Economic evaluation of monitoring virologic responses to antiretroviral therapy in HIV-infected children in resource-limited settings

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Objective: Antiretroviral therapy (ART) management for HIV-infected children is critical in many resource-constrained countries. We investigated the cost-effectiveness and cost-utility of different frequencies of monitoring plasma viral load among HIV-positive children initiating ART in a resource-limited setting.

Design/methods: A stochastic agent-based simulation model was built and directly informed by a cohort of 304 HIV-infected children starting ART in Thailand between 2001 and 2009. The model simulated the expected costs and clinical outcomes over time according to different viral load monitoring frequencies and initiation of second-line therapies when appropriate.

Results: The optimal frequency of viral load monitoring was found to be annual, after a single screening at 6 months. Associated costs of viral load monitoring and appropriate ART would approximately triple current treatment costs. Compared with current conditions, a single screening during the first year of ART led to a 58.4% reduction in the total person-years of virological failure with annual monitoring leading to a 76.6% reduction. The incremental cost per quality adjusted life year gained from the optimal monitoring frequency was estimated as US$ 68 084 when including costs of ART and US$ 7224 without ART costs. The estimated cost attributed to preventing 1 year of virological failure was US$ 3393 with ART costs and US$ 359 without ART costs.

Conclusion: Even infrequent viral load monitoring is likely to provide substantial clinical benefit to HIV-infected children on ART. Viral load monitoring can be considered cost-effective in many resource-limited settings. However, the costs associated with second-line therapies could be a barrier to its economic feasibility.

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Introduction

As the coverage of antiretroviral treatment (ART) continues to expand, improving access to laboratory testing for monitoring responses to treatment is a growing and critical area of need for low and middle-income countries [1–4]. However, due to limited resources monitoring responses to treatment is often not performed in these settings despite the development of relatively inexpensive and reliable technologies [2,5–7].

Children are particularly affected as disease progression associated with their HIV infection is typically more aggressive compared to adults [8]. However, children remain among those least likely to obtain access to HIV viral load monitoring in resource-constrained countries [9]. Many children are often diagnosed several years after infection with advanced disease. The clinical management of children on ART is usually conducted without viral load testing and, in many cases, without CD4 cell counts and is usually based on clinical criteria. However, monitoring treatment responses through immunological and clinical criteria leads to a substantial delay in detection of poor treatment response and lacks both sensitivity and specificity for virological failure [10,11], especially among children [12].

Deciding whether and how often to conduct viral load tests, and the appropriate time to change to a second-line ART regimen is undefined. Viral load testing is rarely performed because of the cost of testing and second-line ART. A mathematical model conducted by Phillips *et al.* [13] argued that monitoring treatment responses among adults via viral load is not cost-effective in resource-limited settings when compared with clinical monitoring, because only a modest benefit was observed in life years and quality-adjusted life years (QALYs). However, no mathematical model to date has been applied to a child population, in which attributed costs and potential for drug-resistant mutations as a consequence of delaying treatment change and disease progression are likely to be different.

Currently, first-line ART for children in Thailand is similar to the treatment given to adults. It is relatively inexpensive and generically produced by the Thai government. It is common practice to use split fixed-dose combination tablets for children, that is a fixed-dose combination of stavudine, lamivudine, and nevirapine (d4T/3TC/NVP), in a single tablet called GPO-VIR S30. A newer regimen of zidovudine (ZDV), 3TC, and NVP is currently rolling out as a single tablet, called GPO-VIR Z250 [14–16]. However, it is only inevitable that as the number of children accessing these treatments increase so will the number of children who fail them. If left unmonitored those children are likely to face increased risk of developing various comorbidities and mortality as well as the accumulation of drug-resistant mutations [17–22] which reduce future drug options [23,24].

To maintain the success achieved by up-scaling the coverage of ART in resource-limited settings, optimal monitoring strategies must be developed. As viral load testing is slowly being introduced for the care of patients living with HIV infection in resource-limited settings, determining the most efficient and cost-effective strategies are essential. The current study addresses this issue through a simulation model of HIV progression in children initiating first-line ART, informed by data from a cohort of children in Thailand, to predict the clinical and economic impact of different frequencies of viral load monitoring.

