Effect on transmission of HIV-1 resistance of timing of implementation of viral load monitoring to determine switches from first to second-line antiretroviral regimens in resource-limited settings

Andrew N. Phillips[a], Deenan Pillay[b], Geoff Garnett[c], Diane Bennett[d], Marco Vitoria[e], Valentina Cambiano[a] and Jens Lundgren[f]

Background: There is concern that antiretroviral therapy (ART) use with only clinical monitoring for failure will result in high rates of transmission of virus with resistance to drugs currently in use.

Methods: A stochastic simulation model of transmission of HIV, natural history and the effect of ART, was developed and used to predict the proportion of new infections with resistance according to whether and when viral load monitoring is introduced.

Results: In our base model, there was predicted to be 12.4% of new HIV infections with primary antiretroviral resistance in 2020 if clinical monitoring is used throughout, compared with 5.4 and 6.1% if viral load-guided switching (based on viral load measured every 6 months, with switch determined by a value >500 copies/ml) was introduced in 2010 or 2015, respectively. The death rate for those on ART was lowest when viral load monitoring was used, but the overall death rate in all infected people was higher if viral load monitoring was introduced at the expense of scale-up in HIV diagnosis and ART initiation beyond their 2010 coverage levels (4.7 compared with 3.1 per 100 person-years).

Interpretation: To preserve current first-line drugs for the long term there is an eventual need for some form of cheap and practical viral load monitoring in resource-limited settings. However, a delay in introduction of 5 years has limited consequences for resistance transmission so the current priority for countries' ART programmes is to increase HIV testing and provide treatment for all those in need of ART.

AIDS 2011, **25**:843–850

Keywords: clinical monitoring, drug resistance, models, resource-limited settings, transmission, transmitted drug resistance, treatment monitoring, viral load, virological monitoring

Introduction

Antiretroviral therapy (ART) is increasingly used in resource-limited settings [1,2], although treatment use on average covers less than half of patients in need, largely due to the costs of setting up and sustaining sufficiently widespread services for diagnosis and treatment and hence limitations in access to care [1,2]. In many settings,

[a]Department of Infection & Population Health, UCL, [b]UCL/MRC Centre for Medical Molecular Virology, Department of Infection, UCL, [c]Department of Infectious Diseases, Imperial College, London, UK, [d]Centers for Disease Control, Atlanta, Georgia, USA, [e]HIV/AIDS Department, World Health Organisation, Geneva, Switzerland, and [f]University of Copenhagen and State University Hospital, Copenhagen, Denmark.

Correspondence to Andrew N. Phillips, PhD, HIV Epidemiology & Biostatistics Group, Department of Infection & Population Health, UCL, Royal Free Campus, Rowland Hill Street, London, UK.

Tel: +44 20 7794 0500x34238; fax: +44 20 7794 1224; e-mail: andrew.phillips@ucl.ac.uk
Received: 26 July 2010; revised: 9 December 2010; accepted: 22 December 2010.

DOI:10.1097/QAD.0b013e328344037a

second-line drug regimens are also available [1,3,4] and it is important to consider how people on first-line ART are monitored, in order to decide if and when a switch to a second-line regimen is needed [5–18]. In most resource-limited settings the decision to switch is based on incidence of clinical events or on CD4 cell count levels, whereas in developed countries a raised viral load level is the criterion used [19,20]. Viral load monitoring is currently unavailable in the majority of resource-limited settings, although cheap and robust viral load measurement approaches suitable for future use in such settings are being developed (e.g. [21–25]). Since loss of CD4 cells can be slow after virologic failure, basing the decision to switch to second line on new clinical events ('clinical monitoring') results in people with virologic failure remaining on their regimens, during which time new resistance mutations may develop [13,26,27].

There has been concern that use of clinical rather than viral load monitoring will lead to a lower efficacy of the second-line regimen, due to increased levels of resistance to nucleoside analogue drugs used in the second-line regimen resulting from the delay in switching, and to increased rates of clinical progression and death. However, it has been demonstrated that delivery of ART and selection of patients for second-line therapy without viral load monitoring can still result in extremely low rates of clinical progression and mortality in parts of sub-Saharan Africa, such as was seen in the Development of Antiretroviral Therapy in Africa (DART) trial in Uganda and Zimbabwe over more than 5 years of follow-up (e.g. [7]). A modelling study from ourselves has suggested that the mortality benefit for people on ART of use of viral load-driven switching may be modest [10]. These studies, however, have not directly addressed the other major concern with use of clinical (or CD4 cell count) monitoring, that of increased transmission of resistant virus, undermining the effects of first-line ART for the future [18]. Models of HIV transmission have been used to predict emergence of transmitted drug resistance (e.g. [28–34]) but analyses of using viral load monitoring to reduce transmission of resistant HIV have been limited to extreme scenarios of no viral load or 100% access [32]. In this study we use a more detailed computer simulation model to predict transmission of drug resistance according to timing of introduction of viral load over the coming years.

