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Projecting the epidemiological effect, cost-effectiveness and transmission of HIV drug resistance in Vietnam associated with viral load monitoring strategies

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Objectives: The objective of this study was to investigate the potential epidemiological impact of viral load (VL) monitoring and its cost-effectiveness in Vietnam, where transmitted HIV drug resistance (TDR) prevalence has increased from <5% to 5%–15% in the past decade.

Methods: Using a population-based mathematical model driven by data from Vietnam, we simulated scenarios of various combinations of VL testing coverage, VL thresholds for second-line ART initiation and availability of HIV drug-resistance tests. We assessed the cost per disability-adjusted life year (DALY) averted for each scenario.

Results: Projecting expected ART scale-up levels, to approximately double the number of people on ART by 2030, will lead to an estimated 18 510 cases (95% CI: 9120–34 600 cases) of TDR and 55 180 cases (95% CI: 40 540–65 900 cases) of acquired drug resistance (ADR) in the absence of VL monitoring. This projection corresponds to a TDR prevalence of 16% (95% CI: 11%–24%) and ADR of 18% (95% CI: 15%–20%). Annual or biennial VL monitoring with 30% coverage is expected to relieve 12%–31% of TDR (2260–5860 cases), 25%–59% of ADR (9620–22 650 cases), 2%–6% of HIV-related deaths (360–880 cases) and 19 270–51 400 DALYs during 2015–30. The 30% coverage of VL monitoring is estimated to cost US$4848–5154 per DALY averted. The projected additional cost for implementing this strategy is US$105–268 million over 2015–30.

Conclusions: Our study suggests that a programmatically achievable 30% coverage of VL monitoring can have considerable benefits for individuals and leads to population health benefits by reducing the overall national burden of HIV drug resistance. It is marginally cost-effective according to common willingness-to-pay thresholds.

Introduction

Plasma viral load (VL) for HIV is a reliable indicator for assessing the success of ART for people living with HIV (PLHIV). Timely VL tests detect early treatment failure and reduce the risks of the emergence and transmission of HIV drug-resistant strains.[1,2] Routine VL monitoring for those receiving ART has been widely adopted in high-income settings. In 2013, the WHO recommended VL monitoring as an integrated component of ART in a series of global efforts to improve service delivery and management for more than 12 million PLHIV on treatment worldwide.[3] VL tests are recommended at 6 months after treatment initiation and every 12 months thereafter; a regimen switch should be applied only to individuals who have two consecutive tests with VL >1000 copies/mL that are 3 months apart.[3]

Large-scale implementation of VL monitoring for PLHIV on treatment has not occurred worldwide, because of potentially insignificant clinical improvements and modest cost-effectiveness compared with conventional monitoring approaches. Efficacy analyses from four randomized, controlled trials—in Cameroon, Uganda, Zimbabwe and Thailand—consistently showed that VL monitoring did not lead to substantial improvements in CD4+ T cell counts, reductions in new AIDS-defining events or deaths compared with CD4+ T cell count and clinical monitoring

alone.[4–7] Ongoing debate over the cost-effectiveness of VL monitoring is also noted;[8] variations in study locations, differences in epidemiological and economic status, uncertainties in modelled variables and differences in evaluation approaches have led to some diverse conclusions. The key subject of debate is how to capture individual and population benefits of VL monitoring in relation to improved treatment adherence[9–11] and reduction in transmission risk of HIV drug resistance.[12] In response, Keebler *et al.*[13] recommended a continuous delay in introducing VL monitoring in resource-limited settings until other lower-cost testing options are exhausted and high ART coverage is established. The analysis, which employed three mathematical modelling approaches, was based on an assumption that all PLHIV on ART have full access to VL monitoring at all times. In reality, VL monitoring is often initiated with a low coverage (i.e. 10%–30% of the ART-treated population) in urban areas and then gradually expanded to the rest of the country. Further, although increasing ART coverage reduces the number of new infections of WT HIV and drug-resistant strains,[14,15] delay in commencing VL monitoring may result in a high level (>15%) of transmitted HIV drug resistance (TDR).[16] In this situation, a more expensive genotypic HIV drug-resistance test will need to be in place for all people initiating therapy for HIV, and a boosted PI regimen is necessary for people with pretreatment drug resistance.[17,18] Most resource-limited settings cannot afford these approaches, due to the lack of technology, facilities, and personnel and financial constraints. Addressing the relationship between postponement of VL monitoring and the risk of an expanding TDR epidemic is complex but important for a well-functioning ART programme.

In Vietnam, an estimated 258 500 people were living with HIV in 2013.[19] It is a concentrated epidemic mainly characterized by the sharing of injection equipment and unprotected sex in female sex workers and MSM. The expanding national ART programme covered 77 867 individuals by 2013, representing a national coverage of about 63% of PLHIV in need of ART (CD4+ T cell count <350 cells/mm^3). The rapid scale-up of ART with limited capacity for VL monitoring and the shortage of salvage therapy have contributed to the emergence and transmission of HIV drug-resistant strains in Vietnam, as in other resource-limited settings. Notably, many previous studies failed to establish the actual trend of TDR in Vietnam due to the necessity of recruiting a sizeable population of people with chronic HIV infection.[20–23] The underlying reason is that the prevalence among these persons usually under-represents the actual transmission level of drug-resistant strains as the less 'fit' strains they host are often outcompeted by the WT. These strains become minorities that are beyond the detection of standard genotyping.[24,25] Using the WHO-recommended TDR survey method, recent studies among young adult attendees (aged 25 years or younger), recruited from voluntary HIV counselling testing services, who are newly HIV-diagnosed and antiretroviral-naive, reported an increase in the prevalence of TDR from a low (<5%) to a moderate level (5%–15%) over the past 10 years in urban Vietnam.[26–29] As treatment coverage continues to improve for PLHIV in Vietnam, strategic monitoring of treatment outcomes that reduce the burden of HIV drug resistance is imperative for the programme. In recent years, Vietnam has recognized the early introduction of VL monitoring for people on ART as a key response to the rising burden of HIV drug resistance. Nevertheless, detailed implementation plans for VL monitoring have not yet been publicized by the Ministry of Health in Vietnam. This approach is possibly due to the absence of local evidence on the additional costs and health effects of VL-monitoring scenarios on preventing the emergence and transmission of HIV drug resistance. This study hence aims to identify the most effective and economical VL-monitoring strategy for an achievable target coverage in a Vietnamese context through a mathematical modelling approach, which is informed by the coverage of local ART programmes, the epidemiological context of HIV drug resistance and the resource availability.