Methods

The Thailand cohort

Longitudinal virological, immunological and clinical data were collected prospectively from 304 HIV-infected children (160 girls and 144 boys) who sought treatment from two large urban treatment centres in Chiang Mai and Bangkok between October 2001 and May 2009 (Table 1). The children were enrolled as part of HIV treatment cohort studies at both sites. The characteristics of the children enrolled (Table 1), with respect to age and disease progression, were similar to that of a large study conducted in Thailand of HIV-infected children [25] and are assumed to be nationally representative of all Thai children with HIV. The protocols were approved by the Institutional Review Boards and all caregivers gave consent for data collection and analyses. A total of 2230 viral load tests were conducted across the cohort with one test per child every 24 weeks, providing 1029 person-years of observation. The median follow-up time per child was 4.6 years.

Treatment response categorization

In this study undetectable viral load (viral suppression) was defined as viral load below 50 RNA copies/ml and virologic failure was defined as a viral load at least 1000 RNA copies/ml. Virologic failure was separated into two categories: incomplete viral suppression, which was defined as having a HIV plasma viral load at least 1000 RNA copies/ml after at least 24 weeks of ART, and viral rebound, defined as increased plasma HIV RNA to at least 1000 RNA copies/ml after having previously undetectable viral load.

CD4 percentage, as the percentage of total lymphocytes in a sample of blood that are CD4-positive, was used to track immunological health among individuals according to the categories: CD4% 7 or less, CD4% more than 7 but less than 16, and CD4% 16 or more. It was the preferred predictive marker for disease progression in children due

Table 1. Demographic and clinical characteristics of the Thailand cohort.

Baseline characteristics	
Sex [*N*(%)]	
Girls	160 (52.6)
Boys	144 (47.4)
Age [years, median (IQR; range)]	7 (4–9; 0.08–15)
Weight [kg, median (IQR; range)]	17 (13–21.5; 4–53.5)
CD4% [median (IQR; range)]	4 (1–11.25; 0–41)
Viral load [log10 RNA copies/ml, median (IQR; range)]	5.3 (5.0–5.8; 1.7–6.0)
Drug treatment (%)	
First-line regimens	
GPO-VIR S30 (lamivudine (3TC) + nevirapine (NVP) + stavudine (d4T))	53.0
GPO-VIR Z250 [3TC + NVP + zidovudine (ZDV)]	13.0
Zilavir (3TC + ZDV) + efavirenz (EFV)	7.5
EFV + d4T + 3TC	26.5
Second-line regimens	
Protease inhibitors	
Lopinavir/ritronavir (LPV/r)	70.0
Indinavir/ritronavir (IDV/r)	20.0
Saquinavir/ritronavir (SQV/r)	10.0
Plus nucleoside reverse transcriptase inhibitors	
ZDV + didanosine (ddI)	30.0
ddI + 3TC	10.0
ZDV + 3TC	60.0
Treatment response [*N* (%)]	
First-line ART	304 (100)
Incomplete viral suppression	45 (14.9)
Suppressed viral replication	258 (85.1)
Viral rebound	17 (6.6% of those who initially suppressed on first-line) (≈1.4% per year).
Second-line ART	44[a] (14.5)
Incomplete viral suppression	4 (11.1)
Suppressed viral replication	32 (88.9)
Viral rebound	1 (3.1% of those who initially suppressed on second-line) (≈2.0% per year)

IQR, interquartile range.
[a]Of these, 36 (81.8%) had clean viral load data for a median follow-up time (on second-line) of 1.6 years.

to the natural reduction and variability in CD4 cell count with increasing age regardless of HIV status and has proven to be a reliable assessment tool for disease progression.

Model structure

A stochastic agent-based simulation model was built using Matlab R2009a. The model consisted of three HIV disease states (based on CD4%), and death (Fig. 1); this is similar to the health states of the model used in a cost-effectiveness analysis conducted for HIV-infected children in Zambia [26]. However, our model allowed forward and backward transitions according to differing treatment responses among simulated individuals. Each simulated child was randomly assigned individual characteristics including age, sex, weight, CD4% and viral load, sampled from the distribution of data from the Thailand Cohort Study. Changes in an individual's weight (kg) were dependent on their age at each time-step in the model and their assigned sex; these characteristics were allowed to change through time based on the growth of an average child in Thailand.

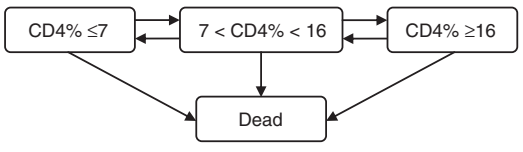

Fig. 1. Schematic diagram of the health states in the simulation model.