Methods

Scenario modelled

We used an individual-based stochastic computer simulation model with the scenario modelled being a setting with a high prevalence heterosexual epidemic which started in 1985. ART is assumed to have been introduced in 2003, with a policy of initiating therapy in those with WHO 4 disease or CD4 cell count below 200 cells/μl. The rate of diagnosis is assumed to be relatively low, such that only around 12% of all people with HIV are on ART by 2010 (44% of those in need, when 'need' is defined based on CD4 cell count 200), close to the overall estimate for sub-Saharan Africa [1]. It is assumed that the first-line regimen used is stavudine (d4T), lamivudine and nevirapine, with switches of d4T to zidovudine and nevirapine to efavirenz if necessary for toxicity. The second-line regimen is assumed to consist of zidovudine, didanosine and lopinavir/r. In the absence of viral load monitoring the need for a switch to second-line ART is assumed determined by use of clinical monitoring (new WHO clinical stage 4 condition at least 9 months after start of ART determines the need to switch). We chose not to include WHO clinical stage 3 conditions as part of the criteria for switching to ensure that we were studying a switch strategy which will generally result in the latest possible switch, potentially allowing most scope for transmission of resistant virus. This will maximize the risks of transmission of resistance with a clinical monitoring strategy. The year 2010 is the starting point for considering the timing of the introduction of viral load monitoring, with three main scenarios considered: introduction immediately in 2010 (which is not a practical option in most settings, but provides a useful comparator), introduction in 2015, and no introduction before 2020. We compared the predicted proportion of new infections with transmitted primary resistance (defined as at least 50% reduced susceptibility to at least one drug) between these scenarios. Viral load monitoring is assumed to consist of 6-monthly assessments with a switch in therapy governed by a confirmed viral load above 500 copies/ml (a value chosen to be approximately consistent with practice in developed countries). After 2010, we assume an increased rate of diagnosis (illustrated in Fig. 1), and a switch in ART initiation strategy so that ART is initiated in people with CD4 cell count below 350 cells/μl, in line with new WHO advice [6]. This represents a rapid, and probably unrealistic, increase in diagnosis and ART initiation rate, which is likely to lead to greater predicted transmission of resistance, and again was chosen to emphasize the risks of transmission of resistant virus.

HIV synthesis transmission model

Sexual risk behaviour is modelled as the number of new and longer-term unprotected sex partners. As for all variables modelled, these are updated in 3-month periods. In any given period, the probability of an uninfected person having an unprotected sex partner who is infected with HIV depends on their number of partners and on the prevalence of HIV amongst partnerships formed by those of the opposite sex, accounting for patterns of age mixing. Given exposure to an infected partner, the probability of transmission depends on the viral load level of the partner (obtained by sampling from the distribution of viral load levels in partnerships formed by HIV-infected people, accounting for gender and age), on the estimated risk of transmission at that viral load,

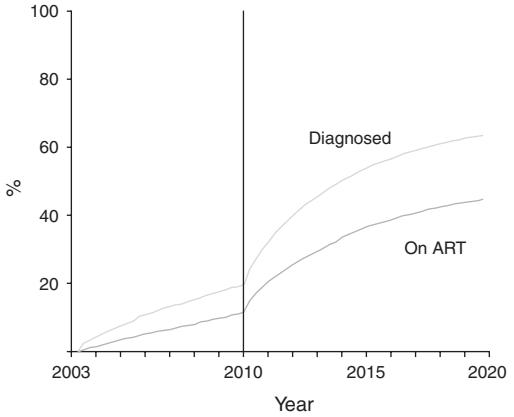

Fig. 1. Trends from 2003 to 2020 in proportion of people with HIV who are diagnosed and proportion of people with HIV who are on ART. 2010 is the date from which diagnosis rates are increased. Based on one run pre-2010 and mean of 80 runs after 2010. Total number with HIV increases from 8920 in 2010 to mean over runs of 13 158 in 2020 (range 11 593 to 14 548).

presence of a concurrent sexually transmitted infection and on gender. It should be noted that presence or not of resistance mutations does not influence the risk of transmission (i.e. virus with resistance mutations present is assumed equally transmissible as virus without such mutations, for a given viral load).

For people who have become infected with HIV the variables modelled include viral load, CD4 cell count, presence of resistance mutations, risk of AIDS and death. Resistance is modelled in terms of the presence or not of mutations specific to the drugs in use [e.g. number of thymidine analogue mutations (TAMS); presence of M184V (yes or no; y/n), K65R (y/n); L74V (y/n); Q151M (y/n), presence of a key non-nucleoside reverse transcriptase inhibitor (NNRTI) mutation (y/n); major protease inhibitor mutations (y/n)]. Distinction is made for each mutation as to whether it is only present in minority virus (if the patient has a mutation present but has stopped drugs that select for that mutation), so assumed not transmissible, or if it is present in majority virus, and hence assumed transmissible. The model of progression of HIV and the effect of ART has been shown to provide a generally close fit to observed data relating to natural progression of HIV infection and the effect of ART ([10,35,36], Supplementary Results 1, http://links.lww.com/QAD/A114).

