**Modelled evaluation of modfications in viral load monitoring in the context of sub-Saharan Africa: modelling to inform WHO guidelines**

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**Introduction**

WHO has a recommended algorithm for viral load monitoring of people on ART and informing decisions on switching to a new line of therapy. Viral load testing is recommended at 6 and 12 months after start of ART and 12 monthly thereafter; if the viral load is found to be > 1000 copies/mL the recommendation is to give an enhanced adherence intervention and to re-measure in 6 months. If the viral load level remains above 1000 then it is recommended to switch to a second line regimen. Consideration has been given to modifications of the algorithm in several aspects, including in the timing of the first viral load, the time period between the initial viral load > 1000 and the next measurement, and in the requirement for a second viral load value > 1000 before switching regimen. Some of these considerations are likely to be dependent on whether the first line regimen is an efavirenz-based regimen (usually in the form of tenofovir DF, lamivudine, efavirenz (TLE)) or, as is now strongly recommended, a dolutegravir-based regimen (usually in the form of tenofovir DF, lamivudine, dolutegravir (TLD)). We applied an existing model of HIV transmission, progression and the effect of specific ARVs, which explicitly considers drug resistance and ARV adherence, to inform the potential effects of such changes.

**Methods**

HIV Synthesis is an individual based simulation model which has been described previously (e.g. 1-2). Each time the model program is run it creates a simulated data set of attributes of a population of adults from 1989 to 2020 and beyond - with updates every 3 month period on variables including the following on the entire adult population: age, gender, primary and short term condomless sex partners, HIV testing, male circumcision, presence of an other sexually transmitted infection, and use of PrEP. In HIV positive people variables include time from infection, CD4 count, viral load, specific antiretroviral (ARV) drugs being used, ARV adherence, and specific drug resistance mutations. The latter three variables jointly determine at any point in time the current levels of suppressive antiviral effect of the regimen. Through sampling of several parameter values we create a series of "setting scenarios" reflecting uncertainty in assumptions and a range of characteristics similar to those seen in southern / east Africa; for example we sample parameters relating to rates of HIV testing; linkage and retention; ART adherence; resistance emergence, transmission and persistence; ART interruption; extent of implementation of viral load monitoring; rate of switching to 2nd line after detected virologic failure. The characteristics of the setting scenarios are shown in Table 1. For each setting scenario, we consider the situation in 2020.5 and compare predicted outcomes of potential modification to the viral load monitoring algorithm with the current algorithm.

The following modifications in the viral load monitoring algorithm were separately considered and compared with the current algorithm. The context in which the comparison is made is shown in parentheses.

1. Timing of repeat viral load, in context of TLE 1st line regimen (no transition to dolutegravir is made before or during follow up): 3 months vs 6 months
2. Timing of repeat viral load, in context of TLD 1st line regimen (transition of all to TLD made pre-baseline): 3 months vs 6 months
3. Timing of initial viral load, in context of TLE 1st line regimen (no transition to dolutegravir is made before or during follow up): 3 months vs 6 months
4. Timing of initial viral load, in context of TLE 1st line regimen (no transition to dolutegravir is made before or during follow up): 3 months vs 6 months
5. Single vs confirmed VL to determine failure, in context of TLE 1st line regimen (in context of ART policy of transition to TLD in new initiators made in 2019; ZLD (zidovudine, lamivudine, dolutegravir) is 2nd line regimen in people with TLE failure from 2019)
6. Single vs confirmed VL to determine failure, in context of TLE 1st line regimen (in context of ART policy of transition to TLD in new initiators made in 2019; ZLD is 2nd line regimen in people with TLE failure from 2019)

Each variation in policy is considered in the context of 50 setting scenarios.

We calculated disability adjusted life years (DALYs) for the whole adult population 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. Unless we state otherwise, absolute numbers of health-related events, costs and DALYs are relevant for a country of population size of approximately 10 million adults in 2018. Cost- effectiveness analysis is conducted from a healthcare perspective, costs and health outcomes were both discounted to present US$ values at 3% per annum, and a cost- effectiveness threshold of US$500 per DALY averted was used. We used this threshold to calculate net DALYs averted. Net DALYs take into account the health consequences of the difference in costs as well as the difference in health and reflect the impact of a policy on overall population burden of disease: Net DALYs averted = DALYs averted + difference in costs / cost effectiveness threshold. Costs and disability weights are shown in the Appendix to (2).

