Predicted levels of HIV drug resistance: potential impact of expanding diagnosis, retention, and eligibility criteria for antiretroviral therapy initiation

Valentina Cambiano\textsuperscript{a}, Silvia Bertagnolio\textsuperscript{b}, Michael R. Jordan\textsuperscript{c}, Deenan Pillay\textsuperscript{d}, Joseph H. Perriëns\textsuperscript{b}, Francois Venter\textsuperscript{e}, Jens Lundgren\textsuperscript{f} and Andrew Phillips\textsuperscript{a}

\textbf{Background:} There is concern that the expansion of antiretroviral roll-out may impact future drug resistance levels and hence compromise the benefits of antiretroviral therapy (ART) at an individual and population level. We aimed to predict future drug resistance in South Africa and its long-term effects.

\textbf{Methods:} The previously validated HIV Synthesis model was calibrated to South Africa. Resistance was modeled at the level of single mutations, transmission potential, persistence, and effect on drug activity.

\textbf{Results:} We estimate 652 000 people (90\% uncertainty range: 543 000–744 000) are living with nonnucleoside reverse transcriptase inhibitor (NNRTIs)-resistant virus in South Africa, 275 000 in majority virus [Non-nucleoside reverse transcriptase inhibitor resistant virus present in majority virus (NRMV)] with an unsuppressed viral load. If current diagnosis and retention in care and eligibility criteria are maintained, in 20 years’ time HIV incidence is projected to have declined by 22\% (95\% confidence interval, CI \(-23\) to \(-21\%\)), and the number of people carrying NNRTI resistance to be 2.9-fold higher. If enhancements in diagnosis and retention in care occur, and ART is initiated at CD4\textsuperscript{+} cell count less than 500 cells/\mu l, HIV incidence is projected to decline by 36\% (95\% CI: \(-37\) to \(-36\%\)) and the number of people with NNRTI resistance to be 4.1-fold higher than currently. Prevalence of people with viral load more than 500 copies/ml carrying NRMV is not projected to differ markedly according to future ART initiation policy, given the current level of diagnosis and retention are maintained.

\textbf{Conclusion:} Prevalence of resistance is projected to increase substantially. However, introduction of policies to increase ART coverage is not expected to lead to appreciably higher prevalence of HIV-positive people with resistance and viral load more than 500 copies/ml. Concern over resistance should not stop expansion of treatment availability.
Introduction

Antiretroviral therapy (ART) continues to be rolled out in sub-Saharan Africa. South Africa is the country with the largest number of people infected with HIV, 5.6 million adults by mid-2011 [1], with an estimated 1.7 million people on ART by the end of 2012 [2]. Although ART is highly effective, there is concern over the potential for emergence and transmission of HIV drug resistance. In one study in South Africa, it has been estimated that 12% of those on treatment at 1 year had a viral load (viral load) above 400 copies/ml [3] and of those with virological failure, between 66 [4] and 83% [5] had resistance detected. Selection of drug resistance is a concern not just for individual patients, who may have reduced treatment options, but also for society because of potential transmission of drug-resistant HIV, which could compromise the effectiveness of available first-line regimens for a substantial portion of the population and increase the need for costly second-line drugs. In the 2012 WHO HIV drug resistance report [6], among 44 population-based surveys conducted in recently infected populations in Africa between 2004 and 2010, the percentage of surveys reporting moderate (5–15%) levels of transmitted drug resistance (TDR) increased from 18% in 2004–2006 to 41% in 2007–2010. A meta-analysis estimating trends in prevalence of HIV-1 drug resistance in recently and chronically infected ART-naïve individuals found a relative increase of 14% per year in the prevalence of nonnucleoside reverse transcriptase inhibitor (NNRTIs) resistance in southern Africa [7]. This is consistent with the finding that the proportion of people with NNRTI resistance at ART initiation increased from 3.4% in 2007 to 5.4% in 2010 in Africa [6]. These data stress the importance of having regular estimates of the incidence and prevalence of HIV drug resistance at country level, and projections of potential future levels.

In July 2013, WHO released new guidelines recommending initiation of ART when the CD4\(^+\) cell count falls below 500 cells/\(\mu\)l rather than 350 cells/\(\mu\)l [8]. In addition, policies recommending initiation of ART in all positive people regardless of CD4\(^+\) cell counts have been considered, given that virally suppressive ART reduces infectivity close to zero [9]. Apart from changing the threshold for ART initiation, another (not mutually exclusive) approach to increase the number of people receiving ART is to concentrate on maximizing rates of diagnosis and linkage and retention in both pre-ART and ART care. Such an approach will require substantial augmentation of health system infrastructure and reduction in social stigma associated with HIV and as such it represents a more ambitious undertaking than modifying the ART initiation threshold.