ART regimen, responses to these treatments, as well as the possibility of death, was also allocated to each simulated child by sampling from the distribution of data obtained from the Thailand Cohort Study (Table 1). A simulated individual was randomly assigned one of four first-line drug regimens at the start of the model. Once assigned a drug regimen, each individual had a possibility of incomplete viral suppression. If viral replication was suppressed in an individual they then had a chance of viral rebound (Table 1). The chance of incomplete viral suppression on second-line treatment varied according to the length of time on a failed first-line regimen. Children from the Thailand Cohort had virological failure for a median of 94 weeks (IQR: 69.5–125.3) before switching to a second-line regimen, and the resultant rate of incomplete virological suppression was 11%. Therefore, matching to a weighted average of 11%, those left on a failed regimen for less than or equal to 70 weeks were

assumed in our model to have a 7% chance of failing their second-line regimen, 11% if left for more than 70 weeks but less than 125 weeks, and 15% if left for 125 weeks or more.

In addition, each simulated individual had a probabilistically defined chance of death at each time-step. Eight patients (2.6%) were recorded to have died during the course of the Thailand Cohort Study (≈0.6% per year). Six of the eight (75%) died with suppressed virus and were on first-line ART, one patient (25%) had failed first-line ART (incomplete viral suppression) but then achieved suppressed virus on second-line ART and the final patient had failed both first-line (viral rebound) and second-line ART (incomplete viral suppression). A slightly higher death rate was found among those with virological failure (either viral rebound or incomplete virological suppression) than those not experiencing failure: one death per 120 person years in virological failure compared to one death per 130 person years not experiencing failure. These mortality rates were applied to the model across all CD4 levels.

The median viral and immune responses were calculated and plotted through time on ART and curves were fit to best represent the data (Fig. 2). To account for the variation between children, simulated children had viral and immune characteristics that were sampled from the distribution of data in the cohort but trends in these variables followed the curve trend of the median. All curves were assumed to reach a plateau after 5 years. According to simulations of these trajectories, the disease state of each child was updated weekly and at each weekly time step the probability of viral failure or death for a child in each state was used for stochastically determining whether each simulated child would experience virological failure or die in the next week. The total time each simulated individual in the model spent with virological failure or in any of the three disease states and the number of simulated deaths was tracked and tallied for 10 years. Summary statistics from a simulated population of 10 000 children across 100 simulated populations were calculated.

The model was used to forecast the expected treatment responses for a larger population of children according to different viral load monitoring strategies. A control arm of no viral load monitoring was simulated along with a number of monitoring intervention strategies: once at 6 months after initiating ART followed by no monitoring or monitoring every 6 months; year; 2 years; 3 years; or 4 years. We also simulated regular viral load monitoring at the same frequencies but without the initial 6-month screening. Individuals in the control arm were not monitored or given second-line regimens. According to each of the viral load monitoring simulations, if an individual was detected with treatment failure they were randomly allocated a second-line regimen.