Methods

Data synthesis

We collated data on reported cases of HIV diagnosis and deaths, the number of people on ART, clinical treatment outcomes and levels of HIV drug resistance in Vietnam from 2005 to 2013 through both ongoing in-country collaborations and a systematic review. A main data source was a prospective cohort of 490 adults consecutively initiating ART in four outpatient clinics.[30] Key endpoint data from this cohort, which was used in the present modelling study, are described in Table 1. In addition, we conducted a systematic review on published English scientific literature to collect relevant information on TDR in Vietnam.[31] The latest national statistics on the number of HIV diagnoses, HIV-related deaths and people on first- and second-line ART were provided by the Vietnam Administration of HIV/AIDS Control (VAAC). The VAAC also provided data on the direct cost of key HIV care and treatment services in Vietnam in 2009,[32] which were adjusted for consumer price index and were represented in 2014 US dollars (Table 1). Indirect costs for full implementation of VL monitoring and genotypic testing were unavailable and therefore not incorporated in this study.

Model

We constructed a compartmental mathematical model to examine the emergence and transmission of HIV drug resistance in Vietnam on the basis of a previous model developed by Hoare *et al.*[33] (Figure 1). Briefly, the model followed HIV disease progression in three HIV-infected populations based on the type of HIV strains they were harbouring: WT, detectable drug-resistant (DR) and undetectable drug-resistant (DRU) viruses. We define drug resistance as the emergence of HIV viral mutations that are genetically resistant against at least one of the antiretroviral drug classes. In the absence of HIV treatment, the model permits a reversion from DR or DRU viruses to WT at a rate of 0.14 to 0.23 per year.[34] The key health states included infected but not diagnosed (*I*), diagnosed but not on ART (*D*), on ART (*T*) and treatment failure (*F*). The movement between the states was defined though a system of ordinary differential equations informed by average rates of biological, behavioural and clinical data obtained from published literature. We assumed that infection with a given HIV strain and the corresponding progression across the health states occurred separately. Because of little knowledge of exact disease progression of various DR strains by gender, population groups and interactions among populations in resource-limited settings, we did not include these factors in this modelling exercise.

We tracked the occurrence of virological treatment failure during ART instead of immunological/clinical treatment failure, thus disease progress defined by declining CD4+ T cell level was not modelled. Treatment failure is defined as a persistently detectable VL above 400 copies/mL, whereas VL <400 copies/mL with HIV treatment was assumed to be viral suppression. Aleman *et al.*[35] showed that almost all (93%) people with low-level viraemia (500–1000 copies/mL) developed new resistance mutations less than 1 year after VL rebound. In view of this evidence, we assumed that all people with detectable VL developed acquired drug resistance (ADR) within a year. All model parameters, definitions and values are listed in Table 1.

Table 1. Summary of model parameters

Parameter	Description	Value (range used in calibration and sensitivity analysis)	Source
Estimate of number of new infections per year			
α_{Ψ}^{sex}	per-act probability of transmission via unprotected sex during established infection	0.0004–0.0011	71
α_{Ψ}^{inj}	per-act probability of transmission via needle sharing during established infection	0.0041–0.0092	71
Ψ	set-point VL (copies/mL)	10^4–10^5	72,73[a]
ν^{sex}	VL in people who are sexually infected with HIV and failed with ART (copies/mL)	1910–201 000	40
ν^{inj}	VL in people who inject drugs and failed with ART (copies/mL)	37 300–652 000	40
η^{sex}	average number of sexual acts	23–39 per year	[b]
ε	proportion of consistent condom use	60%–85%	38
φ^{con}	efficacy of condoms	80%–99%	74–76
η^{inj}	average number of injections at-risk	38–64 per year	[b]
κ	proportion of consistent sterile needle-syringe use	35%–90%	[c]
χ	proportion of active injection in the past month among HIV-infected people	46.9%–49.9%	38
φ^{inj}	efficacy of cleaning syringes	80%–99%	77–79
ω	average number of partners	0.6–0.8 per year	80
β_0	the per-partnership probability of transmission in treated people who achieve VL <400 copies/mL	0.0002–0.0113	81
θ	reduction in relative fitness of DR strains	0.6–1.0	[d]
π	probability of detection of TDR patterns	50%–66%	24
Estimate of health-state progress			
ρ	rate of lost drug-resistance pattern	14%–23% per year	34
γ	rate of being diagnosed	9%–14% per year	[c]
τ	rate of people eligible for ART	2%–7% per year	[c]
	rate of HIV-related death		
δ_I	infected but undiagnosed people	4.1%–14.6% per year	82
δ_D	diagnosed but untreated people	1.0%–8.8% per year	[c]
δ_T	treated people with VL <400 copies/mL	0.4%–0.59% per year	83
δ_F	ART-treated people with VL >400 copies/mL	0.7%–1.0% per year	83,84
	rate of lost to follow-up or stopping of ART		
μ^W	people with WT HIV	2.5%–5.0% per year	40[e]
μ^R	people with detectable/undetectable drug resistance	1.3%–14.5% per year	40[e]
	rate of treatment failure (VL >400 copies/mL)		
σ^W	people with WT HIV	1.3%–4.3% per year	40[e]
σ^R	people with detectable/undetectable drug resistance	2.4%–6.0% per year	40[e]
Υ	background rate of people diagnosed with treatment failure, switched to second-line therapy	2.5%–10.3% per year	40
ς	rate of development of ADR mutations within a year among people with treatment failure	100%	85
Unit cost and health disutility			
Disutility	infected and diagnosed people, non-AIDS stages	0.146–0.310	48,49
	infected and diagnosed people, AIDS stage	0.382–0.715	
	ART-treated people with VL <400 copies/mL	0.034–0.079	
	ART-failed people, non-AIDS stages	0.034–0.079	
	ART-failed people, AIDS stage	0.382–0.715	
Cost	cost of HIV testing	US$6–10 per client	32[f]
	non-ART cost	US$104–168 per year	
	first-line ART cost	US$356–449 per year	
	second-line ART	US$1582–2011 per year	
	cost of VL	US$38–47 per test	
	cost of drug-resistance test	US$66–75 per test	

Continued

Table 1. *Continued*

VL scenarios (8), based on testing frequency and criteria for switching for each 10-incremental coverage level of VL monitoring					
Frequency of VL	Rate of switch to second-line therapy with different switch criteria among people failing ART within a year				
	>1000 copies/mL, without a drug-resistance test	>400 copies/mL, without a drug-resistance test	>1000 copies/mL, with a drug-resistance test	>400 copies/mL, with a drug-resistance test	Source
Yearly or biennially	70%–92%	88%–100%	31%–66%	34%–69%	40[g]

