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Viral load versus CD4 monitoring and 5-year outcomes of ART in HIV-positive children in Southern Africa: cohort-based modelling study

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Abstract

Objectives—Many paediatric antiretroviral therapy (ART) programmes in Southern Africa rely on CD4 counts to monitor ART. We assessed the benefit of replacing CD4 by viral load (VL) monitoring.

Design—Mathematical modelling study.

Methods—Simulation model of HIV progression over 5 years in children on ART, parameterised by data from seven South African cohorts. We simulated treatment programmes with 6-monthly CD4 count or 6- or 12-monthly VL monitoring. We compared mortality, second-line ART use, immunological failure and time spent on failing ART. In further analyses we varied the rate of virological failure, and assumed that the rate is higher with CD4 than with VL monitoring.

Results—About 7% of children were predicted to die within 5 years, independent of the monitoring strategy. Compared with CD4 monitoring, 12-monthly VL monitoring reduced the 5-year risk of immunological failure from 1.6% to 1.0% and the mean time spent on failing ART from 6.6 to 3.6 months; 1% of children with CD4 compared to 12% with VL monitoring switched

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L.S., O.K., M.E. and J.E. designed the study. L.S., N.B. and J.E. developed the mathematical model. A.H. and L.S. analysed the cohort data. K.T., V.C., B.E., H.R., J.G., H.M. and R.W. were involved in data acquisition and management. K.T. and M.D. provided clinical expertise on paediatric HIV. L.S. wrote the first version of the manuscript, which was revised by O.K., M.E. and J.E. All authors contributed to the interpretation of the results and to the final version of the manuscript.

Conflicts of interest
The authors declare no conflicts of interest.

to second-line ART. Differences became larger when assuming higher rates of virological failure. When assuming higher virological failure rates with CD4 than with VL monitoring, up to 4.2% of children with CD4 compared to 1.5% with VL monitoring experienced immunological failure; the mean time spent on failing ART was 27.3 months with CD4 monitoring and 6.0 months with VL monitoring.

Conclusions—VL monitoring did not affect 5-year mortality, but reduced time on failing ART, improved immunological response and increased switching to second-line ART.

Keywords

antiretroviral therapy; children; sub-Saharan Africa; viral load monitoring; mathematical model

Introduction

HIV viral load (VL) is routinely monitored in paediatric antiretroviral therapy (ART) programmes in high-income countries whereas in sub-Saharan Africa most programmes rely on CD4 count or clinical monitoring to detect treatment failure [1]. However, clinical and immunological criteria are poor predictors of virological failure for both children and adults [2, 3]. The lack of VL monitoring can lead to delayed and unnecessary switches to second-line therapy, promoting the development of resistance and limiting future treatment options [4, 5].

In adults several modelling studies [6–8] and two randomised controlled trials [9–11] showed that routine VL monitoring may reduce mortality slightly, and substantially increase costs. These results cannot be generalised to children: progression of HIV is faster in children than in adults, the CD4 cell count declines with age, and ART regimens differ [1, 12–14]. ART coverage in treatment-eligible children was only about 30% in 2012 in sub-Saharan Africa, much lower than in treatment-eligible adults [15, 16]. As coverage increases and eligibility criteria change, the question on how to best monitor ART becomes more important.

Few studies have assessed ART monitoring in children. One modelling study [17] found the optimal VL monitoring strategy to be yearly monitoring, plus a first measurement six months after treatment start, as recommended by the World Health Organization (WHO) [1]. The authors estimated that the strategy would entail a 3-fold increase in the costs of treatment [17]. A recent randomised trial found that routine CD4 and toxicity monitoring conferred minimal benefits when compared to monitoring based on clinical progression and toxicity alone [18].

There is no empirical study that compared VL and CD4 monitoring in children. We developed a mathematical model for HIV progression in children on ART in Southern Africa to address this question.