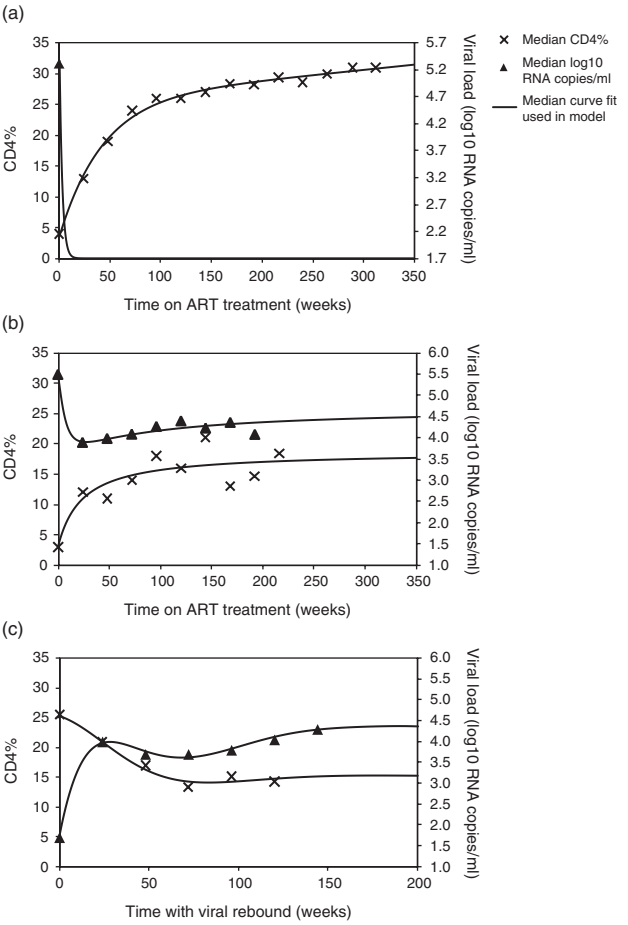

Fig. 2. Change in viral load and CD4% on first-line ART according to treatment response. Data points represent the median of Thailand cohort data. (a) Immunological recovery/viral suppression. The curve for CD4% was fit with the sum of two exponentials. (b) Incomplete viral suppression. The curve for CD4% was fit with the quotient of two linear expressions and the curve for viral load was fit with the quotient of cubic polynomials. (c) Viral rebound.

Cost estimation

Costs represent the direct costs that can be allocated to viral load monitoring, including physician, laboratory and drug costs and were obtained from clinical experience in Thailand and the Thai National Health Security Office (NHSO) (Table 2). The laboratory-associated costs of a single viral load test was assumed to be 1500 Baht (US$45) and the total cost for physical examination and drug distribution was estimated to be 500 Baht/visit (US$15.47). Drug costs were dependent on the total drug intake of each simulated individual, and are based on the recommended dose according to a child's weight. Children in the Thailand Cohort Study who weighed less than 15 kg were given syrup formations. Syrups are generally about 1.5 times the price of tablets due to their short shelf-life and logistics. Therefore simulated children weighing less than 15 kg were assigned to syrups and these were assumed to cost 1.5 times more than their corresponding tablets.

Table 2. Unit cost data.

Unit costs		Cost US$ (2010)
Direct infrastructure costs		
Laboratory-associated costs per viral load test		45.00
Physical examination and drug distribution per viral load test		15.47
Drug costs (per pill)		
GPO-VIR S30 [lamivudine (3TC) + nevirapine (NVP) + stavudine (d4T)]	150/200/30 mg	0.465
GPO-VIR Z250 [3TC + NVP + zidovudine (ZDV)]	150/200/250 mg	0.615
Zilavir (3TC + ZDV)	300/150 mg	0.63
EFV	600 mg	0.81
d4T	30 mg	0.12
3TC	150 mg	0.255
ZDV	100 mg	0.165
NVP	200 mg	0.36
Didanosine (ddI)	250 mg	2.43
Lopinavir/ritronavir	100/25 mg	0.72
Indinavir	400 mg	0.36
Saquinavir	500 mg	2.40
Ritronavir	100 mg	1.08

Cost-effectiveness and cost-utility analysis

There is little published information on utility weights for disease progression among HIV-infected children. Therefore utility values used in the current study were based on a cost-utility analysis with similar health states conducted for children in Zambia [26] and a large meta-analysis of utility estimates for HIV/AIDS among adults [27]. The incremental cost-effectiveness of viral load monitoring in terms of QALYS, q, as health-related quality-of-life weights were assigned to each of the three disease states and to death in the model: $q(\text{CD4\%} \geq 16) = 0.94$, $q(7 < \text{CD4\%} < 16) = 0.82$, $q(\text{CD4\%} \leq 7) = 0.70$, and $q(\text{death}) = 0$. Summary statistics from a population of 10 000 children across 100 simulated populations were then used to estimate the cost-effectiveness, defined as cost per year of virological failure averted, and cost-utility, defined as cost per QALY gained, of all monitoring options using the no monitoring strategy as a baseline. Discounting was applied to all costs as well as all effectiveness and utility outcomes at 0, 3 and 5%.

Sensitivity analyses

We examined the sensitivity of the results to the estimated cost of viral load tests, physical examinations, and ART (all costs ± 50%). We also investigated sensitivity of results to utility weights ($q' = q \pm 0.5(1 - q)$) and the probability of incomplete viral suppression on second-line ART (±50%).