For a newly infected person, the probability of being infected by a person with resistant virus as their majority virus population is determined by the probability, for the given viral load level of the person from whom the virus has been acquired, that drug resistance mutations are present in the concurrent infected population, again taking into account gender, age and number of partnerships formed. It is not assumed that all resistance mutations present in majority virus of the source partner are established as a mutation in virus in the newly infected person. This is dependent on the specific mutation, in which M184V, for example, if present in the source partner is assumed to have only a 20% chance of being established as a mutation in virus in the new host (and hence compromising subsequent therapy), whereas for NNRTI mutations this is 80%. If a mutation is transmitted and established in the new host it is assumed to persist in majority virus indefinitely, with the exception of the M184V mutation which is assumed to revert to a minority variant immediately on infection. We also consider the possibility of a person who is already infected becoming super-infected, as this is potentially relevant for transmission of drug-resistant HIV. Full model details are in the Supplementary Methods (http://links.lww.com/QAD/A113).

We performed uncertainty and sensitivity analysis in which we assessed the impact on our primary comparison (difference between scenarios in proportion of new infections with transmitted drug resistance in 2020) of changes in the assumptions in the model [37]. The model projections were re-run 10 000 times, each time randomly choosing from two or three options for 40 different possible changes to the model assumptions (see Supplementary Results 2, http://links.lww.com/QAD/A115). The model is programmed in SAS 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

Figure 1 shows trends in the proportion of people with HIV who are diagnosed and on ART. These both show a modest rate of increase between 2003 and 2010, reflecting the kind of scale-up seen so far in many African countries. Table 1 shows the characteristics of the simulated HIV-infected population in 2010, which broadly reflects that of infected people in many countries (44% of those in need of ART being on ART corresponds to the UNAIDS estimate for end of 2008 for sub-Saharan Africa [1]). After 2010 (Fig. 1), the proportion of people with HIV who are diagnosed is predicted to rise considerably, to 54% in 2015 and then more gradually to 63% in 2020, and likewise the proportion of all people with HIV who are on ART, predicted to rise to 37% in 2015 and 45% in 2020. This sharp rise is due to our optimistic assumption of an increase in diagnosis rate and availability of treatment after 2010.

Figure 2 shows the predicted outcomes between 2010 and 2020, broken down according to the timing of introduction of viral load monitoring. Figure 2a shows that of those on ART, the proportion with viral load suppression is predicted to remain high, although this differs somewhat according to timing of introduction of viral load monitoring. Use of clinical monitoring to

Table 1. Breakdown of the simulated HIV infected population in 2010[a].

Female sex	53%
Age[b]	36.00 (29.25–44.00)
Proportion of patients in need of ART who have started ART	44%
People undiagnosed (%)	80%
CD4 cell count in 2010[b]	474 (285–653)
Previous WHO 3	22%
Previous WHO 4	7%
Years since infection	5.25 (2.50–8.5)
People diagnosed but ART naïve (%)	8%
CD4 cell count in 2010[b]	455 (291–647)
Previous WHO 3	37%
Previous WHO 4	14%
Years since infection[b]	7.75 (5.25–11.00)
People on ART (%)	12%
Years since start[b]	3 (1.5–5.00)
With VL <500	77%
With resistance[c] present	17%
CD4 cell count at start ART[b]	161 (85–237)
CD4 count in 2010[b]	360 (211–539)
Previous WHO 3	77%
Previous WHO 4	55%
Years since infection[b]	11.75 (8.75–15.25)
Specific drugs[d]	
Stavudine	88%
Zidovudine	10%
Lamivudine	97%
Didanosine	3%
Nevirapine	93%
Efavirenz	4%
Lopinavir/r	3%
People ART experienced but off ART	1%

[a]Based on one model run (8920 simulated people infected with HIV by 2010, out of 61 044 people aged >15 and alive. This is out of the total 100 000 people who are alive age 15 or above at least at some point between 1985 and 2025).
[b]Median and IQR.
[c]Predicted ≥50% reduced susceptibility to at least one of the first or second line drugs included in the modelling.
[d]Percents of all on ART.

determine switch to second-line regimens often means that those people who have experienced virological failure of the first-line remain on that virologically failing first-line regimen for a sustained period of time, until such time as clinical failure occurs. For example, of those experiencing virologic failure within 5 years from start of ART, the median time from this failure to the time of fulfilling the switch criterion if clinical monitoring is used is 2.5 years. The predicted proportion of those on ART who are on second line is higher after viral load monitoring is introduced (Fig. 2b), and is 4.0 times higher in 2020 if viral load monitoring was introduced in 2010, compared with if clinical monitoring is used throughout.