Methods

Data sources and eligibility criteria

We analysed data on children aged <16 years from seven South African cohorts participating in the International epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) collaboration to parameterise the model [19, 20]: Gugulethu and Khayelitsha townships, Tygerberg Hospital and Red Cross Hospital in Cape Town; Rahima Moosa Mother and Child Hospital and Harriet Shezi Children's Clinic in Johannesburg; McCord Hospital in Durban. We included all children who started ART 2000 to 2012 with two nucleoside reverse transcriptase inhibitors (NRTI) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI). We excluded children who started with ritonavir and NRTIs: this regimen is no longer used [21–23].

All cohorts measure VL routinely. The 2004 South African guidelines recommended 6-monthly VL monitoring. Decisions to switch therapy following virological failure were taken after assessing growth, CD4 measures and adherence [24]. Since 2010 the guidelines recommend VL monitoring after 6 months, 12 months and yearly thereafter. If VL is >400 copies/ml, children and caretakers are counselled for adherence [25]. If VL is >1000 copies/ml, it is measured again three months later and if confirmed switching to second-line ART is recommended. Children failing a PI-based regimen are switched only if adherence was high and drug resistance documented [25].

Statistical analyses and model structure

We analysed the cohorts to estimate the parameters for a mathematical model (see Table 1 and Appendix Table S1 for list of parameters). We fitted Weibull, exponential and piecewise exponential cumulative distribution functions to time from ART start to: (i) virological failure (>1000 copies/ml); (ii) drop in CD4 percentage to <15% and <10% in children aged <5 years or drop in CD4 count to <200 and <100 cells/μl in children aged ≥5 years; and (iii) death. We defined a drop below the upper CD4 thresholds as immunosuppression. The lower CD4 thresholds correspond to WHO immunological failure criteria [1] and we refer to a drop to below these thresholds as immunological failure. We also fitted exponential cumulative distribution functions for time from virological failure to the first CD4 measurement below the above-mentioned thresholds. We analysed immunological progression stratified by virological status (failure or no failure) and mortality stratified by immunological status (no immunosuppression, immunosuppression or immunological failure). We used a demographic model for Africans in the Western Cape 2007 [26] to estimate HIV-free mortality, as in a previous study in adults [27].

We formulated a multistate model for HIV progression in children on ART and implemented it using the R package *gems* [28]. Simulated children were assigned baseline characteristics including age, sex, ART regimen and exposure to prevention of mother-to-child transmission (PMTCT) prophylaxis, based on the cohort data. Children progressed through 26 states combining several strata of VL, CD4 measures, and death (see Appendix Text S1 and S2, Figure S1 and S2). We defined two VL categories (failure and no failure) and three CD4 categories (no immunosuppression, immunosuppression and immunological

failure). For each pair of states, we specified the hazard function of the transition. Times for all possible transitions were sampled from each state; the first event determined the patient's next state.

Monitoring and switching strategies

We modelled three strategies separately for children who started ART aged <5 and ≥5 years: (i) 6-monthly CD4 monitoring, switching according to WHO immunological criteria [1]; (ii) 6-monthly VL monitoring; and (iii) VL monitoring yearly (plus an additional first measurement 6 months after initiation). For both CD4 and VL monitoring, we required a second measurement 3 months later to confirm failure. The child was switched to second-line ART immediately after confirmed failure unless he or she was on a PI first-line regimen and aged <3 years at the time of failure as recommended by the WHO [1]. Second-line ART was assumed to be as effective as first-line ART.

Outcomes

The main outcomes of interest were mortality, proportion of children who experienced immunological failure, proportion of children who switched to second-line therapy, proportion of unnecessary switches (i.e. without virological failure), and time spent on failing NNRTI-based and PI-based ART. We report all outcomes at 5 years from ART start.

Analysis I: Effect of VL monitoring using cohort parameter values

In a first analysis we simulated 100,000 children for each monitoring strategy and age group i.e. 600,000 in total. We used parameter values from the statistical analyses of the South African cohorts. In addition to the 5-year outcomes, we also report cumulative incidences of mortality and immunological failure, and cumulative time spent on failing ART over the first 5 years. We assigned NNRTI- or PI-based first-line regimens according to the distribution observed in the cohorts. In this analysis we assumed a Weibull hazard of virological failure (Table 1).