Models generally agree that a policy of earlier initiation of ART will lead to a reduction in HIV incidence, although they differ in their assessment of the most cost-effective policy for South Africa [10]. The potential for increased emergence of drug resistance is one factor to consider when comparing such potential new policies. Wider ART coverage is highly likely to lead to an increase in the proportion of new infections with TDR. However, it is difficult to predict whether the benefits of reduced incidence will outweigh this risk of higher levels of resistance. As countries consider embarking on ART-based approaches to HIV prevention, an increased understanding of the potential effects of this policy shift on resistance is needed.

In this study, we use a detailed, validated individual-based simulation model (HIV Synthesis) calibrated to South Africa’s epidemic to estimate and project current and future incidence and prevalence of drug resistance (acquired on ART and transmitted) under the current conditions. These outcomes are compared to the projected level of resistance in the context of expanded eligibility criteria for ART, and enhancements in diagnosis and retention.

Methods

Synthesis transmission model
We use the HIV Synthesis model [11,12] to simulate the heterosexual transmission of HIV in the adult population of South Africa and, in those infected, the progression of infection and the effects of ART. Details about the model, data used in its calibration, input parameters, and a full description of the current analyses are presented in the Supplementary Material, http://links.lww.com/QAD/A417. It is important to note that for the reduction in HIV incidence from 2012 to 2032, both the 95% confidence interval (CI) and the 90% uncertainty range are presented. The first reflects the stochastic variability, whereas the second the uncertainty on the parameters. The model has been calibrated to South Africa based on HIV prevalence among adults (age 15–49) and young people (age 15–25) [13], the proportion of people who ever had an HIV test [13], the number who started ART [14], and the proportion of new diagnoses with resistance [6]. Projected population growth is also incorporated [15].

Cascade of testing and care
HIV testing and diagnosis, linkage to pre-ART care, monitoring and retention in pre-ART care, ART initiation, monitoring and retention while on ART are modeled, as are clinic visits and timing of measurement of CD4\(^+\) cell count and viral load. People on first-line regimens are monitored measuring viral load 6-monthly until mid-2010, while from mid-2010 at 6 and 12 months, and then annually afterwards. Before mid-2010, the criterion to switch people to second-line regimen is a viral load measurement above 400 copies/ml followed by
another above 5000 copies/ml [16]; after mid-2010, the recommended threshold for the confirmatory viral load is 1000 copies/ml [16,17]. Once virological failure is confirmed, it is assumed that the median time to switch to second-line is 5 months [24]. It is possible that the switching rates at national level are even lower and that, if anything, we have overestimated the current number of people on second-line of treatment. More details are available in the Supplementary Material, http://links.lww.com/QAD/A417.

Resistance
Resistance is modeled in terms of the presence or absence of mutations specific to the drugs in use. Distinction is made for each mutation as to whether it is only present in minority virus, and thus assumed nontransmissible, even if viral load is high, or if it is present in majority virus. The presence or absence of resistant mutations does not influence the infectivity of a person, for a given viral load. For a newly infected person, the probability that the source partner has resistant virus in the majority circulating virus is determined by the prevalence of resistance among those (stratified by type of partnership) at that viral load level, taking into account number of partnerships formed. It is not assumed that all resistance mutations present in majority virus in the source partner are established in the circulating virus of the newly infected person. Establishment of drug-resistant virus in the majority quasispecies of a newly infected individual for whom the source partner had resistance mutation(s) varies by drug-resistance mutations: 11% chance for M184V and K65R, 56% for NNRTI mutations, and 45% for thymidine analogue mutations (TAMs), L74V, Q151M, and protease inhibitors mutations [18,19]. Once the mutation is transmitted and established in the new host, the rate of loss of drug-resistant mutation from majority virus is 0.16 per year [20].