[a]Levels of VL among Vietnamese women on ART were estimated to be 3.83 $\log_{10}$ copies/mL, relatively similar to that of 4.19 $\log_{10}$ copies/mL for men.[86] The predominant modes of HIV transmission in Vietnam are heterosexual exposure among women and injecting drug use among men. The average levels of VL during chronic infection among PLHIV infected by injection sharing and sexual exposure are assumed to be similar.[30]
[b]These numbers are based on a national behavioural survey of people living with HIV in Vietnam.[87,88] See Table S1 for further details.
[c]Increase from 2005 to 2013.
[d]Assumed data.
[e]This proportion is adjusted at the rate of 0.25–0.5 using data from the 12 month cohort of people on ART in Vietnam.
[f]Cost of HIV testing, VL and drug-resistance test was obtained through ongoing stakeholder collaborations.
[g]Assumptions that are made to investigate the impacts of VL monitoring on levels of TDR.

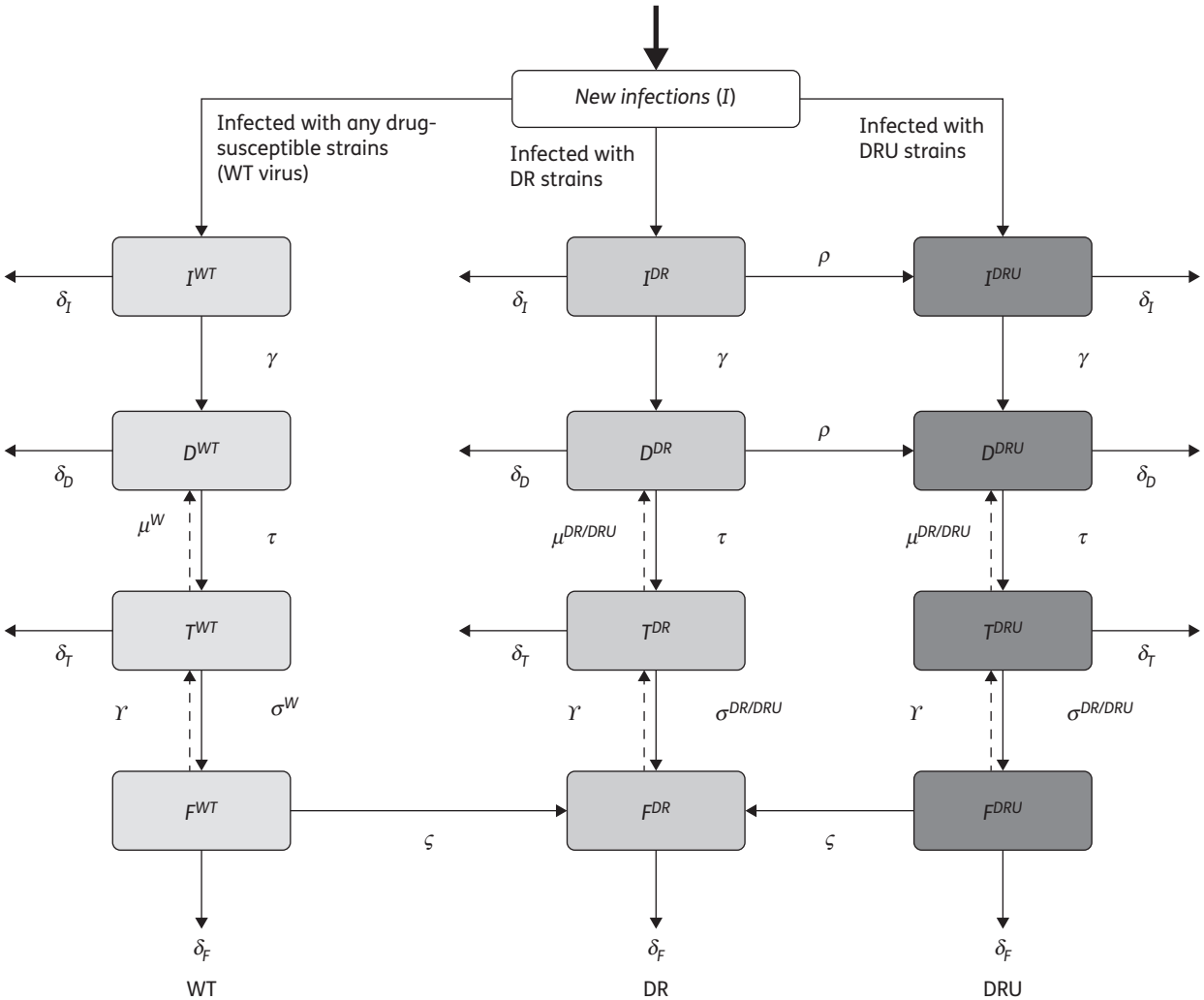

Figure 1. Model schematic for HIV drug resistance. The model structure was adopted from a model developed by Hoare *et al.*[33] This model stratifies HIV infection by the type of strain, including WT, DR and DRU viruses. Health states, shown in boxes, included in the model were as follows: infected but not diagnosed (*I*), diagnosed but not on ART (*D*), on ART (*T*) and treatment failure (*F*). The movement between states is shown by arrows, with their definitions and values shown in Table 1.

One key model parameter is the per-act probability of transmission that was taken to be dependent on VL as described by Wilson *et al.*[36] Based on the method of Røttingen and Garnett,[37] our model calculated the average force of infection by taking into consideration risks due to both injection sharing and unsafe sexual practices. With an assumption that the sexual partnership among PLHIV is insignificant, this enables the estimation of the number of new infections through projections of average onward transmissions per HIV-infected person in the population. Overall, the model was based on four key facts and assumptions. A survey of 4300 PLHIV in 20 Vietnamese provinces suggested that overlapping of injecting drug use and unprotected sex is prevalent among PLHIV.[38] Moreover, a study on cascade of HIV services in Vietnam in 2012 demonstrated that the ART coverage among PLHIV who inject drugs (35%) is similar to that in the overall PLHIV population (36%).[39] Further, an exploratory study in a large cohort of ART patients in Vietnam[40] indicates insignificant differences in the percentage of detectable VL and ADR after 12 months on ART between injectors and non-injectors, similar to findings from previous reports in the literature.[41,42] Lastly, we assumed that the reduction in transmission probability due to ART for injecting transmission is similar to that of sexual transmission.[43,44]

As part of the Monte Carlo process,[45] a total of 10000 sets of all model parameters were sampled using the Latin Hypercube sampling. Results of each simulation from the 10000 model runs were calibrated against historical trends of observed data (Figure S1, available as Supplementary data at *JAC* Online and Table S1); the model was calibrated starting from 2004, when Vietnam planned for its national ART programme, and with only 500 people receiving ART nationwide, the overall prevalence of TDR was assumed to be low.[31] We ranked simulations by the mean square error between modelled estimates and observed data. Descriptive statistics were calculated based on the first 100 simulations with the lowest mean square error. Further details of the model construction and calibration are provided in the Supplementary data.