Analysis II: Effect of VL monitoring for different treatment efficacy scenarios

The South African programmes with frequent laboratory monitoring and effective regimens based on ritonavir-boosted lopinavir (LPV/r) [29–31] differ from those in other countries in Southern Africa. Moreover, the scale-up of PMTCT may have affected treatment efficacy. We therefore simulated cohorts of 100,000 children for all three monitoring strategies with virological failure rates increasing in steps of 0.01 from 0.01/year to 0.30/year, approximating the failure rate that corresponds to the risk reported in a systematic review [32]. In this analysis and Analysis III we assumed first-line ART to be NNRTI-based and second-line ART to be PI-based, and a constant virological failure rate over time.

Analysis III: Effect of VL monitoring assuming that it improves adherence

We assumed that VL monitoring prevents virological failure by improving adherence [33]. We calculated the rate ratio between unconfirmed (one VL measurement >1000 copies/ml) and confirmed failure (2 values >1000 copies/ml) rates from the data. We used this ratio as a proxy for the ratio of virological failure rates in sites without and with routine VL

monitoring, mimicking a retrospective study of VL in stored blood samples in CD4 monitoring sites. In sites with routine VL monitoring, a first high VL triggers adherence counselling. If the second value is also elevated, the patient is switched and VL becomes undetectable. Without VL monitoring, the first elevated VL value is missed, there is no adherence counselling, and we expect VL to remain high. We used the same range of failure rates for CD4 monitoring as in Analysis II and simulated cohorts of 100,000 children for all three monitoring strategies. The virological failure rates with VL monitoring were calculated by dividing the rate in the CD4 monitoring simulation by the rate ratio between unconfirmed and confirmed failure.

Additional analyses

In additional analyses, based on Analysis I, we introduced a hypothetical scenario with no monitoring and no switching to second-line ART and compared mortality at 5 years between the no monitoring and the three monitoring strategies, both for all children and for children who experienced virological failure. Finally, we compared predicted outcomes under the different monitoring strategies with outcomes observed in the IeDEA cohorts.

Results

Description of study population

The dataset consisted of 11,903 children who were followed up for 30,633 person-years (Appendix Table S2). Median age at ART start was 3.6 years (interquartile range [IQR]: 1.0–7.5). Median baseline CD4 percentage was 15.6% (IQR: 10.0–22.8) for age <5 years, and median baseline CD4 count 231 cells/μl (IQR: 80–424) for age ≥5 years. Median follow-up duration was 2.1 years (IQR: 0.7–4.2). The number of children followed for more than 48 weeks on first-line ART was 8,363 (70.3%). A total of 1,317 children (11.1%) were lost to follow-up, i.e. had not been seen in the clinic for at least one year. The number of children who had sufficient measurements to detect and confirm treatment failures was 6,484 for VL and 7,036 for CD4 monitoring. The median number of months between laboratory measurements was 5.7 (IQR: 4.3–7.2) for VL and 6.1 (IQR: 5.3–7.4) for CD4. The majority of children (57%) started with a NNRTI-based first-line regimen; the most common NNRTI was efavirenz (EFV, 94%). The remaining children (43%) started with a LPV/r-based regimen.

Analysis I: Effect of VL monitoring using cohort parameter values

With CD4 monitoring, about 1.1% of children switched therapy within the first five years of follow-up whereas in both VL monitoring scenarios the corresponding proportion was above 12% (Table 2, Figure 1a). The mean time spent on failing regimens decreased from 6.6 months with CD4 monitoring to 3.6 months with 12-monthly and 3.3 months with 6-monthly VL monitoring (Figure 1c). The time spent on failing NNRTI-based regimens was reduced by 73% but the time spent on failing PI-based regimens increased slightly when comparing 12-monthly VL monitoring to CD4 monitoring (Appendix Figure S3). With CD4 monitoring 44% of children who switched to second-line ART switched without virological failure, and 97% of virological failures had been missed. With 6-monthly VL monitoring, the proportion of missed failures dropped to 10% (Table 2).