The probability of selection of drug-resistant virus among people on ART is determined by the number of active drugs in the regimen (wherein activity level for each drug ranges from 0 to 1, except for boosted protease inhibitors, which are assumed to have double potency, based on its effects as a monotherapy, and is determined by presence of relevant resistance mutations), viral load, and individuals’ current adherence (see Supplementary Material, http://links.lww.com/QAD/A417). Mutations acquired while on ART can be lost from majority virus after the drug selecting for it is discontinued, although these mutations will remain in minority virus [21,22]. The probability of reversion to wild type varies by mutation. It is estimated that by 3 months after discontinuation of the drug selecting for a specific mutation, the chance of losing it from the majority virus is 80% for M184V; 60% for K65R, L74V, and Q151M; 40% for TAMs; and 20% for NNRTIs and protease inhibitors mutations [21,22]. Mutations will remain detectable in the majority virus if the drug selecting for the mutation is replaced by another that selects for the same mutation, otherwise they will remain only in minority virus. Mutations present in minority virus re-emerge in majority virus when one of the corresponding drugs is restarted.

Potential scenarios and antiretroviral therapy initiation policy changes modeled
We consider two potential scenarios regarding diagnosis and retention. In one (‘enhanced diagnosis and retention’) significant improvements in HIV testing, linkage to care and retention in pre-ART care are made so that 80% of people who become eligible for ART are in care, and retention on ART is improved so that 92% of patients are retained on ART 1 year after ART initiation (representing a 50% reduction in loss to follow-up while on ART). This is compared with a scenario assuming no change after 2012 in these factors. Within each of these two scenarios, three different ART initiation policies are considered: at CD4+ cell count below 500 cells/μl (currently recommended by WHO), at time of diagnosis regardless of CD4+ cell count, or continuation of the existing policy in South Africa of initiation at CD4+ cell counts below 350 cells/μl.

Results
The characteristics of the epidemic, as predicted by the model, at the end of 2012, are summarized in Table 1. The median and 90% range across the simulations with the best fit to the South African epidemic are reported. The median CD4+ cell count at diagnosis, across all those who have been diagnosed up to the end of 2012, is assumed to be relatively high at 367 cells/μl. However, the median CD4+ cell count at ART initiation, across all those who have initiated ART up to 2012, is much lower, at 116 cells/μl. Based on fitting to data on the proportion with TDR among those thought to be recently infected with HIV from the WHO surveillance data from sub-Saharan Africa up to 2010, the modeled percentage of newly diagnosed people with drug-resistance mutations present in majority virus in 2012 is 5.9% and the proportion initiating ART with Non-nucleoside reverse transcriptase inhibitor resistant virus present in majority virus (NRMV) is 3.7%. Additionally, the median percentage of people infected with HIV in 2012 who have TDR is much higher at 13.8%, with a slightly lower proportion infected with key NNRTI-associated mutations (10.4%).

Figure 1a presents the number of people HIV-positive and receiving first and second-line treatment under the two different diagnosis and retention scenarios and the three ART initiation policies. In 2012, 5.3 million are estimated to be HIV-positive and 1.8 million adults to be receiving ART, of which 9.9% second-line regimens.
By 2032, assuming current levels of diagnosis and retention and ART initiation eligibility criteria are maintained, 3.3 million are projected to be receiving ART, with 35% (1.1 million) on second-line regimens. Changing the threshold at which a person is eligible for treatment is predicted to have minimal impact on the number of people on ART and on the number requiring second-line regimens. However, under a scenario of enhanced diagnosis and retention, between 4.9 and 5.2 million will be on ART, of whom 40–42% (2.0–2.1 millions) on a second-line regimen.

Figure 1b shows the estimated number of people living with NNRTI-resistant virus in 2012 and projected numbers in 20 years’ time. In 2012, 652 000 are estimated to have NNRTI resistance, of whom 42% (approximately 275 000) are people with NRMV with viral load above 500 copies/ml (see footnote of Figure 1b), and therefore have an increased risk transmitting NNRTI drug-resistant virus [23]. If existing policies continue, the number of people living with NNRTI resistance is predicted to be 2.8-fold higher in 2032 (from 652 000 in 2012 to 1 862 000). Of these, 68% are predicted to be on ART with suppressed viral load or to have resistance in minority virus. Therefore, the subset of the population with an increased risk of transmitting NNRTI-resistant virus (viral load >500 copies/ml and NRMV) is approximately 594 000. Modifying the CD4⁺ cell threshold at which a person is eligible to start ART from 350 to 500 cells/μl or to all people diagnosed with HIV, regardless of CD4⁺ cell count, without the enhancement in diagnosis and retention, results in a 3.0-fold and a 3.2-fold increase, respectively, in the number of people living with NNRTI resistance, compared with the level in 2012.

Alternatively, with enhanced diagnosis and retention and people with CD4⁺ cell between 350 and 500 cells/μl additionally becoming eligible to initiate ART, the number of people carrying NNRTI resistance in 2032 is expected to be 4.1-fold higher than in 2012. However, 73% are predicted to be on ART with suppressed viral load or have the resistant virus in minority virus, yielding approximately 719 000 individuals with a viral load above 500 copies/ml and NRMV.