Results

Virological and immunological outcomes

Compared with the status quo, of no viral load monitoring, all frequencies of viral load monitoring and access to second-line ART led to significant reductions in the average number of person-years in which children experienced ART failure (Table 3). Higher frequencies of monitoring were most effective in lowering the total time spent with virological failure: a single viral load test after 6 months of ART led to an estimated 58.4% reduction in the total person-years of ART failure; repeat viral load monitoring every 4 years, without a screen in the first year, led to an average 46.2% reduction, and viral load monitoring every 6 months led to an average 77.8% reduction (Table 3). Specifically, of the total person-years simulated by the model (100 000 years), no viral load monitoring led to approximately 17.5% of this time spent in virological failure compared to 3.9% when viral load testing every child every 6 months for 10 years (Table 3).

Only marginal differences in immunological outcomes were observed between the status quo and the various monitoring interventions. This is because most simulated individuals (as in the actual cohort study) initiated treatment with CD4% below 16 and then progressed into the highest CD4% category after the initiation of first-line ART regardless of monitoring intervention type. Therefore, only a modest gain in QALYs was observed: a single viral load test after 6 months of ART led to a median 457 QALYs gained per 10 000 children over 10 years and viral load testing every 6 months for 10 years led to a median of 644 QALYs gained per 10 000 children.

Costs

The status quo, of no viral load monitoring and supplying only first-line ART for 10 years, was estimated to cost a median of US$ 21.1 million per 10 000 children over 10 years. All monitoring intervention strategies led to added costs, increasing with the frequency of monitoring: ranging between a median of US$42.9 million per 10 000 children over 10 years for a one-off viral load test after 6 months of ART and US$ 74.2 million per 10 000 children over 10 years for viral load testing every child every 6 months (Table 3).

The greatest contributing factor to the total cost of care was supplying first-line and second-line ART. The cost of viral load monitoring alone was significantly less: ranging between a median of US$ 552 332 per 10 000 children

Table 3. Model-based outcomes of therapy responses according to different monitoring interval strategies.

Discounted 3%	No monitoring	One-off screening at 6 months	Every 6 months	Every year	Every 2 years	Every 3 years	Every 4 years
Effectiveness evaluation							
Total person-years spent with virological failure	17 482 (17 288 – 17 673)	7 273 (7 159 – 7 386)	3 883 (3 816 – 3 979)	4 665 (4 574 – 4 743)	6 614 (6 493 – 6 689)	8 034 (7 957 – 8 158)	9 398 (9 299 – 9 505)
Percentage of total person-years spent with virological failure	17.5 (17.3 – 17.7)	7.3 (7.2 – 7.4)	3.9 (3.8 – 4.0)	4.7 (4.6 – 4.7)	6.6 (4.5 – 6.7)	8.0 (8.0 – 8.2)	9.4 (9.3 – 9.5)
Costs							
Median cost (US$), including ARTs costs (millions)	21.1 (21.0 – 21.2)	42.9 (42.5 – 43.2)	74.2 (73.8 – 74.8)	65.2 (64.8 – 65.8)	59.4 (58.9 – 59.8)	55.3 (54.9 – 55.8)	51.8 (51.4 – 52.1)
Median Δ costs, including ARTs costs (millions)	–	21.7 (21.4 – 22.1)	53.1 (52.7 – 53.7)	44.1 (43.6 – 44.7)	38.3 (37.8 – 38.6)	34.2 (33.8 – 34.6)	30.7 (30.3 – 31.0)
Median cost (US$) (not including ART costs) (millions)	0	0.55 (0.44 – 0.55)	9.90 (9.89 – 9.91)	4.75 (4.74 – 4.75)	2.33 (2.33 – 2.34)	1.40 (1.40 – 1.40)	0.93 (0.93 – 0.93)
Median Δ costs (not including ART costs) (millions)	–	0.55 (0.44 – 0.55)	9.90 (9.89 – 9.91)	4.75 (4.74 – 4.75)	2.33 (2.33 – 2.34)	1.40 (1.40 – 1.40)	0.93 (0.93 – 0.93)
Cost-utility analysis							
Median QALYs	76 671 (76 579 – 76 756)	77 121 (77 051 – 77 210)	77 315 (77 231 – 77 389)	77 333 (77 250 – 77 417)	77 217 (77 115 – 77 305)	77 164 (77 090 – 77 242)	77 081 (76 983 – 77 186)
Median Δ QALYs	–	457 (320 – 598)	644 (520 – 767)	647 (547 – 790)	553 (410 – 671)	518 (361 – 603)	404 (292 – 538)
ICER (US$) (including ART costs)	–	47 421 (36 131 – 62 139)	83 256 (69 500 – 101 906)	68 698 (55 856 – 80 558)	69 485 (57 145 – 92 587)	67 170 (56 687 – 94 803)	74 524 (56 326 – 100 643)
ICER (US$) (not including ART costs)	–	1 183 (911 – 1 591)	15 399 (12 921 – 19 035)	7 346 (6 011 – 8 678)	4 228 (3 480 – 5 692)	2 703 (2 318 – 3 874)	2 249 (1 721 – 3 081)
Cost-effectiveness analysis							
Median years of virological failure averted (over 10 years)	–	10 216 (10 022 – 10 404)	13 586 (13 411 – 13 762)	12 806 (12 685 – 12 932)	10 882 (10 755 – 11 023)	9 431 (9 345 – 9 543)	8 070 (7 967 – 8 147)
Cost per year of virological failure averted (including ART costs)	–	2 131 (2 106 – 2 154)	3 913 (3 868 – 3 942)	3 443 (3 409 – 3 476)	3 512 (3 475 – 3 551)	3 622 (3 588 – 3 656)	3 799 (3 760 – 3 844)
Cost per year of virological failure averted (not including ART costs)	–	54 (53 – 55)	729 (720 – 738)	371 (367 – 374)	215 (212 – 217)	148 (147 – 150)	116 (114 – 117)