Since people with detectable viral load (defined here as >500 copies/ml) have a much greater infectivity than those with undetectable viral load [38], those with detectable levels can essentially be thought of as the source of most new infections. Thus, a critical determinant of the proportion of new infections with transmitted drug resistance is the proportion of all people with detectable viral load (which will include people who are on ART and people who are not on ART, including those undiagnosed) who carry drug resistance as majority virus. This is shown in Fig. 2c and indicates that this proportion is greater in the absence of viral load monitoring, with the difference reducing after introduction of viral load monitoring in 2015. Figure 2d shows the proportion of newly infected people who carry drug resistance. Patterns tend to mirror those in Fig. 2c, except percentages are lower due to that not 100% of people infected from a person with resistant virus will themselves carry resistant virus. Of new infections, the predicted percentage with resistance in 2020 is 5.4% if viral load monitoring was introduced in 2010, 6.1% if introduced in 2015, and 12.4% if clinical monitoring (WHO stage 4 condition) were used throughout.

Figure 3 shows the main results from multivariable uncertainty analysis, which indicates the overall level of uncertainty. The estimate and the spread around this estimate as depicted in the figure is derived from multivariable uncertainty analysis and indicates the overall level of uncertainty of the model taking various combinations of the assumptions into account. The analysis also indicates the effects of varying assumptions in the model on the predicted difference between strategies in the percentage of new infections with resistance in 2020 (see Supplementary Results 2 for details, http://links.lww.com/QAD/A115). Introduction of viral load monitoring in 2010 results in a median 0.3% lower prevalence of transmitted resistance in 2020 (95% plausibility range −2.9 to 4.7%) compared with introduction in 2015, and median 4.2% lower prevalence (95% plausibility range 0.6 to 14.5%) compared with no introduction of viral load monitoring before 2020. This does not overlap 0 and hence indicates that over all 10 000 scenarios over 97.5% result in a situation in which there is a higher proportion with transmitted drug resistance if viral load monitoring is not introduced before 2020.

We also considered modifications to the viral load monitoring strategy in order to help understand what are the most essential elements of the viral load monitoring strategy. For these purposes, we assumed viral load monitoring was started in 2010. Use of a threshold of 5000 copies/ml, rather than 500 copies/ml, led to a predicted proportion of newly infected people who carry drug resistance in 2020 to 6.0% (compared with 5.4% in our main analysis). Reduction of the frequency of monitoring to once every 3 years, with the first measure at year 1, led to a value of 7.2%, whereas use of a single viral load measurement at 1 year (and no subsequent measures) led to a value of 8.5%.

Finally, we considered the death rate in the HIV-infected population between 2010 and 2020 (Table 2). This was 2.7 (2.4 when restricting to those on ART) per 100 person-years with use of viral load monitoring from 2010, 2.8 (2.7) with use of viral load monitoring from 2015, 3.1 (3.3) per 100 person-years with use of WHO 4 clinical