Effectiveness and cost-effectiveness analysis

We simulated 10% incremental coverage levels of VL monitoring from 2015 to 2030, and for each we considered eight scenarios combining the frequency of VL monitoring (annually or every 2 years), second-line ART switch criterion (VL >1000 copies/mL or >400 copies/mL), and the use or absence of genotypic resistance testing to confirm the treatment failure status (Table 1). The detection limit of a genotypic resistance test was assumed to be 400 copies/mL based on the recent improvements in resistance testing in low-level viraemia, specifically the application of the commercial ViroSeq HIV-1 Genotyping System.[46,47] Notably, a provision of these switch criteria is expected to change the rate of switching among people for whom ART is failing, which was observed through monitoring of ADR in Vietnam (Table 1). To quantify the effectiveness, the calibrated model, which contains assumptions of what would or will have occurred in Vietnam under the status quo of no VL monitoring, was first used to simulate the epidemic according to the changed rate of switching. Modelled new TDR infections, ADR acquisition, HIV-related deaths, disability-adjusted life years (DALYs) and total health-related costs were compared between all scenarios and the status quo. We quantified absolute DALYs based on available disutility weights.[48,49] The incremental cost-effectiveness ratios (ICERs) for each scenario were also calculated by dividing the additional cost by the calculated DALYs averted due to the provision of the scenario.

We assessed the cost-effectiveness of VL monitoring strategies based on ICER and the government's willingness to pay. So far, the Vietnamese government has not established a general willingness-to-pay threshold for a health intervention. We hence adapted the WHO-recommended threshold for cost-effectiveness [one to three times of the per capita gross domestic product (GDP)].[50–52] Vietnam's GDP per capita in 2014 was estimated to be US$2052. During our study, the Vietnamese Ministry of Health was also consulted to ensure that recommended scale-up is affordable in the actual governmental budgets. A discount rate of 3% per year was applied for both costs and DALYs.

Sensitivity analysis

All sampled clinical, biological and virological parameters were included in a sensitivity analysis to investigate their effects on the prevalence levels of TDR and ADR. We also examined the sensitivity of estimated ICERs to costs of HIV care and treatment, and VL and genotypic resistance tests, in which all clinical, biological and virological parameters were fixed. Partial rank correlation coefficients were calculated to measure the magnitude of the relationship between model outputs and sampled parameters.

Results

Our model closely reflected the past HIV epidemic and level of drug resistance in Vietnam over the period of 2005 to 2013 (Figure 2 and Figure S1). According to the current growth trend, the estimated number of people on ART is expected to increase from 98000 (95% CI: 86000–112000 people) in 2015 to 189000 (95% CI: 157000–225000 people) by 2030. The proportion of PLHIV on second-line ART will increase from 3.9% (95% CI:3.1%–4.6%) to 20.7% (95% CI: 16.5%–25.1%) in the same period. This treatment expansion will result in an estimated 18512 new TDR infections (95% CI: 9117–34597 infections) and 55178 new ADR cases (95% CI: 40539–65903 cases) (Table 2), corresponding to prevalence levels of 15.5% (95% CI: 11.0%–23.6%) and 17.9% (95% CI: 14.5%–20.4%) in 2030, respectively. Despite a remarkable increase in TDR prevalence, the actual number of new TDR cases is relatively low (830–1444 cases per year), owing to the large reduction in the overall number of new HIV infections over time (Figure 2b). The expansion of ART will also maintain the low number of deaths and lead to a substantial reduction in the number of DALYs (Figure S1 and Table 2). Sensitivity analysis showed that the most influential factors for TDR and ADR prevalence levels were the relative fitness of DR strains and the rate of virological failure among WT-infected people on ART, respectively (Figures S2 and S3).

Compared with the status quo, following the current WHO recommendation of VL monitoring and switching[3] will lead to reduced burden of ADR by 2030 (Figure 2f). Our analysis indicated that more than half [55.4% (95% CI: 50.3%–59.9%)] of new ADR cases may be averted if 30% of people on ART have access to VL monitoring by 2030 (Figure 3b). This large reduction makes it possible to stabilize the growing prevalence of ADR to 7.3% (5.9%–8.6%) by 2030 (Figure 2f). However, providing VL monitoring at any coverage level leads to a large increase in the total number of people on second-line ART (Figure 2c and d), leading to a substantial increase of 8.8%–30.4% in the total cost of ART programmes during 2015–30 (Figure 3d). Implementing the WHO recommendation will also reduce new TDR cases by 13.2%–47.9% over the same period (for 10%–100% access coverage of VL monitoring; Figure 3a). With this low-to-moderate impact on TDR, projected TDR prevalence will continue to increase from 2015 to 2030 regardless of the monitoring coverage (Figure 2e); however, higher coverage levels of VL monitoring will have greater potential to reduce the growing trend of TDR prevalence and contain it below 15% by 2030. In particular, 10% of VL monitoring coverage according to WHO recommendations may lead to a