**Results and Discussion**

Shown in Table 1 are the characteristics of the setting scenarios in 2020. Table 2a and b show the effect of varying the timing of the confirmatory viral load between 3 and 6 months. Table 2a is in the context of no transition to dolutegravir being made before or during follow up, while Table 2b is in the context of transition of all ART being made to TLD made pre-baseline. Specific ARV use, viral suppression, death rates, DALYs, costs and net DALYs are compared. In neither context is there any discernible difference in predicted outcomes, so any effect of the policy modification is likely to be very small. Likewise (Table 2c, 2d) there is little discernible effect of varying the timing of the first viral load measure after start of ART.

In contrast, in the context of an ART policy of transition to TLD in new initiators made in 2019, and with ZLD as 2nd line regimen in people with TLE failure from 2019, a policy of single VL to determine failure in people on TLE 1st line regimen amongst people, brings health benefits and is cost-effective based on a cost effectiveness threshold of $500 per DALY averted (Table 2e). This was also the case if the policy of single VL to determine failure applies only to those people with a WHO stage 3 or 4 condition in the past 3 months, or a CD4 count < 200 /mm3 (Table 2f).

**Table 1.** Description of setting scenarios in 2020.

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| --- | --- | --- |
| **Characteristic** | **Model (2020)**  (median, range) | **Examples of observed data\*** |
| HIV prevalence (age 15-49) | 13% (4% - 30%) | Zimbabwe 2016 13%, Tanzania 2017 5%, Uganda 2017 6%, Lesotho 2017 24%, Eswatini 2017 27%, Malawi 2016 10%, Namibia 2017 12%, Zambia 206 11%, Cameroon 2017 3.4%, Cote d'Ivoire 2017/18 2.5%, Mozambique 11% |
| HIV incidence age 15-49 (/100 person years) | 0.96 (0.20 – 3.02) | Malawi 2016 0.37, Zambia 2016 0.66, Zimbabwe 2016 0.45, Lesotho 2017 1.55, Namibia 2016 0.40, eSwatini 2017 1.48, Tanzania 2017 0.27, Cameroon 2017 0.27 |
| Proportion of HIV positive people diagnosed | 91% (73% - 96%) | Malawi 2016 77%, Zambia 2016 67%, Zimbabwe 2016 74%, Namibia 2017 86%, Tanzania 2017 52%, Ethiopia 2018 72%, Cote d'Ivoire 2017/18 37%, Cameroon 2017 47% |
| Proportion of diagnosed HIV+ people on ART | 94% (84% - 98%) | Lesotho 2016/17 92%, South Africa 2017 71%, Eswatini 2016/17 87%, Namibia 2017 96%, Zambia 2016 87%, Tanzania 2016/17 94%, Ethiopia 99%, Malawi 2016 91%, Uganda 2016/17 90%, Cameroon 2017 91%, Zimbabwe 2016 87%, Cote d'Ivoire 2017/18 88%, Cameroon 2017 91%. |
| Proportion of all HIV positive people with VL < 1000 copies/mL | 69% (47% - 83%) | Zambia 2016 60%, Malawi 2016 68%, Zimbabwe 2016 60%, eSwatini 2017 73%, Lesotho 2017 68%, Tanzania 2017 52%, Uganda 2017 60%, Namibia 2017 77%, Ethiopia 2018 70%, Cote d'Ivoire 2017/18 40%, Cameroon 2017 47%. |
| Proportion of ART experienced people who have started 2nd-line ART | 10% (2% - 26%) | Malawi ~3%% (Malawi MoH Quarterly Reports) |
| Of people on ART, proportion with VL < 1000 | 86% (65% - 95%) | Zambia 2016 Men/Women 88%/90%, Malawi 2016 90%/92%, Zimbabwe 2016 84%/88%, Namibia 2017 92%/90%, Tanzania 2017 89%/83%, Ethiopia 2018 95%/87%, Cote d'Ivoire 2017/18 76%, Cameroon 2017 80%. |
| Of people on ART, proportion with CD4 < 500 | 47% (40% - 58%) | eSwatini 40% 2016/17, Malawi 52% 2016, Tanzania 2017/17 55%, Zambia 2016 59%. |
| Of ART naïve ART initiators % with NNRTI resistance | 30% (8% - 58%) | Angola 2012 14%, Botswana 2016 8%, South Africa 2017 14%, Zimbabwe 2015 10%, Namibia 9%, Uganda 2016 16%, Cameroon 8%. (HIV drug resistance report 2017) |
| Mother to child transmission rate | 9% (0% - 28%) | (including breastfeeding period) Botswana 5%, South Africa 5%, Namibia 6%, Uganda 8%, Zimbabwe 7%, Malawi 9%, Tanzania 12%, Ethiopia 21%, Cote d'Ivoire 16%, Cameroon 15% (UNAIDS 2019) |
| Proportion of women age 15-49 who are sex workers | 2.2% (0.8% - 5.2%) |  |
| Proportion of people on PrEP | 0.06% (0% - 0.27%) |  |
| Proportion of men circumcised | 32% (12% - 54%) |  |