Median estimates (IQR) per 10 000 children from 100 simulated populations are shown. Discounted at 3.0%. Outcomes discounted at 0% and 5% are available upon request of the authors. ART, antiretroviral therapy; ICER, incremental cost-effectiveness ratio; IQR, interquartile range; QALY, quality-adjusted life year.

for a one-off viral load test 6 months after the initiation of ART and US$ 9.9 million per 10 000 children for viral load testing every child every 6 months for 10 years (Table 3).

Cost-effectiveness and cost-utility analysis

As the frequency of monitoring increased so did the associated clinical benefits and costs. The cost attributed to 1 year of virological failure averted, including the cost of first-line and second-line ART, ranged from a median of US$ 2131 for a one-off viral load test 6 months after the initiation of ART to US$ 3913 for viral load testing children every 6 months (Table 3). However, due to only a modest gain in immunological outcomes compared with the status quo, monitoring viral load and supplying second-line ART for those on a failing regimen was not considered economical in terms of utility: the incremental cost per QALY ranged between a median of US$ 47 421 for a one-off viral load test 6 months after the initiation of ART and US$ 83 256 for viral load testing every child every 6 months. But when considering the costs associated with monitoring and not including the cost of ART, the incremental cost per QALY dropped substantially to a median of US$ 1183 for a one-off viral load test 6 months after the initiation of ART and US$ 15 399 for viral load testing every child every 6 months.

Optimal screening frequency

The most economic viral load monitoring strategy can be assessed based on cost-effective and cost-utility analyses. In Fig. 3, we present the additional cost of each strategy compared to the status quo versus the QALYs gained and years of virological failure averted. It is clear that the least cost per gain in health is achieved by a single viral load test 6 months after the initiation of ART; this is the strategy associated with the incremental cost-effectiveness ratio (ICER) line with the lowest gradient (Fig. 3). However, we also found that there is an optimal frequency of regular monitoring. For example, the cost per year of virological failure averted is US$ 3913 at 6-monthly monitoring, it decreases to US$ 3443 for yearly monitoring, and it increases to US$ 3512 for 2-yearly monitoring and further increases for less frequent monitoring (Table 3); that is, a minimum cost-effectiveness ratio exists at annual monitoring. This optimal frequency was not affected by different quantitative assumptions explored in our sensitivity analysis.

We simulated combinations of one-off and regular monitoring frequencies and compared the incremental cost-effective and cost-utility ratios. We found that there was an optimal strategy combination which resulted in the lowest cost per year of virological failure averted (and cost per QALY gained). The best viral load monitoring strategy was found to be annual screening intervals after a single viral load test at 6 months and providing second-line therapies for children who have failed first-line ART (Fig. 3). According to this strategy our model predicted a