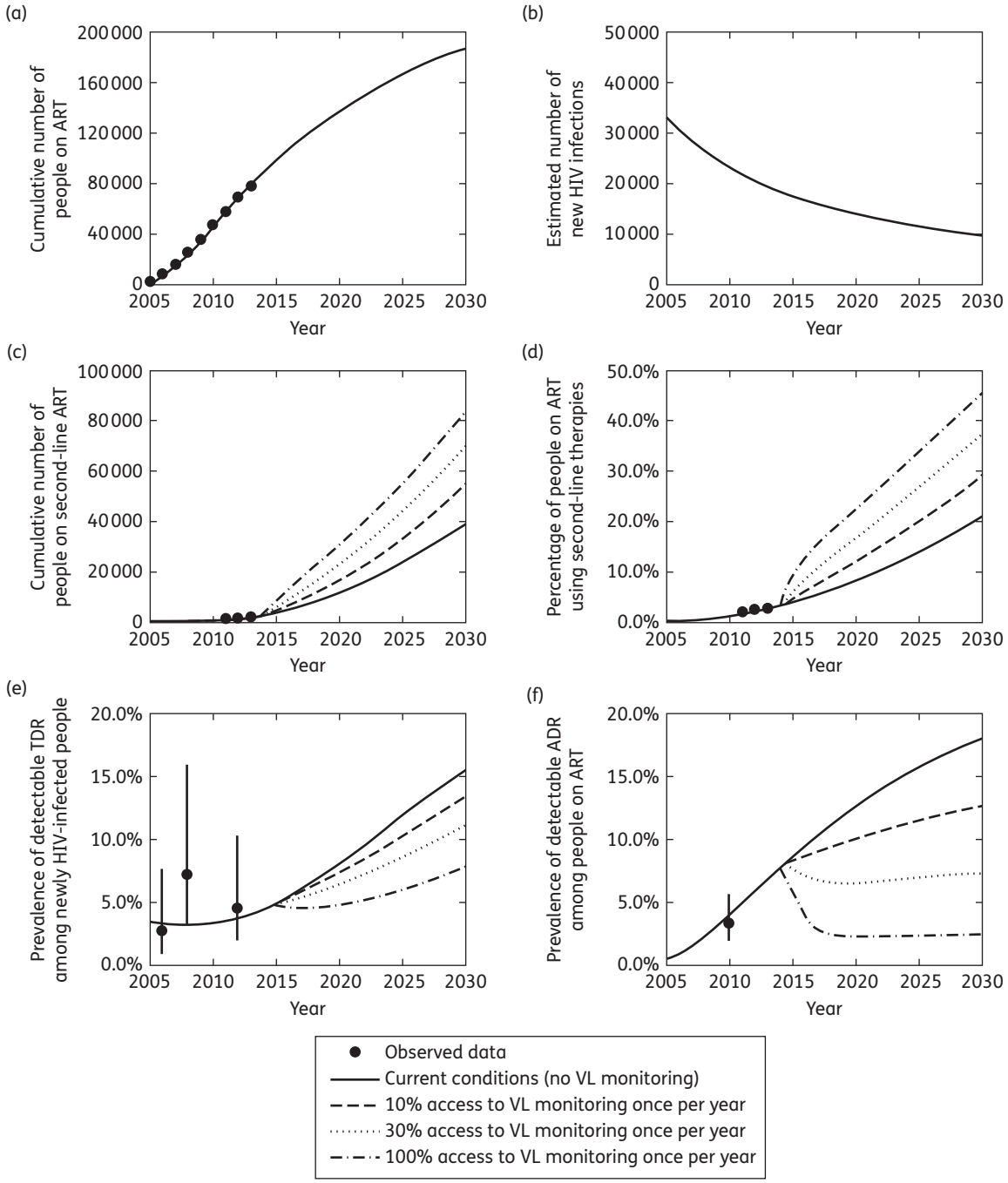

Figure 2. Median change in the number of people on ART, new HIV infections and levels of TDR and ADR in Vietnam if treatment response is monitored by VL once per year and the switch criterion is a presence of two consecutive VL tests with >1000 copies/mL without an HIV drug-resistance test (the WHO-recommended switching strategy). (a) Cumulative number of people on ART. (b) Estimated number of new HIV infections. (c) Cumulative number of people on second-line ART. (d) Percentage of people on ART using second-line regimens. (e) Prevalence of detectable TDR among newly infected people. (f) Prevalence of detectable ADR among people on ART.

TDR prevalence of 13.4% (95% CI: 9.5%–19.7%) in 2030; however, lower prevalence levels of 11.0% (95% CI: 7.6%–16.0%) and 7.7% (95% CI: 5.2%–11.2%), respectively, may be achieved if the coverage is increased to 30% or even to 100% by 2030.

Figure 4 compares the findings from cost-effectiveness analyses of our eight scenarios with a feasible 30% VL monitoring coverage over a short-term period (2015–20), a medium-term period (2015–25) and a long-term period (2015–30). Our analysis indicates that across these three time periods, monitoring VL every 2 years with resistance tests performed for PLHIV with VL >1000 copies/mL to determine whether to switch to second-line ART is projected to have the least additional cost (US$20

Table 2. Projections of the base-case number of new TDR infections, new ADR acquisitions, deaths and DALYs in Vietnam over the period 2015–29

Year	New TDR infections	New ADR acquisitions	Deaths	DALYs
2015–19	4561 (2620–7784)	14051 (10656–16532)	4265 (3491–4868)	383140 (262570–548190)
2020–24	5727 (2905–10597)	17538 (13261–21042)	4682 (3748–5426)	334670 (231982–483146)
2025–29	6739 (3004–13269)	19528 (14612–23392)	5184 (4030–6268)	295430 (207470–436710)

Figures are medians (with 95% CI), which were obtained from 100 simulations mostly fitted with observed data.

million in 2015–20, US$40 million in 2015–25 and US$105 million in 2015–30). The most expensive scenario is to monitor people on ART annually and allow early switching to second-line ART at low detected VL levels (>400 copies/mL). This approach will result in additional costs of US$53 million, US$113 million and US$268 million over the three time horizons, respectively. Across all scenarios, a 30% coverage of VL monitoring is expected to result in 2264–5855 (11.9%–31.3%) fewer new TDR infections, 9615–22645 (25.0%–59.1%) fewer new ADR acquisitions and 363–877 (2.4%–6.0%) fewer HIV-related deaths by 2030. This outcome will in turn lead to the prevention of an estimated 19270–51400 DALYs over the same period, corresponding to US$4848–5154 per DALY averted (Table S2 and Figure S4). Furthermore, in all VL monitoring coverage, the median ICER values from the study scenarios, compared with the status quo, fall on a relatively straight line (Figure 4 and Figure S5). This finding suggests that the cost-effectiveness of VL-monitoring scenarios is unlikely to rely on the coverage level. VL monitoring every 2 years is associated with lower ICER values. Implementing the WHO-recommended VL monitoring over the period 2015–20 results in an ICER of US$5243 (95% CI: US$3961–9433) per DALY averted, which only slightly reduces over longer time horizons [US$4858 (95% CI: US$3762–US$8499) over 2015–30] (Figure S5). Sensitivity analysis revealed that the cost of second-line ART is the most influential factor of the ICERs (Figure S6).