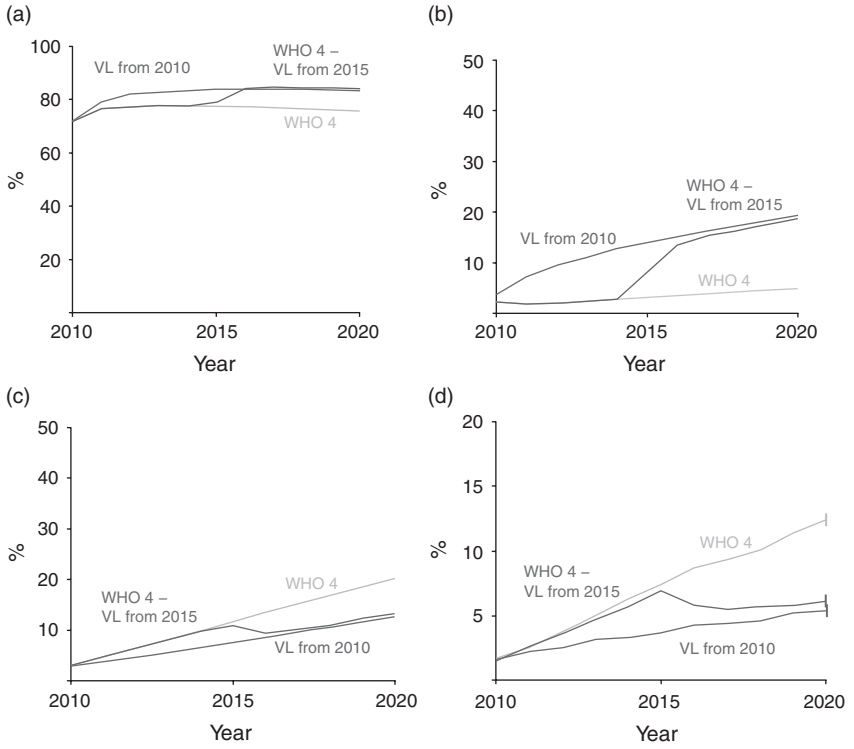

Fig. 2. Predicted outcomes from 2010–2020. Trends from 2010 to 2020 in (a) proportion of ART-treated patients with viral load suppression, (b) proportion of patients on ART who are on second-line, (c) proportion of those with viral load above 500 (including those undiagnosed and hence not on ART) with resistance in majority virus, and (d) proportion of new infections with resistance, according to timing of introduction of viral load monitoring. Based on mean of 80 runs. Standard deviations and standard errors for the estimates for 2020 are as follows: (a) VL from 2010: 0.2%, 0.04%, respectively, WHO 4 – VL from 2015: 0.2%, 0.05%, respectively, WHO 4: 0.3%, 0.05%, respectively; (b) VL from 2010: 0.2%, 0.05%, respectively, WHO 4 – VL from 2015: 0.3%, 0.06%, respectively, WHO 4: 0.1%, 0.03%, respectively; (c) VL from 2010: 0.4%, 0.1%, respectively, WHO 4 – VL from 2015: 0.5%, 0.1%, respectively, WHO 4: 0.5%, 0.1%, respectively; (d) VL from 2010: 1.2%, 0.3%, respectively, WHO 4 – VL from 2015: 1.2%, 0.3%, respectively, WHO 4: 1.7%, 0.3%, respectively. 95% confidence intervals are shown in graph (d) for 2020. For graphs (a–c) the confidence intervals are not shown as they are hardly discernable from the point estimates shown.

monitoring throughout the period [2.9 (2.7) per 100 person-years with monitoring based on WHO clinical stage 3 or 4 conditions]. However, if the assumed marked increase in HIV diagnosis (and hence ART coverage) since 2010 was not to occur (and the diagnosis rate remains at the level in 2010), then the death rate in the HIV-infected population is predicted to be 4.7 per 100 person-years, even with use of viral load monitoring throughout the decade.

Discussion

Our results suggest that if we are to preserve current first-line drugs as widespread treatment options for future generations, there is a long-term need for introduction of some form of cheap, practical, and sustainable viral load monitoring in resource-limited settings with generalized epidemics which can be used in rural as well as urban settings. This represents a critical challenge for researchers over the next few years. These tests could be qualitative, that is do not need to be able to do more than distinguish those with viral load levels of above and below some low threshold such as 500 copies/ml. Even very infrequent (e.g. 3 yearly) monitoring is likely to provide significant benefit in reducing resistance transmission.

However, delay in introduction of viral load monitoring of around 5 years, whereas practical assays complete their development, is likely to result in only a small increase in transmission of resistant virus, compared with the theoretical, but not feasible, option of immediate use of viral load monitoring to determine regimen switching. We also found that the death rate in HIV-infected individuals can be lowered more substantially if the diagnosis rate can be increased to the level assumed in our main analysis (regardless of use of viral load monitoring), than by introduction of viral load monitoring that is not accompanied by an increase in diagnosis rate. These results indicate that increased and more geographically widespread testing and treatment access to ensure universal access to ART in those in need is the highest priority for resource-limited countries, and that lack of

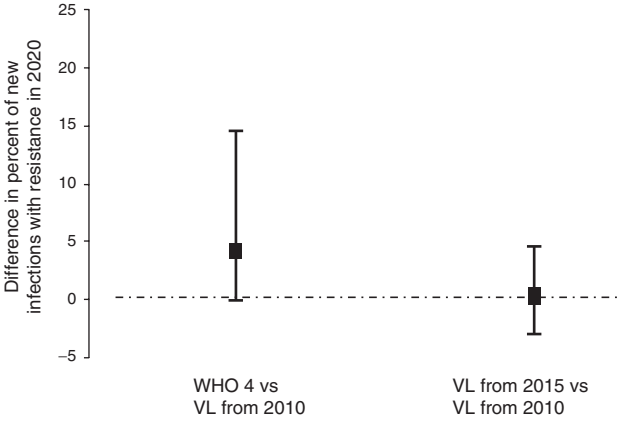

Fig. 3. Uncertainty analysis on difference between viral load monitoring scenarios in proportion of new infections with resistance in 2020. Median (and range within which 95% of values lie, referred to as 95% plausibility limits), difference in percentage with resistance in 2020 between viral load monitoring scenarios over 10 000 runs in which parameter estimates are chosen at random from two or three options, emphasizing the extremes of plausibility. This illustrates the overall level of uncertainty in our comparisons.

available viral load or other laboratory monitoring should not prevent this from occurring [39]. The ability to deliver a successful ART programme with very low mortality rates without viral load monitoring has been demonstrated (DART) [7]. These findings take on an even greater significance given the increasing limitation on ART treatment slots with current global financial constraints. It should be noted, however, that it was not within the scope of this study to perform an economic analysis that explicitly takes relative costs of increased HIV testing and of viral load measurements, thus we are not at this point able to quantify the trade-off in detail.