Overall, the percentage of people with resistant virus that can be originally ascribed to TDR is predicted to increase from 33% in 2012 to 38% in 2032 without enhancement of diagnosis and retention, but to remain stable at
**Predicted levels of HIV drug resistance** Cambiano et al. 519

Fig. 1. (a) Estimated number of people HIV-positive, on antiretroviral therapy (ART), stratified by first-line or second-line of treatment regimen [median value and 90% uncertainty range (UR)]; (b) Estimated number of people living with nonnucleoside reverse transcriptase inhibitor (NNRTI) drug resistance in South Africa in 2012 and in 2032 (median value and 90% UR); (c) HIV incidence with drug-sensitive and drug-resistant virus in 2012 and in 2032 (average and 95% confidence interval for HIV incidence change), according to access to care and retention on ART and ART initiation policy.
approximately 33% should an enhancement in diagnosis and retention and a change in the CD4$^+$ cell threshold at which people are eligible to initiate ART to CD4$^+$ cell count less than 500 cells/µl, occur.

In Figure 1c, the average HIV incidence, stratified by whether the virus is drug-sensitive or drug-resistant in 2012 and in 20 years’ time is displayed. Overall HIV incidence is predicted to be 22% lower (95% CI: −23%, −21%) in 20 years’ time under the current scenario. With no enhancement in diagnosis and retention, changing ART eligibility criteria, from 350 to 500 cells/µl, has only a moderate effect: an additional 3 and 6% reduction in incidence, respectively (up to 28%). The same reduction in HIV incidence (28%) can be achieved if, instead, there is an enhancement in diagnosis and retention and the ART initiation threshold is maintained at CD4$^+$ cell count less than 350 cells/µl. A change in initiation threshold to CD4$^+$ cell count less than 500 cells/µl, in addition to the enhancement in diagnosis and retention, has a negligible impact on future incidence of new infections with TDR, whatever the scenario on diagnosis and retention.

Discussion

There is great interest in expanding ART by increasing the number of HIV-positive people in care and by changing the initiation threshold. Our results suggest that prevalence of drug resistance and need for more expensive second-line regimens are likely to increase substantially in future years as ART roll-out continues, even if policies are not changed. This is an inevitable consequence of having an increasing number of people on ART. Nevertheless, if current levels of diagnosis, retention, eligibility criteria to initiate ART (CD4$^+$ cell count <350 cells/µl), and viral load monitoring are maintained, in 20 years’ time, over 60% of people with drug resistance to first-line agents are projected to be on a suppressive, second-line regimen. Likely due, largely, to the increase in the number of people on ART with viral replication suppressed, overall HIV incidence is predicted to drop by 22% in 20 years, if current levels of diagnosis and retention are maintained. It is noteworthy that by substantially improving diagnosis and retention, while
maintaining as ART initiation policy CD4⁺ cell count less than 350 cells/µl, it is possible to achieve the same reduction in HIV incidence as a change in the ART initiation to all people diagnosed, with the important difference that the first will avoid ART initiation in persons for whom the individual health benefits remain unproven. However, the feasibility of implementing our scenario of enhanced diagnosis and retention is difficult to assess.

The decrease is predicted to be 36%, if diagnosis and retention are increased substantially and a policy of ART initiation at CD4⁺ cell count below 500 cells/µl is adopted. Incidence of HIV infections with TDR is predicted to remain stable. However, due to an overall decrease in HIV incidence, the proportion of new infections with TDR is projected to increase substantially (from 14% in 2012 to 30% in 20 years’ time).

It must be recognized that the high levels of increase in diagnosis and retention assumed in these simulations would require major investment, not only to provide treatment to higher numbers of people, but to significantly strengthen health systems to dramatically improve pre-ART and on ART retention. Public health interventions to promote social acceptance and reduce stigma will be necessary to achieve these high levels of diagnosis, linkage to care and retention. Interventions such as home-based counseling and testing [26], self-testing [27], and mobile voluntary counseling and testing supported by community mobilization [28] have demonstrated to be feasible and effective in increasing the number of people tested for HIV. Provision of point-of-care CD4⁺ cell measurement at the same time and place of HIV testing [29] and formal pre-ART care services providing counseling, regular review, clinical staging, social and psychological support and prevention and management of opportunistic infections, such as tuberculosis (TB), have been shown to increase, both, the proportion evaluated for ART eligibility and, the second, initiated on ART [30]. Once on ART, allowing patients to visit the clinic less often and providing adherence monitoring with community groups have been found to be effective in minimizing the number of people lost to follow-up [30].