Discussion

We projected a low level of TDR incidence of an estimated 830–1444 cases each year during 2015–30. Together with other key factors, such as declining HIV incidence,[53] the widespread use of combined ART regimens,[54] and the national commitment to HIV prevention services,[55] we anticipate that the projected slowly expanding TDR epidemic will not be a major hurdle for the scale-up of current ART programmes in Vietnam. This finding is consistent with findings from other resource-limited settings.[14,15] Our results additionally demonstrate that a moderate VL-monitoring coverage of 30% of people on ART with adequate availability of second-line ART is projected to prevent 2260–5860 new TDR infections, 9620–22650 new ADR acquisitions and 360–880 HIV-related deaths. The prevention of these infections and deaths leads to an estimated 19270–51400 fewer DALYs. Implementing these strategies has a cost-effectiveness ratio of US$4848–5154 per DALY averted, which is only marginally cost-effective according to the WHO cost-effectiveness threshold. It is quite high compared with most willingness-to-pay thresholds in Vietnam. The high cost of second-line ART is the major challenge in implementing the proposed strategies.[8]

In recent years, many resource-limited countries, such as Botswana, Brazil, Cameroon, Côte d'Ivoire, Malawi, South Africa, Thailand and Ukraine, have already initiated VL monitoring in their national ART programmes.[56] However, Vietnam has little momentum to adopt this approach despite recently establishing a target for national VL monitoring. Our results indicate that if Vietnam continues the current CD4+ and symptom-based monitoring strategy but does not increase the coverage of VL monitoring and availability of second-line ART for people on treatment, controlling ADR will be a challenge in the future. A global review by Rutherford *et al.*[57] highlighted that CD4+ and symptom-based monitoring often leads to an unnecessary switch to costly salvage therapy due to its poor accuracy in detecting VL. Immunological and clinical monitoring also result in late detection of actual treatment failure, leading to drug-resistance-associated mutations, failed ART regimen and transmission of DR strains. The accumulation of multiple mutations may increase the threshold for managing further ART and laboratory monitoring in people in whom ART is failing.[58] Furthermore, when people in whom ART is failing are switched to second-line ART late, the DR strain that they harbour is provided a great chance to improve its fitness, which enables it to be transmitted to other persons and increase the prevalence of TDR in the community. Notably, our findings suggest that although most VL monitoring scenarios have relatively high ICERs and only modest differences in ICERs, a moderate coverage of VL monitoring for 30% of people on ART may be sufficient to sustain a low-to-moderate prevalence of TDR in Vietnam by 2030. This finding also means that the current standard first-line ART regimens are expected to continue to effectively suppress the virus in most people receiving ART. Expensive scale-up plans, such as changes in the national guidelines to include boosted PIs in initial treatment regimens, early VL testing after initiating ART and the inclusion of routine pretherapeutic genotypic resistance testing for all ART entrants may not be necessary. Given the rising prevalence of pretreatment drug resistance, particularly resistance to NNRTIs, in low- or middle-income settings,[59] and with the poor cost-effectiveness of the late responses in settings with a high level of drug resistance,[60] VL monitoring should be implemented as soon as possible for people receiving ART in Vietnam.

Overall, our findings indicate borderline cost-effectiveness for implementing VL monitoring over the medium-to-long term. A modelling study conducted in the sub-Saharan African region indicated VL monitoring is cost-effective,[61] yet other studies for similar settings found these strategies not to be cost-effective.[13,62–66] Our study, for a middle-income country in Asia, has found consistent ICERs within the range of those found in studies conducted in other settings. The WHO and previous studies have recommended annual VL monitoring and have allowed two consecutive VL tests with >1000 copies/mL to be

the criterion for switching to higher-line ART.[3,67] However, our analysis indicates that this approach is one of the most expensive strategies and requires an additional US$112 million to US$390 million for providing VL monitoring to 10%–100% of people on ART over 2015–30. This expense far surpasses Vietnam's available resources. In contrast, we find that the most economical approach is to conduct a VL test every 2 years and provide second-line ART to individuals with a VL >1000 copies/mL and detectable HIV

