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Cutting the cost of South African antiretroviral therapy using newer, safer drugs

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Antiretrovirals are a significant cost driver for HIV programmes. Current first-line regimens have performed well in real-life programmes, but have a low barrier to virological resistance and still carry toxicity that limits adherence. New drug developments may mean that we have access to safer, more robust and cheaper regimens, but only if the appropriate clinical trials are conducted. We briefly discuss these trials, and demonstrate the large cost savings to the South African HIV programme if these are successful.


South Africa (SA) may be able to provide antiretroviral therapy (ART) to several million more people with HIV by 2019, using the current drug budget. While planned simplification of HIV service delivery promises to reduce expenditure, the drug cost of ART provision consumes the bulk of most HIV programme budgets, and is unlikely to decrease significantly, as multiple generic competitors have realised manufacturing efficiencies for current formulations. SA has the largest ART programme in the world, with domestic funding accounting for >75% of all HIV spending.[5,6] For the year 2014 - 2105, USD350 million was spent on ART for just <3 million people living with HIV, most of it on current formulations. SA has the largest ART programme in the world, using a quarter of global production. Two drugs, dolutegravir (DTG) and a new prodrug variant of tenofovir, tenofovir alafenamide (TAF), have been or are currently in the process of being licensed to multiple generic manufacturers by originator manufacturers directly or through voluntary licensing via Medicine Patent Pool (United Nations, Switzerland) processes. In short, replacing EFV, which is very vulnerable to resistance and drives most first-line side-effects, with DTG provides a better tolerated and cheaper drug with a high resistance barrier, limiting transition to expensive and less well-tolerated, toxic next-line treatments. TAF is substantially cheaper than TDF, a major cost driver of first-line therapy, and provides some bone and renal toxicity benefits.[5,7] Co-formulating the two drugs with FTC or 3TC would also substantially reduce the size of the current tablet, making it easier to manufacture, while saving on packaging and storage space. However, the two drugs – TAF and DTG – are manufactured by competing companies, where commercial
Lower drug costs of DTG/TAF-containing regimens compared with current first-line drugs. The cost of current first-line therapy is ~USD110/patient/year.[3,6] We have estimated an initial 20% saving (a conservative estimate provided to the authors by manufacturers for DTG/TAF cost saving over the current regimen of EFV/TDF/FTC) and a 50% saving once volumes are met (as estimated by the Clinton Health Access Initiative (CHAI), USA).

- Limiting transition of patients from first- to second-line therapy owing to better tolerability and robustness of DTG/TAF-containing regimens. These savings are expected to accumulate through lower second-line drug costs (second-line therapy costs ~USD350[3,6]), but also lower service delivery costs and decreased viral load monitoring.

The rate of transition from first-line to second-line regimens is not available. Since 2004, the number of SA patients on second-line treatment have increased to 145 000. These figures may have been initially inflated owing to the use of more toxic stavudine-containing regimens in use until 2010. In the calculations, we assume a 2% annual transition from first- to second-line treatment for anyone on the EFV-containing regimen (DoH assumed 4% for the previous tender, but the limited data suggest that this is an underestimate). In comparison, as no DTG-related virological failure due to resistance has occurred in the initial 600 000 patients on first-line treatment in Europe or the USA, we assumed that there would be no significant switching to second-line therapy in the years modelled.[3,6] For simplicity, and because the numbers are small, we have not factored in the effect on third-line initiations.

A move to DTG-TAF-based regimens will have to be phased as manufacturers scale-up and patients (both new initiations and established patients) transition to the new regimen. In this analysis, we compare three transition scenarios of different scale-up assumptions with the current status quo:

- Status quo: EFV/TDF/FTC remains the first-line regimen, with 300 000 people initiating first-line treatment annually and 2% migrating to second-line treatment.
- Conservative scenario: continued initiation at 300 000 annually – at first only new initiations qualifying for DTG/TAF/FTC, others remaining on EFV/TDF/FTC and slowly transitioning to the new regimen over 3 years.
- Moderate scenario: initiations at 400 000 annually, with at first only new initiations qualifying for DTG/TAF/FTC, and transitioning over 2 years.
- Aggressive scenario: initiations at 500 000 annually, with everyone moving to DTG/TAF/FTC within a year.

