 | 37,800  34,400-41,200  8,800-79,600 | 53,900  48,800-59,000  10,000-112,700 | 32,900 (5.4%)  29,700-36,100  2,500-73,300 | 42,100 (18%)  38,500-45,700  6,500-88,600 | 60,900 (14%)  55,800-66,000  13,000 - 131,700 | 76,000 (63%)  70,200-81,800  22,100-162,300 |
| Contraception has 50% effectiveness instead of 80% | 24,000  21,300-26,700  2,600-54,900 | 36,900  33,000-40,800  2,700-87,700 | 41,500  37,500-45,500  9,400-89,600 | 64,500  58,500-71,100  8,400-142,700 | 34,700 (0.6%)  30,700-38,700  5,700-83,500 | 47,300 (0.6%)  43,800-51,800  9,600-105,800 | 62,300 (19%)  56,000-68,600  14,700-137,900 | 83,200 (80%)  75,800-90.600  19,300-178,400 |
| Efavirenz has potency 1.5 | 20,200  17,400-23,000  -500 - 50,500 | 28,300  24,100-32,400  -0 - 84,600 | 35,300  30,500-40,100  2,700-91,000 | 50,600  53,900-57,300  6,800-132,200 | 29,600 (0.8%)  25,600-33,600  4,100-73,000 | 38,100 (1.5%)  33,100-43,100  5,100-98,900 | 54,000 (15%)  47,300-60,700  12,800-133,700 | 68,000 (82%)  60,400-75,600  19,200-158,500 |
| Viral load threshold 50 copies/mL | 18,100  15,000-21,200  -5,200-48,600 | 28,800  24,400-33,200  1,200-69,000 | 30,000  25,800-34,200  4,800-66,600 | 50,000  43,100-56,900  4,800-108,000 | 28,800 (0.0%)  24,100-33,500  -700 - 67,200 | 40,300 (5.6%)  34,900-45,700  6,800-80,800 | 50,900 (9%)  43,800-58,000  6,700-106,800 | 68,100 (86%)  59,700-76,500  16,000-139,200 |
| Atazanavir resistance rate 3 fold lower | 22,600  18,600-26,600  4,200-60,800 | 33,100  26,600-39,600  7,500-85,700 | 37,500  31,900-43,300  7,300-86,400 | 56,600  46,400-66,800  17,000-128,000 | 34,600 (0.0%)  28,200-41,000  6,600-78,900 | 45,700 (1.7%)  38,100-53,300  12,200-107,300 | 60,400 (15%)  49,800-71,000  13,100-130,300 | 78,200 (83%)  66,200-90,200  23,900-150,000 |
| 50 year time horizon | 49,000  41,800-56,200  700-136,000 | 60,000  50,800-69,200  15,800-178,800 | 84,200  72,800-95,600  9,800-218,700 | 93,200  79,500-106,900  8,800-269,300 | 57,800 (0.0%)  50,400-65,200  1,800-127,900 | 69,100 (0.0%)  60,600-77,600  4,200-161,500 | 99,800 (0%)  88,600-111,000  15,600-211,200 | 107,200 (100%)  94,600-119800  12,600-242,200 |

& *TLE for all* policy is the most cost effective in 0% of all setting-scenarios. ^ disability weight for child living with NTD is 0.5, cost is $5000 in first year (costs of surgery) and $1000 per year (costs of ongoing care and support) thereafter.