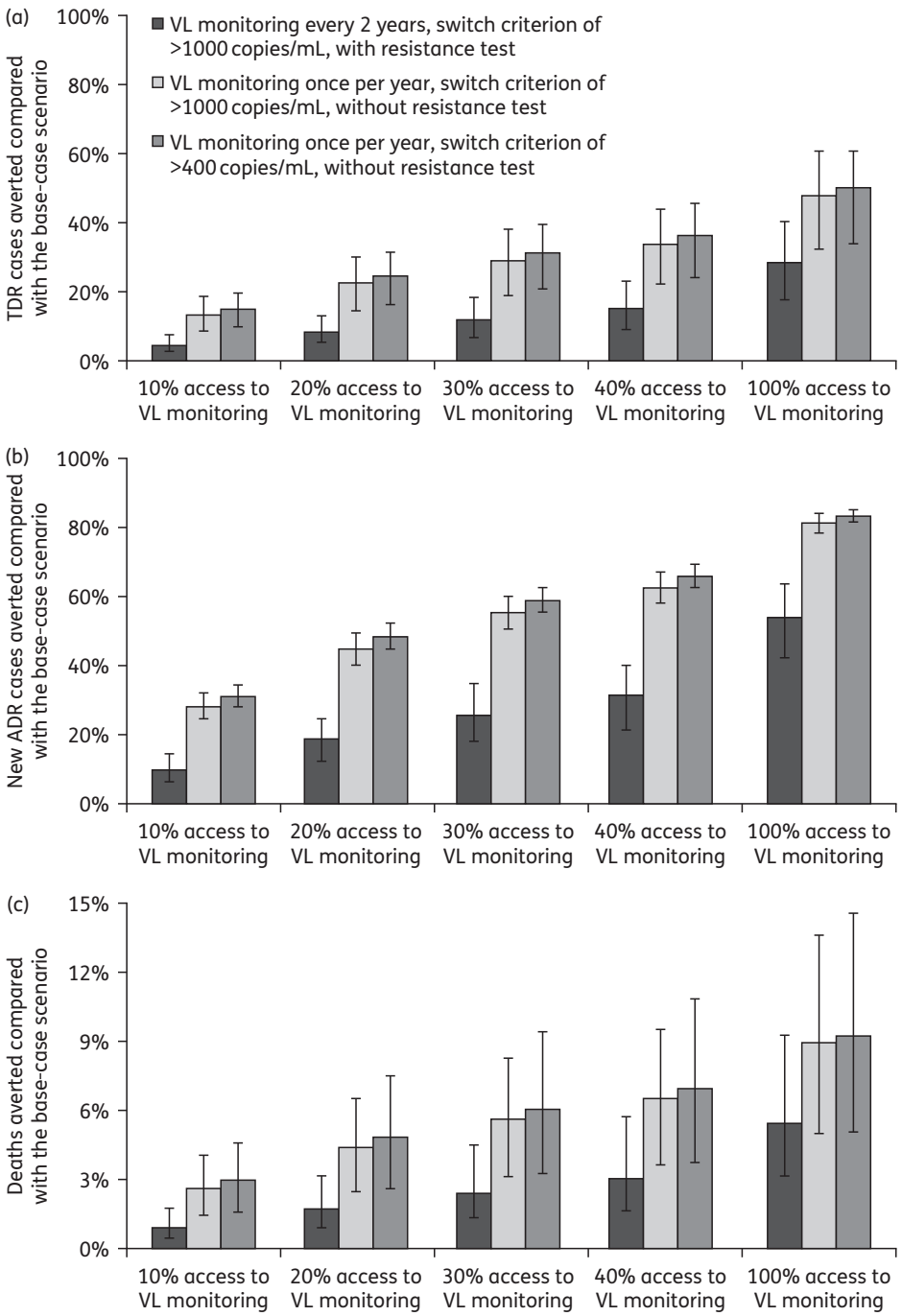

Figure 3. Overall differences in TDR infections, ADR incident cases and deaths and increase in cost due to HIV care intervention using VL monitoring compared with the current situation (no VL monitoring). Dark grey bars represent the median (with 95% CI) of the indicators for strategies with VL monitoring every 2 years and a switch criterion of >1000 copies/mL with a resistance test (the least expensive cost-effective scenario); light grey bars represent the median (with 95% CI) of the indicators for strategies with VL monitoring once per year and a switch criterion of >1000 copies/mL without a resistance test (the WHO-recommended strategy); and grey bars represent the median (with 95% CI) of the indicators for strategies with VL monitoring once per year and a switch criterion of >400 copies/mL without a resistance test (the most expensive cost-effective scenario).

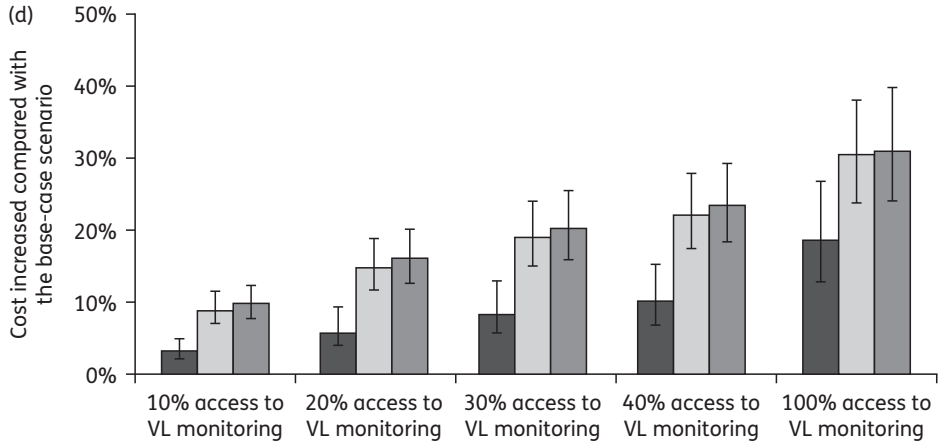

Figure 3. Continued.