Calculations are for expected savings in drug costs for 4 years from 2019; USD values are used, as manufacturing is largely dependent on USD-based acquisitions of materials. The USD450 million baseline is the estimated cost of ART in 2019, based on the current costs for 2014-2015 and the estimated programme growth. We note that there are currently wide currency fluctuations, introducing manufacturing and other uncertainties. Future costs have not been discounted, nor lost-to-follow-up costs or decreased costs associated with less second-line monitoring; we have also not factored in costs of the introduction of new regimens, such as training.

### Results

As shown in Figs 1 and 2, all scenarios for the introduction of DTG/TAF-based regimens translate into substantial reductions in ART drug costs for SA. The aggressive model with new drugs treats 800 000 people more than the status quo over 4 years, and with >USD200 million saving. Moreover, using the current budget for ART drugs, we could cover the ART drug costs of treating an additional 2 million people.

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**Table 1. Summary of the ADVANCE study**

| Investor driven, study drug donated by company | USAID and UNITAID |
| Non-inferiority design, ~1 100 participants, over 96 weeks | Conducted in Johannesburg, start date: beginning 2017 |
| Eligibility criteria | Needing first-line ART |
| No CD4 threshold | >12 years of age, >40 kg |
| Compares three combinations: DTG/TAF v. DTG/TDF v. EFV/TDF (current first line in SA), all with FTC | Primary endpoint is viral suppression at 48 weeks |
| Pharmacokinetic sampling of both DTG/TAF in those who contract TB or become pregnant | **USAID** = United States Agency for International Development. |

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co-ordinated locally by CHAI, in partnership with the DoH. If TAF is not registered in time, or if problems arise in the TB or pregnancy studies, the DTG/TAF/FTC regimen also being tested in ADVANCE confers significant clinical and cost benefits. Finally, ART drug costs account for about a quarter of cost of HIV care in SA (it is a greater proportion in countries where salaries are lower and laboratory monitoring is more limited); therefore, attention to systemic cost drivers are still needed.[7,10]

If successful, patients will benefit with a much safer and more forgiving regimen in a smaller tablet, government and other funders will save money, while pharmaceutical producers will have simplified manufacturing, using lower volumes of active pharmaceutical ingrediants. In an age of escalating medical costs, we are seldom presented with a win-win scenario with regard to clinical care. The clinical studies and registration processes to secure inclusion of these two new drugs, if successful, would be a huge SA victory to complement the current successful ART roll-out, with knock-on effects for the entire region and other low- and middle-income countries.

Disclosure. Several authors are involved in the ADVANCE studies and sub-studies, with the support of the United States President’s Emergency Plan for AIDS Relief (PEPFAR)/United States Agency for International Development (USAID) and UNITAID, in a broader collaboration addressing drug formulation and introduction, called OPTIMIZE. The study drug is donated by the originator companies, ViV HealthCare (UK) and Gilead Sciences (USA). The views of this study are those of the authors and do not necessarily reflect the views of USAID, UNITAID or the SA or US governments. Raw data may be requested from the corresponding author, W D F Venter (fventer@wrhi.ac.za).

Fig. 1. Estimated increase in patients needing ART in SA. Number of people on antiretrovirals in SA (status quo = 300 000 initiating therapy annually, 2% migration to second line, conservative = 300 000 annually, transition from old regimen (EFV/TDF/FTC) to new (DTG/TAF/FTC) over 3 years; moderate = new regimen, 400 000 annually, transition over 2 years; aggressive = new regimen, 500 000 annually, transition over 1 year).

Fig. 2. Estimated crude savings on antiretroviral drugs (assuming implementation of new regimen in 2019 - 2020). Cumulative savings compared with status quo (conservative = 300 000 annually, transition from old regimen to new over 3 years; moderate = new regimen, 400 000 annually, transition over 2 years; aggressive = new regimen, 500 000 annually, transition over 1 year).

Conclusion

The introduction of DTG/TAF-based regimens could potentially translate into substantial savings to the SA health budget, if ADVANCE is completed rapidly and is successful, and if manufacturing is quickly scaled up to meet demand. Essentially, with the current ART budget, we could purchase DTG/TAF/FTC for everyone taking ART at the end of 4 years, even assuming the high end of 500 000 new patients needing treatment annually.

Clinical evidence of the efficacy of both drugs is compelling, although questions remain around drug interactions with rifampicin and use in pregnancy, all being evaluated in clinical trials. In tandem, addressing the complex registration of new drugs (TAF has yet to be registered by the MCC) and combinations, including those of generic manufacturers, will need synchronisation, currently being planned for a March 2017 timeframe. A successful conclusion to these processes would allow for earlier patient access and would mean that a win-win scenario with regard to clinical care is possible.

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