The target of eventual introduction of viral load monitoring is also important for minimizing the mortality risk of people on ART. Our results (see also [10]) indicate that there are mortality benefits in treated people from use of viral load monitoring, albeit relatively modest when compared with more sensitive clinical monitoring strategies that also take account of WHO clinical stage 3 conditions (although to implement such strategies would require simple clinical algorithms which would need to be developed and tested in practice and their feasibility is not yet clear). On the basis of the low rates of death and clinical disease progression in DART [7], the clinical monitoring arm as well as the laboratory monitoring arm, the HIV-related death rates are lower than those assumed previously [10].

It is important to consider that the cost of viral load monitoring is not just in the cost of the tests and the infrastructure but also in the probable resulting increased number of people on second-line ART, which has a cost over six times higher (in drug costs alone) than first-line ART [40]. Most people who are virologically failing first-line regimens are clinically asymptomatic for a long period of time. Introduction of viral load monitoring will only be of value if the cost of second-line (and hopefully, eventually, third line) regimens is sufficiently low to allow programmes to afford to adopt virologically determined switching. This is currently not the case in all countries, particularly given the projected increase in number of people who will be on ART, so reductions in prices of second-line drugs is of critical importance. Only 2% of people on ART are on second line [1], but this may reflect the fact that many people have started ART only recently, in addition to it reflecting the cost and availability of second-line drugs. It should also be noted that without viral load testing some people who are not virologically failing will be inappropriately switched to second line when virus levels are suppressed [41–43] (a phenomenon which occurs also in our model [10]), most usually because of early clinical events in those initiating therapy at low CD4 cell counts, and viral load testing to confirm failure is likely to be cost saving for such individuals.

Without eventual introduction of viral load monitoring and switching of drugs to second line based on virologic failure it is likely that the choice of standard first-line drugs in patients starting ART will at some point have to change, due to the high proportion of ART-naive patients who carry virus resistant to first-line drugs, although our results suggest this is unlikely to be necessary in the next 10 years. Loss of current drug options over the long term, due to substantial resistance transmission, might not have serious negative consequences, if there are sufficient newly developed and widely available drugs

Table 2. Predicted death rates 2010–2020 for all those with HIV and for those on ART according to timing of introduction of viral load monitoring and diagnosis rate 2010–2020.

	Monitoring strategy			
	VL from 2010	WHO 4 – VL from 2015	WHO 4	VL from 2010
	HIV diagnosis rate increase from 2010[a]			No HIV diagnosis rate increase from 2010
People with HIV	2.7	2.8	3.1	4.7
People on ART	2.4	2.7	3.3	2.6

[a]Diagnosis rate increase as illustrated in Fig. 1.

with nonoverlapping resistance profiles. Nevertheless, the prospect of extensive transmission of virus with NNRTI mutations associated with resistance to nevirapine and/or efavirenz would be likely to remain a concern for the foreseeable future. WHO has recently recommended that countries move towards replacement of d4T in first-line regimens with tenofovir, due to reduced toxicity [6]. Use of such regimens, when they can be afforded, is not likely to greatly change the implications of our main findings. Resistance to tenofovir, in the form of the K65R mutations, does not appear to occur at an appreciably higher rate compared with the emergence of resistance to stavudine, in the form of thymidine analogue mutations [44]. Likewise, it seems likely that our findings would hold were different second-line nucleoside analogue drug combinations selected, such as abacavir/didanosine or tenofovir/emtricitabine, but this will require confirmation in future modelling.

In conclusion, transmission of drug resistance represents a long-term threat to the continued optimal virologic efficacy of drugs currently used in resource-limited settings. Eventual introduction of viral load monitoring to help to determine the need for switching to second-line regimens will substantially reduce this threat. However, the number of people living with advanced HIV infection which is untreated should be the key priority for national ART programmes. Concern over lack of viral load monitoring must not be allowed to inhibit universal roll out of HIV diagnosis and ART availability over the coming few years.

Acknowledgements

The research leading to these results has received part funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under the project 'Collaborative HIV and Anti-HIV Drug Resistance Network (CHAIN)' – grant agreement n° 223131. We would like to thank Azra Ghani and Rebecca Baggaley for valuable advice in developing this model. Support for development of an early version of this model was provided by Pfizer, UK. We also thank Research Computing, UCL for use of Legion distributed memory computing cluster, without which this work would not be possible.

Author contributions: All authors discussed the concept of the analysis and had substantive input into the decisions made about how to set up the scenario and the comparisons. In addition, D.P. and D.B. offered specific advice on modelling resistance emergence and transmission, J.L. provided advice from a clinical and epidemiologic perspective, M.V. and D.B. provided advice from a WHO standpoint, G.G. provided advice on aspects of the modelling, particularly as they related to UNAIDS work. A.P. and V.C. programmed the model and led on the work.