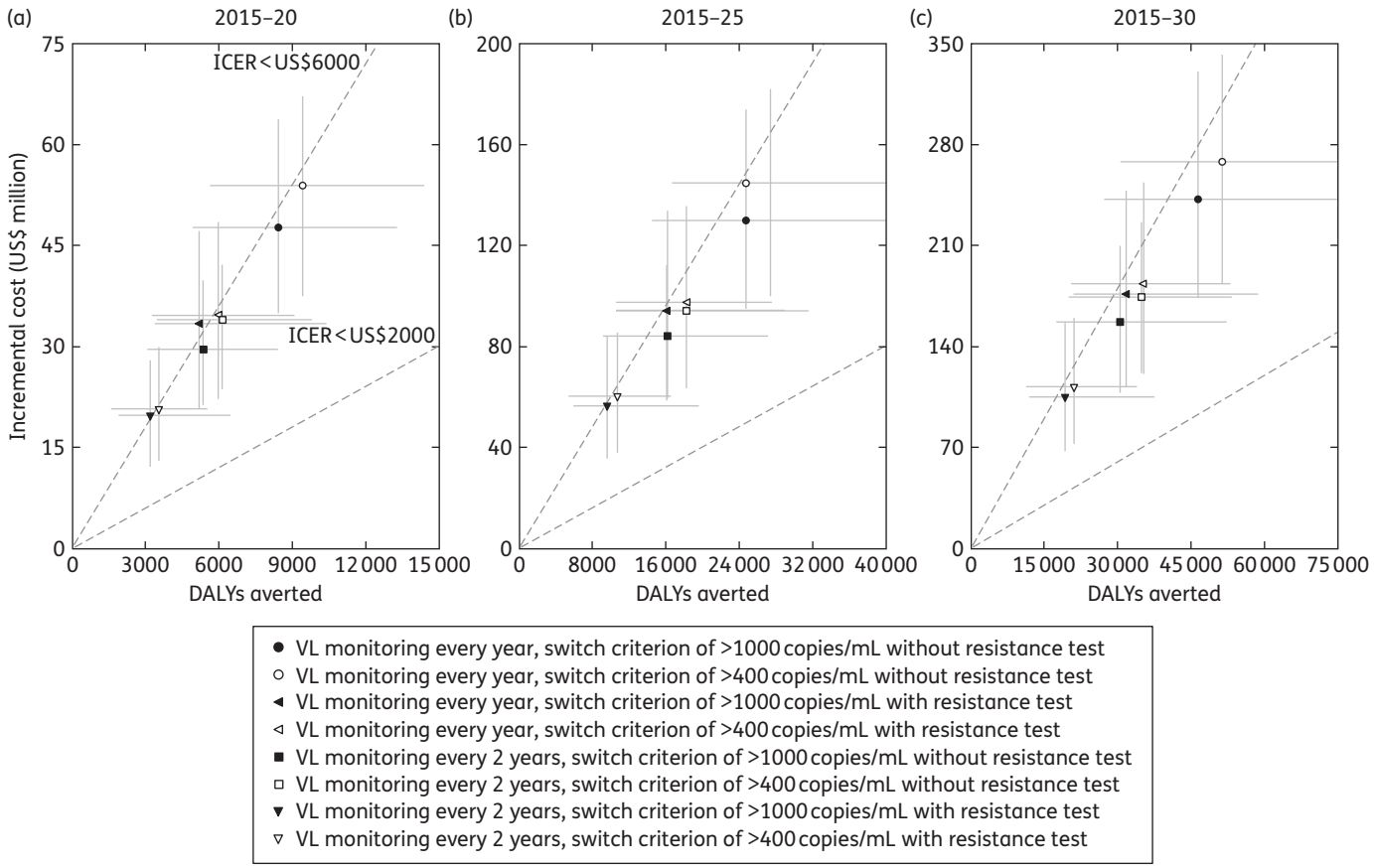

Figure 4. Cost-effectiveness plans of VL monitoring strategies with a target of 30% of people on ART assessing routine VL monitoring over three time horizons of 2015–20 (a), 2015–25 (b) and 2015–30 (c). For each scenario, the median ICER is given (with horizontal and vertical grey lines representing the 95% CI of the incremental costs and total DALYs averted in comparison with the status quo, respectively). The two broken grey lines (from left to right) represent the ICER thresholds of less than 3 and 1 GDP per capita (~US$6000 and 2000 in Vietnam in 2014).

drug resistance; a VL monitoring target of 30% of people on ART is recommended for Vietnam in view of the current laboratory infrastructure, affordable testing investment and clinical significance. Full-scale implementation of VL monitoring can first be initiated in urban Vietnam, such as in Hanoi and Ho Chi Minh City, where ART programmes account for more than 30% of people on treatment in the entire country. These two major urban hubs play a central role in the emergence and transmission of HIV drug resistance in Vietnam and accordingly have advanced testing laboratories and well-organized healthcare systems established. Notably, this

study recommends VL monitoring to be delivered to a priority patient group. Implementing this suggestion may require further ethical considerations and cooperation between local health workers, health services and community-based organizations of PLHIV. As testing coverage did not influence the cost-effectiveness of VL monitoring, Vietnam could recommend full coverage for all people on ART. However, the expansion to the rural and remote areas will require innovative financing, low-cost point-of-care VL and resistance tests, and cheaper second-line ART regimens.[68,69]

Our model was calibrated to the numbers of notified HIV cases, drug-resistance level and people on ART in Vietnam over the past decade. The reflection of the past HIV epidemic provides reliable population-level projections for the trend of ART uptake and HIV drug resistance in the future. However, we acknowledge a number of limitations of our model. Notably, this model did not separately track the transmission of HIV strains (WT, DR and DRU viruses) by gender and population groups such as people who inject drugs, female sex workers and their clients, MSM and low-risk males/females. We therefore were unable to provide the projected prevalence of all and individual strains of HIV or to calibrate the model outcomes with known trends in the overall prevalence of HIV in these risk groups.[70] It is important to note that specific surveillance systems of TDR and ADR among these at-risk groups were not available in Vietnam. Given such a contextual constraint on the data for a complex mathematical model for the transmission of HIV WT and DR strains, we developed a simple model to estimate the average onward transmission of the strains. The dearth of ART efficacy data for preventing the risk of HIV transmission through injection further limited our attempts to extend the current analysis for different modes of transmission.

Furthermore, the model structure did not take into consideration CD4+ T cell levels, HIV stage or specific drug-resistance classes, so we were unable to fully capture HIV disease progression or to estimate the levels of specific mutations and resistance to specific antiretroviral drug classes. Notably, the inability to adjust the current analysis for mutant strains that may revert to WT at different rates or be resistant to specific drug classes and to include the likely impacts of programmatic changes in ART regimens (e.g. from dual to triple drug regimens and from potent first-line stavudine-based to tenofovir-based regimens) may lead to biases in estimating the disease burden of TDR and ADR in Vietnam. Although our simple model can explore in part the overall dynamic of HIV drug resistance in Vietnam, its model type, a population-based design, makes it impossible to capture the transmissible event of WT or DR strains. Future modelling efforts are needed to address these model limitations.

Other major limitations of this model are associated with a range of model parameters and assumptions. It is important to note that the model was largely based on a single prospective cohort study,[40] which may overestimate some clinical treatment outcomes due to its short duration of follow-up (maximum 24 months). Furthermore, our assumption of 100% sensitivity and specificity for both VL and genotypic resistance tests may not be realistic.[62] In this study, we evaluated only the impacts of VL monitoring in confining the emergence and transmission of HIV drug-resistant strains, but we excluded other potential benefits, such as improvement in treatment adherence.[9–11] This drawback may be modest because we used a low rate for virological failure from the aforementioned observational cohort. This finding may be attributable to the current management of VL blips by detecting poor adherence early and offering adherence counselling onsite. Indirect costs associated with large-scale implementation of VL monitoring and genotypic HIV drug-resistance testing were not included in our cost-effectiveness analysis. Thus, we may need to be slightly more pessimistic about the actual cost-effectiveness of VL monitoring.

Our findings project an increasing trend of both TDR and ADR as a result of future ART scale-up in Vietnam. VL monitoring has been shown to be borderline cost-effective to reduce the disease burden of HIV and its drug-resistant strains. It warrants discussion of potential improved access to VL monitoring in low- or middle-income settings and procurement of second-line ART, especially regarding the costs involved, to treat the growing population of PLHIV.

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Transparency declarations

None to declare.

Author contributions

Q. D. P. conceived and designed the study, performed the analysed, interpreted the findings and participated in the writing of the manuscript. D. P. W. and L. Z. were involved in the design and analysis of the model, reviewed the manuscript and overviewed the study. N. T. D. and T. V. N. provided empirical data on notified HIV/death cases, detailed ART programming and HIV drug-resistance levels in Vietnam, gave advice on behaviour trends and were involved in the editing of the manuscript. L. X. T. provided advice on immunological and virological insights and participated in the editing of the manuscript. L. T. N. contributed to the interpretation of the findings and was involved in the editing of manuscript. All authors saw and approved the final version of the manuscript.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Vietnamese Ministry of Health, the Vietnam Authority of HIV/AIDS Control, the Pasteur Institute—Ho Chi Minh City or the Kirby Institute.

Supplementary data

Figures S1 to S6, Tables S1 and S2 and further details of the model construction and calibration are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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