\* all data from PHIA surveys (Population Health Impact Surveys. <https://phia.icap.columbia.edu/>), South Africa (HSRC survey), Botswana (BCPP 2013-15) unless stated

**Table 2 a**

|  |  |  |
| --- | --- | --- |
| **Timing of repeat viral load, in context of TLE 1st line regimen (****no transition to dolutegravir is made before or during follow up) (n=50 setting scenarios)** | | |
| **Outcomes (mean over 3 month periods) over 20 years** | **Repeat VL after 3 months** | **Repeat VL after 6 months** |
| Of people on ART, percent on efavirenz | 82.0% | 82.5% |
| Of people with who have ever started ART, proportion with current VL < 1000 | 70.8% | 70.6% |
| Of people on ART, proportion with current VL < 1000 | 79.5% | 79.2% |
| All cause death rate in people on ART | 3.58 | 3.62 |
| HIV death rate in all people with HIV | 2.54 | 2.57 |
| DALYs incurred per year | 1,309,719 | 1,310,170 |
| DALYs averted\* | ---- | -409 |
| Total cost of HIV programme | $256.5m | $255.5m |
| Difference in cost\* | ---- | -$0.98m |
| Net DALYs | 1822672 | 1821171 |
| Difference in net DALYs\* | ---- | - 1501 (standard error 1117) |

\* discounted at 3% per annum

**Table 2 b**

|  |  |  |
| --- | --- | --- |
| **Timing of repeat viral load, in context of TLD 1st line regimen. Context:** **transition of all to TLD made pre-baseline. (n=50 setting scenarios)** | | |
| **Outcomes (mean over 3 month periods) over 20 years** | **3 months** | **6 months** |
| Of people on ART, percent on dolutegravir | 94.7% | 95.0% |
| Of people with who have ever started ART, proportion with current VL < 1000 | 80.0% | 80.0% |
| Of people on ART, percent with current VL < 1000 | 88.0% | 87.9% |
| All cause death rate in people on ART | 2.54 | 2.57 |
| HIV death rate in all people with HIV | 1.51 | 1.52 |
| DALYs incurred per year | 1245507 | 1246499 |
| DALYs averted\* | ---- | -1054 |
| Total cost of HIV programme | $212.2m | $211.5m |
| Difference in cost\* | ---- | -$0.63m |
| Net DALYs | 1,669,856 | 1,669,594 |
| Difference in net DALYs\* |  | -263 (standard error = 987) |

\* discounted at 3% per annum

**Table 2 c**

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| **Timing of initial viral load, in context of TLE 1st line regimen. Context: no transition to dolutegravir is made before or during follow up. (n=50 setting scenarios)** | | |
| **Outcomes (mean over 3 month periods) over 20 years** | **1st VL 6 months** | **1st VL 3 months** |
| Of people on ART, percent on efavirenz | 83.2% | 83.0% |
| Of all people who started ART 12 months ago, percent with VL < 1000 | 70.8% | 70.5% |
| Of people who started ART 12 months ago and are currently on ART, proportion with VL <1000 | 82.7% | 82.5% |
| Of people with who have ever started ART, proportion with current VL < 1000 | 70.8% | 70.6% |
| Of people on ART, percent with current VL < 1000 | 79.5% | 79.2% |
| All cause death rate in people on ART | 3.46 | 3.45 |
| HIV death rate in all people with HIV | 2.40 | 2.39 |
| DALYs incurred per year | 1,313,188 | 1,312,899 |
| DALYs averted\* |  | 292 |
| Total cost of HIV programme | $263.5m | $264.4m |
| Difference in cost\* | ---- | +$0.88m |
| Net DALYs | 1,840,252 | 1,841,724 |
| Difference in net DALYs\* |  | +1472 (standard error = 1488) |