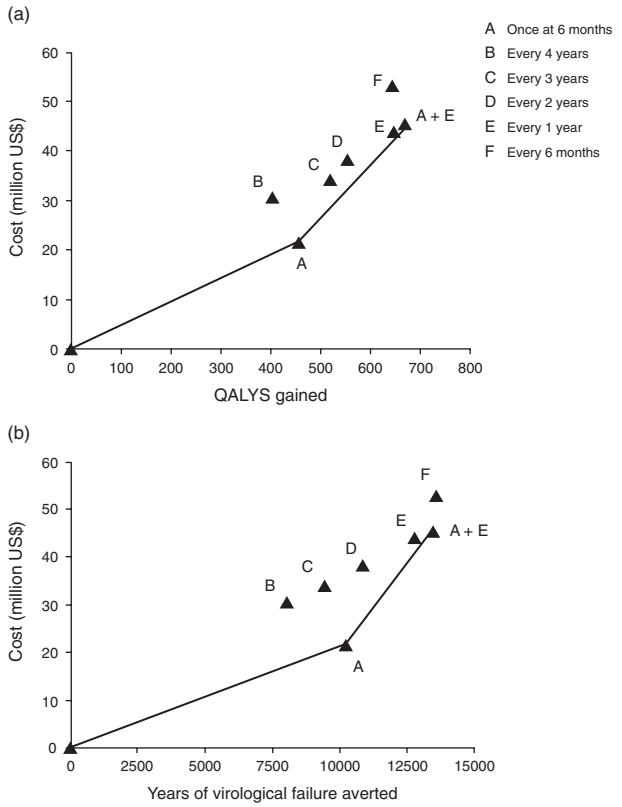

Fig. 3. Incremental cost-effectiveness and cost-utility ratios. (a) Difference in QALYs accumulated between status quo and the viral load testing frequency over the difference in cost. (b) Difference in years of virological failure accumulated between status quo and the viral load testing frequencies over the difference in cost.

median added cost of US$ 45.5 million per 10 000 children over 10 years when including costs of ART and US$ 4.8 million without ART costs. In terms of the effects of this level of monitoring, one QALY gained cost a median of US$ 68 084 when including costs of ART and US$ 7224 without ART costs, whereas 1 year of virological failure averted cost an estimated US$ 3393 when including costs of ART and US$ 359 without ART costs. These ratios dominate over more costly higher frequencies of monitoring, for example, monitoring every 6 months (Fig. 3), and is therefore considered the optimal screening strategy.

Sensitivity analysis

The ICER was found to be most sensitive to the cost of monitoring and treatment and utility values, but not substantially to the rate of incomplete viral suppression on second-line ART. The cost per year of virological failure averted was found to be sensitive to the cost of monitoring and treatment and also to a lesser extent the rate of incomplete virological failure on second-line ART. However, overall the qualitative results and conclusions of our analysis were not influenced by changes in these quantitative assumptions (results not shown but available upon request).

Discussion

Our model illustrates that although children often present with late HIV infection, with low CD4 percentages, viral load monitoring and access to second-line ART have substantial short-term to medium-term clinical benefits. Our study estimated that a single viral load test during the first year of ART would lead to an estimated 58.4% reduction in the total person-years spent with virological failure after 10 years. More frequent monitoring saw further reductions: an estimated 77.8% reduction was associated with monitoring every 6 months. The incremental cost-effective and cost-utility ratios of our analyses suggest that the best viral load monitoring strategy is to conduct a viral load test 6 months after initiating ART and then to follow this with annual viral load tests.

The costs of implementing viral load monitoring include not only the cost of viral load tests and infrastructure but of medications, as people with virological failure initiate second-line ART, that are significantly more costly than first-line regimens. However, providing antiretroviral drugs that are effective in suppressing HIV should be considered the best standard of care and thus provision of second-line therapy for children in need could be considered part of the baseline. Conservatively incorporating costs of antiretrovirals into our scenario analyses we found that the cost attributed to averting 1 year of virological failure is reasonably cost-effective (at ~US$ 2000–4000). However, to implement a monitoring intervention with the optimal screening frequency found in the current study while introducing unfettered access to second-line therapies for children, our model predicted one QALY gained cost an estimated US$ 68 084. These benefits and costs would not be considered economical from a utility perspective. These results are similar to that found in an economic evaluation of viral load monitoring among the adult population [13]. Prospective public health technologies are usually deemed cost-effective when within three times of the national gross domestic product (GDP) per capita. According to the International Monetary Fund's World Economic Outlook Database the Thai GDP (per capita) in 2009 was US$ 3973 and therefore the cost-effectiveness threshold would be approximately US$ 11 919.