Data on new infections with TDR come mainly from WHO surveillance studies. In these, a resistance test is conducted among samples from newly diagnosed individuals less than 25 years of age and/or with a CD4⁺ cell count more than 500 cells/µl (if available) and no previous pregnancy, if female [31]. These criteria increase the likelihood that people surveyed are likely to have been recently infected with HIV and ART-naive. In our work, the modeled proportion of new diagnoses with resistance in 2012 is 5.9%, similar to that obtained when restricted to people with the criteria used in WHO surveys (data not shown). This figure is much lower than the estimated 14% of new infections with TDR. The difference between the proportion with TDR at infection and at diagnosis may be explained by the time-lag between infection and diagnosis, in that those currently diagnosed with HIV may have been infected earlier, when resistance levels were lower. In addition, some drug-resistance mutations may not persist in majority virus after infection [20].

Other mathematical models find that in resource-limited settings, the prevalence of acquired and transmitted resistance will increase with greater ART availability [32,33]. Blower et al. [32] predicted that providing ART to 10–50% of an HIV infected population was likely to result in 5.9% of new infections having resistance in 10 years after treatment roll-out [32]. Given the initial plan to roll out ART in Africa to 3 million individuals [34] corresponding to 5–10% of the HIV-infected population, Blower et al. [35] estimated that after 10 years, the proportion of new infections with TDR to be below 5%. Recently, Wagner et al. (19) investigated the impact of universal access to treatment compared to a universal ‘test and treat’ strategy in South Africa on HIV incidence and TDR. They predicted that the incidence of TDR would remain below 0.1% and that widespread access to treatment could, in some cases, even reduce transmission due to the increased selection of drug-resistant strains in people on ART, which were assumed to be 50% less transmissible than wild-type strains.

These general trends in drug resistance we have predicted for South Africa may well be relevant for other countries in sub-Saharan Africa, but there are differences worth noting. One main factor is that viral load monitoring is routinely available in South Africa; therefore, people failing first-line regimen may be expected to switch to second-line more quickly after virologic failure than in other settings and we have previously shown that TDR levels are diminished with introduction of viral load monitoring [27]. Furthermore, levels of adherence, virologic suppression, and rates of ART interruption between settings would likely result in differences in resistance [36], but we suggest that any relatively small difference between countries in these factors would have a modest impact on our main overall predicted trends.

In 20 years’ time, which is the time frame used in this analysis, it is possible that in South Africa, current NNRTI will not be part of the first-line regimen anymore. Integrase inhibitors, such as dolutegravir, could potentially be available soon in fixed-dose combination with a similarly low cost and lower level of toxicity. The new South African guidelines recommend a third-line regimen [25], but currently the public health service offers two lines of treatment. Given the uncertainty regarding when these drugs will actually become available, it was considered appropriate to assume as antiretroviral regimen those currently in use in South Africa; therefore, those who fail the second-line regimen will remain on a boosted protease inhibitor regimen.
It is plausible as well that, in the future, point-of-care viral load will become available with possibility for more frequent viral load measurements which could slightly reduce TDR. Therefore, our estimates are potentially conservative for predicted NNRTI resistance. In addition, if high levels of TDR emerge, it is possible that WHO would recommend, for example, changing the first-line to a boosted protease inhibitor regimen. This possible policy change has not been included in these simulations and would sharply curbs the transmission of resistant virus. Our model projections can be updated over time as it becomes clearer that important changes in ART programmes such as this will occur in future.

In conclusion, our results suggest that whereas increases in prevalence of drug resistance are likely as ART coverage is increased, incidence of resistance is unlikely to significantly rise and concern over resistance development should not, in itself, inhibit increases in ART coverage. Health system strengthening to improve treatment diagnosis and retention in care, to increase community acceptance and to reduce stigma may limit incident infection and mitigate transmitted and acquired drug resistance.

Acknowledgements

The authors acknowledge the use of the UCL Legion High Performance Computing Facility (Legion@UCL), and associated support services, in the completion of this work, the World Health Organization, and one reviewer who provided very helpful comments that improved the paper. Michael R. Jordan acknowledges funding from The Tufts Center for AIDS Research (CFAR): CFAR P30AI42853.

Conflicts of interest

The modeling work has been funded by the World Health Organization.

No relevant conflicts of interest

References