\* discounted at 3% per annum

**Table 2 d**

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| --- | --- | --- |
| **Timing of initial viral load, in context of TLD 1st line regimen. Context: transition to TLD 1st line regimen is made in2019 – people already on TLE are not moved to TLD. (n=50 setting scenarios)** | | |
| **Outcomes (mean over 3 month periods) over 20 years** | **1st VL 6 months** | **1st VL 3 months** |
| Of people on ART, percent on efavirenz | 42.2% | 42.3% |
| Of all people who started ART 12 months ago, percent with VL < 1000 | 88.2% | 88.6% |
| Of people who started ART 12 months ago and are currently on ART, proportion with VL <1000 | 91.3% | 91.8% |
| Of people with who have ever started ART, proportion with current VL < 1000 | 79.5% | 79.5% |
| Of people on ART, percent with current VL < 1000 | 87.7% | 87.7% |
| All cause death rate in people on ART | 2.72 | 2.72 |
| HIV death rate in all people with HIV | 1.74 | 1.75 |
| DALYs incurred per year | 1,313,006 | 1,312,209 |
| DALYs averted\* |  | 788 |
| Total cost of HIV programme | $239.9m | $240.4m |
| Difference in cost\* | ---- | +$0.46m |
| Net DALYs | 1,792,842 | 1,792,975 |
| Difference in net DALYs\* |  | +133 (standard error = 1053) |

\* discounted at 3% per annum

**Table 2 e**

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| **Single vs confirmed VL to determine failure, in context of TLE 1st line regimen. Context: ART policy of transition to TLD in new initiators made in 2019; ZLD is 2nd line regimen in people with TLE failure from 2019. (n=50 setting scenarios)** | | |
| **Outcomes (mean over 3 month periods) over 20 years** | **Confirmed VL** | **Single VL** |
| Of people on ART, percent on efavirenz | 41.9% | 37.6% |
| Of people on ART, percent on dolutegravir | 50.8% | 55.1% |
| Proportion of people who have fulfilled criteria of 1st line ART failure | 14.4% | 20.7% |
| Of people with who have ever started ART, proportion with current VL < 1000 | 79.1% | 80.0% |
| Of people on ART, proportion with current VL < 1000 | 87.6% | 89.2% |
| All cause death rate in people on ART | 2.75 | 2.53 |
| HIV death rate in all people with HIV | 1.70 | 1.51 |
| DALYs incurred | 1,238,017 | 1,227,204 |
| DALYs averted\* | ---- | 10,773 |
| Cost incurred | $209.1m | $210.4m |
| Difference in cost\* | ---- | +$1.21m |
| Net DALYs | 1,656,297 | 1,647,912 |
| Difference in net DALYs\* | ---- | -8385 (standard error = 1451) |

\* discounted at 3% per annum

**Table 2 f**

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| **Single vs confirmed VL to determine failure, in context of TLE 1st line regimen for people with advanced HIV disease (CD4 count < 200 or recent WHO stage 3 or 4 condition). Context: ART policy of transition to TLD in new initiators made in 2019; ZLD is 2nd line regimen in people with TLE failure from 2019. (n=50 setting scenarios)** | | |
| **Outcomes (mean over 3 month periods) over 20 years** | **Confirmed VL** | **Single VL** |
| Of people on ART, percent on efavirenz | 41.4% | 40.1% |
| Of people on ART, percent on dolutegravir | 51.6% | 52.4% |
| Proportion of people who have fulfilled criteria of 1st line ART failure | 13.3% | 16.5% |
| Of people with who have ever started ART, proportion with current VL < 1000 | 79.6% | 79.9% |
| Of people on ART, proportion with current VL < 1000 | 87.6% | 88.2% |
| All cause death rate in people on ART | 2.75 | 2.54 |
| HIV death rate in all people with HIV | 1.66 | 1.49 |
| DALYs incurred | 1,254,337 | 1,243,444 |
| DALYs averted\* | ---- | 10,931 |
| Cost incurred | $248.6m | $251.4m |
| Difference in cost\* | ---- | +$2.86m |
| Net DALYs | 1,751,507 | 1,746,327 |
| Difference in net DALYs\* | ---- | -5180 (standard error = 1459) |

\* discounted at 3% per annum

**References**

1. Phillips AN, Venter F, Havlir D, Pozniak A, Kuritzkes D, Wensing A, et al. Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study. Lancet HIV. 2019;6(2):e116–27.
2. Phillips AN, Bansi-Matharu L, Venter F, Havlir D, Pozniak A, Kuritzkes, et al. Updated assessment of risks and benefits of dolutegravir versus efavirenz in new antiretroviral treatment initiators in sub-Saharan Africa: modelling to inform treatment guidelines. VOLUME 7, ISSUE 3, E193-E200, MARCH 01, 2020