If ART costs are not included in the evaluation of the ICER, as they may be considered the standard of care, the cost per QALY gained with our optimal viral load monitoring strategy would be US$ 7224, and would therefore be considered cost-effective. Also worth mentioning is this evaluation was not compared against the baseline of not providing any therapy, which would

render regular viral load monitoring and provision of second-line ART substantially more cost-effective. This is particularly worth noting since the greatest contributing factor to the total cost of care in our model was supplying first-line and second-line ART, whereas the cost of viral load monitoring was substantially lower. Furthermore, an additional benefit of increased access to viral load monitoring is likely to be the reduction of misclassifications of treatment failure among virologically suppressed patients and therefore the premature switching to more expensive second-line regimens [10,11]. This would not only lead to a reduction of the cost of treatment overall but also minimize exhausting second-line ART.

It is also important to consider that although we have suggested 6-monthly followed by yearly viral load testing as an optimal general strategy there may be other monitoring strategies that have more optimal economic outcomes for particular subgroups. For example, we found that immunological outcomes were dependent upon baseline CD4%: those with lower CD4% were significantly more likely to have poorer immunological responses to treatment than those who started treatment with high CD4%. Such findings have been well established in previous literature [28] and are indicative that a scenario in which less frequent monitoring is implemented for those with higher baseline CD4% and more frequent for those with lower baseline CD4% could yield a similar QALY at lower cost as calculated in the current study.

At present, the most reliable method to ensure suppressed virus in patients is regular viral load monitoring and a timely change to a second-line therapy when first-line treatment has failed [10,29,30]. The clinical consequences of delaying ART switching and allowing ongoing virological failure are likely to be serious [31,32] and they should be considered when determining the appropriate clinical management for children on ART in resource-limited settings. Our model demonstrated that if monitoring is conducted every 6 months only 4% of the total proportion of person-years would likely be spent in virological failure, compared to almost 20% when left unmonitored. If such a large proportion of people were allowed to remain indefinitely on a failed first-line regimen there will be an accumulation of drug-resistant mutations [17–22] that may spread further in the population and compromise the long-term efficacy of first-line and second-line ART [23,24].

Our model only considered the short-term to medium-term outcomes of variable viral load monitoring frequencies. The potential long-term impact on the development of specific mutations and the influence on second-line and third-line regimens as well as the spread of resistance among the wider population were not considered in our model and is the primary limitation of the current study. Confirmation of such long-term clinical implications would need to be determined by further studies of second-line ART. A further limitation of our model was that it was primarily informed by a relatively small cohort of children who presented with low CD4 percentages and high viral loads who were generally older and in the later stages of HIV infection than the demographic and disease state distributions of most populations of children living with HIV globally. It is likely that they are a surviving population and are therefore not representative of all children initiating ART globally; however, the Thai cohort from which data are used in our calculations are considered representative of children currently initiating treatment in Thailand [25] and most likely other similar resource-constrained settings. Age was not found to be a predictive marker of virological outcomes at 24 weeks after initiation of treatment ($t_{259} = -1.404$, $P = 0.161$), nor after 48 weeks ($t_{235} = -0.449$, $P = 0.654$) and was therefore not considered in the current study. However, Walker *et al.* [33] found that starting treatment at a young age increases the risk of poor virological response. Future analyses may need to consider the association of other demographic and immunological variables to the optimal frequency of viral load monitoring to further refine guidelines. Finally, it is important to apply some caution when interpreting health outcomes that are derivative of certain utilities, for example QALYs. Using QALYs to identify the optimal allocation of scare resources has been shown to be somewhat capricious [34]. In our study, the QALYs were based on data obtained from an adult population, which may have different quantities than the true quality of life utilities of children.

There is a need to introduce an affordable, feasible and sustainable system for viral load monitoring in resource-limited contexts. Despite the enormous progress made in the access to first-line ART for HIV-infected children around the world, many challenges remain in access to laboratory testing for the clinical management of children who fail ART in resource-limited settings. This, along with access to second-line therapies, remains a critical area to be overcome for the assurance of long-term efficacy of ART in these settings. Our model shows large differences in the total time spent with virological failure between different frequencies of monitoring, in which it was particularly valuable to conduct a viral load test and change the ART of children with incomplete viral suppression after approximately 6 months of commencing ART and then to follow this up with testing on a yearly basis to detect incidents of viral rebound. On the basis of the findings of previous empirical studies [24,29], early detection of virological failure is likely to provide more options and better long-term treatment outcomes.

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