References

1. UNAIDS. Towards universal access. Scaling up priority HIV/AIDS interventions in the health sector. Progress Report 2009. www.unaids.org.
2. WHO, Department of HIV/AIDS. Towards universal access. Scaling up priority HIV/AIDS interventions in the health sector. June 2008 progress report. http://www.who.int/hiv.
3. Pujades-Rodríguez M, O'Brien D, Humblet P, Calmy A. **Second-line antiretroviral therapy in resource-limited settings: the experience of Médecins Sans Frontières.** *AIDS* 2008; **22**: 1305–1312.
4. WHO, HIV Department. Prioritizing second-line antiretroviral drugs for adults and adolescents: a public health approach. Report of a WHO working group meeting. 2007 http://www.who.int/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf.
5. WHO. Antiretroviral therapy for adults and adolescents. Recommendations for a public health approach. 2006. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf.
6. WHO. Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents. Nov 30, 2009. http://www.who.int/hiv/pub/arv/advice/en/index.html.
7. DART Trial team. **Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised noninferiority trial**. *Lancet* 2010; **375**:123–131.
8. Elliott JH, Lynen L, Calmy A, De Luca A, Shafer RW, Zolfo M, *et al*. **Rational use of antiretroviral therapy in low-income and middle-income countries: optimizing regimen sequencing and switching.** *AIDS* 2008; **22**:2053–2067.
9. Coutinho A, Mermin J, Ekwaru J, Were W, Bunnell R, Kaharuza F, *et al*. **Utility of routine viral load, CD4 cell count, and clinical monitoring among HIV-infected adults in Uganda: a randomized trial**. In: *15th Conference on Retroviruses and Opportunistic Infections*, Boston, MA, USA; 3–6 February 2008. p. 125 (abstract).
10. Phillips AN, Pillay D, Miners A, Bennett D, Gilks CF, Lundgren JD. **Outcomes from monitoring of patients on antiretroviral therapy in resource-limited settings with viral load, CD4 cell count, or clinical observation alone: a computer simulation model.** *Lancet* 2008; **371**:1443–1451.
11. Moore DM, Mermin J. **Monitoring antiretroviral failure in resource-poor settings.** *Lancet* 2008; **371**:1396–1397.
12. Lawn SD, Bekker LG, Calmy A, Wood R. **Monitoring of antiretroviral therapy in low-resource settings.** *Lancet* 2008; **372**: 287–288.
13. Calmy A, Ford N, Hirschel B, Reynolds SJ, Lynen L, Goemaere E, *et al*. **HIV viral load monitoring in resource-limited regions: optional or necessary?** *Clin Infect Dis* 2007; **44**:128–134.
14. Gupta RK, Hill A, Sawyer AW, Cozzi-Lepri A, von Wyl V, Yerly S, *et al*. **Virological monitoring and resistance to first-line highly active antiretroviral therapy in adults infected with HIV-1 treated under WHO guidelines: a systematic review and meta-analysis.** *Lancet* 2009; **9**:409–417.
15. Hosseinipour MC, van Oosterhout JJG, Weigel R, Phiri S, Kamwendo D, Parkin N, *et al*. **The public health approach to identify antiretroviral therapy failure: high-level nucleoside reverse transcriptase inhibitor resistance among Malawians failing first-line antiretroviral therapy.** *AIDS* 2009:231127–231134.
16. Sawe FK, McIntyre JA. **Monitoring HIV antiretroviral therapy in resource-limited settings: time to avoid costly outcomes.** *Clin Infect Dis* 2009; **49**:463–465.
17. Wilson D, Keiluhu AK, Kogrum S, Reid T, Seriratana N, Ford N, *et al*. **HIV-1 viral load monitoring: an opportunity to reinforce treatment adherence in a resource-limited setting in Thailand.** *Trans Roy Soc Trop Med Hygiene* 2009; **103**:601–606.
18. Smith DM, Schooley RT. **Running with scissors: using antiretroviral therapy without monitoring viral load.** *Clin Infect Dis* 2008; **46**:1598–1600.

19. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 1 December 2009. pp. 1–161. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
20. Gazzard BG, on behalf of the BHIVA Treatment Guidelines Writing Group. **British HIV Association guidelines for the treatment of HIV infected adults with antiretroviral therapy 2008.** *HIV Med* 2008; **9**:563–608.
21. Leelawiwat W, Young NL, Chaowanachan T, Ou CY, Culnane M, Vanprapa N, *et al*. **Dried blood spots for the diagnosis and quantification of HIV-1: stability studies and evaluation of sensitivity and specificity for the diagnosis of infant HIV-1 infection in Thailand.** *J Vir Meths* 2009; **15**:109–117.
22. Marconi A, Balestrieri M, Comastri G, Pulvirenti FR, Gennari W, Tagliazucchi S, *et al*. **Evaluation of the Abbott real-time HIV-1 quantitative assay with dried blood spot specimens.** *Clin Microbiol Infect* 2009; **15**:93–97.
23. Monleau M, Montavon C, Laurent C, Segondy M, Montes B, Delaporte E, *et al*. **Evaluation of different RNA extraction methods and storage conditions of dried plasma or blood spots for HIV-1 RNA quantification and PCR amplification for drug resistance testing.** *J Clin Microbiol* 2009; **47**:1107–1118.
24. Point of care VL tests. http://nciia.org/node/110.
25. UNITAID. Viral load testing in low resource settings. www.unitaid.eu/en/Requests-for-proposals.html.
26. Kantor R, Shafer RM, Follansbee S, Taylor J, Shilane D, Hurley L, *et al*. **Evolution of resistance to drugs in HIV-1 infected patients failing antiretroviral therapy.** *AIDS* 2004; **18**:1503–1511.
27. Cozzi-Lepri A, Phillips AN, Martinez-Picado J, Monforte AD, Katlama C, Hansen ABE, *et al*. **Rate of accumulation of thymidine analogue mutations in patients continuing to receive virologically failing regimens containing zidovudine or stavudine: implications for antiretroviral therapy programs in resource-limited settings.** *J Infect Dis* 2009; **200**:687–697.
28. Blower S, Bodine E, Kahn J, McFarland W. **The antiretroviral rollout and drug-resistant HIV in Africa: insights from empirical data and theoretical models.** *AIDS* 2005; **19**:1–14.
29. Blower S, Ma L, Farmer P, Koenig S. **Predicting the impact of antiretrovirals in resource-poor settings: preventing HIV infections whilst controlling drug resistance.** *Curr Drug Targets Infect Disord* 2003; **3**:345–353.
30. Vardavas R, Blower S. **The emergence of HIV transmitted resistance in Botswana: 'when will the WHO detection threshold be exceeded?'.** *PLoS ONE* 2007; **2**:e152.
31. Smith RJ, Okano JT, Kahn JS, Bodine EN, Blower S. **Evolutionary dynamics of complex networks of HIV drug-resistant strains: the case of San Francisco.** *Science* 2010; **327**:697–701.
32. Baggaley RF, Garnett GP, Ferguson NM. **Modelling the impact of antiretroviral use in resource-poor settings.** *PLOS Med* 2006; **3**:e124.
33. Baggaley RF, Ferguson NM, Garnett GP. **The epidemiological impact of antiretroviral use predicted by mathematical models: a review.** *Emerg Themes Epidemiol* 2005; **2**:9.
34. Abbas UL, Anderson RM, Mellors JW. **Potential impact of antiretroviral therapy on HIV-1 transmission and AIDS mortality in resource-limited settings.** *JAIDS* 2006; **41**:632–641.
35. Phillips AN, Sabin CA, Pillay D, Lundgren JD. **HIV in the UK 1980–2006: reconstruction using a model of HIV infection and the effect of antiretroviral therapy.** *HIV Med* 2007; **8**:536–546.
36. Bansi LK, Sabin C, Delpech V, Hill T, Fisher M, Walsh J, *et al*., for the UK CHIC Study Steering Committee and the Health Protection Agency. **Trends over calendar time in antiretroviral treatment success and failure in HIV clinic populations.** *HIV Med* 2010; **11**:432–438.
37. Blower SM, Dowlatabadi H. **Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example.** *Int Statist Rev* 1994; **62**:229–243.
38. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, *et al*. **Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group.** *N Engl J Med* 2000; **342**:921–929.
39. Phillips AN, van Oosterhout J. **DART points the way for antiretroviral treatment programmes.** *Lancet* 2010; **375**:96–98.
40. WHO AIDS Diagnostic and Medicine Service, Transaction prices for antiretroviral medicines and HIV diagnostics from 2008 to April 2009. A summary report from the Global Price Reporting Mechanism (http://www.who.int/hiv/amds/GPRMsummaryReportJune2009.pdf).
41. Mee P, Fielding K, Charalambous S, Churchyard GJ, Grant AD. **Evaluation of the WHO criteria for antiretroviral treatment failure among adults in South Africa.** *AIDS* 2008; **22**:1971–1977.
42. Lynen L, An S, Koole O, Thai S, Ros S, De Munter P, *et al*. **An algorithm to optimize viral load testing in HIV-positive patients with suspected first-line antiretroviral therapy failure in Cambodia.** *J Acquir Immune Defic Syndr* 2009; **52**:40–48.
43. Kantor R, Diero L, DeLong A, Kamle L, Muyonga S, Mambo F, *et al*. **Misclassification of first-line antiretroviral treatment failure based on immunological monitoring of HIV infection in resource-limited settings.** *Clin Infect Dis* 2009; **49**:454–462.
44. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JMAH, Miller MD, *et al*. **Efficacy and safety of tenofovir DF vs. stavuldine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial.** *J Am Med Assoc* 2004; **292**:191–201.