VL monitoring did not reduce mortality. Mortality at 5 years was 7.1% with CD4 monitoring and 6.9% with both VL monitoring strategies (Table 2). The proportion of children who experienced immunologic failure was 1.6% with CD4 monitoring, but 1.0% with VL monitoring (Figure 1b), a 40% reduction.

Analysis II: Effect of VL monitoring for different treatment efficacy scenarios

In Figure 2 we present predicted 5-year treatment outcomes by rate of virological failure and include the observed virological failure rates from three recent studies [18, 34, 35]. The rates in these studies ranged from 0.05 in the ARROW trial [18] to 0.17 in the routine programme in Cambodia [34]. The percentage of children switched to second-line ART was much higher with VL than with CD4 monitoring (Figure 2a), and the difference increased with increasing virological failure rates. The differences in the percentage of children who developed immunological failure (Figure 2b), and in the time spent on a failing regimen (Figure 2c) also increased with the rate of virological failure. For the highest virological failure rate assumed (0.30/year), 12-monthly VL monitoring decreased the proportion of children with immunological failure from 4.2% to 2.5% and the mean time spent on a failing NNRTI regimen from 27.1 to 5.9 months, compared with CD4 monitoring. The mean time spent on a failing PI regimen increased from 0.2 months with CD4 monitoring to 8.0 months with 12-monthly VL monitoring. Consistent with Analysis I, mortality was similar for the three monitoring strategies.

Analysis III: Effect of VL monitoring assuming that it improves adherence

The rate of unconfirmed failure was 0.12/year and the rate ratio of unconfirmed to confirmed failure was 2.08 in the South African cohort data. We therefore assumed that with CD4 monitoring the virological failure rate was 2.08-fold higher than with VL monitoring. With the highest failure rates (0.30/year for CD4 monitoring, 0.14/year with VL monitoring), predicted 5-year mortality was 7% in all monitoring strategies. As expected, the difference in the percentage of children switched to second-line ART between VL and CD4 monitoring was smaller than in Analysis II (Figure 3a). The percentage of children who experienced immunological failure was 4.2% with CD4 and 1.5% with 12-monthly VL monitoring (Figure 3b), and the mean time spent on failing ART was 27.3 months (27.1 on NNRTI, 0.2 on PI) with CD4 and 6.0 months (3.0 on NNRTI, 3.0 on PI) with VL monitoring (Figure 3c). Compared to CD4 monitoring VL monitoring thus prevented 63% of immunological failures and decreased the average time spent on a failing regimen by 21 months (a 78% relative reduction).

Additional analyses

As expected, mortality was slightly higher at 5 years with the hypothetical no monitoring and no switching scenario; 7.2% compared to 6.9% with viral load monitoring (Appendix Figure S4). Differences in mortality were more pronounced when restricting the analyses to children who experienced virological failure (Appendix Figure S5). Unsurprisingly, modelled outcomes under the different monitoring strategies were similar to the outcomes observed in the IeDEA cohorts (Appendix Table S3).

Discussion

This mathematical modelling study showed that routine VL monitoring does not reduce mortality of children during the first 5 years on ART. However, a clear benefit of VL monitoring was evident in terms of preventing immunodeficiency through more timely identification of virological failure. VL monitoring substantially increased the demand for second-line ART, but it also prevented many unnecessary switches and reduced the average time spent on failing ART by at least 3 months. Outcomes were very similar with 6-monthly and 12-monthly VL monitoring suggesting that the WHO recommendation of 12-monthly viral load tests is appropriate [1].

The lack of any important effect on mortality is consistent with the results of modelling studies in adults [6–8], suggesting that VL monitoring will improve survival only minimally in the short term. The main driver of total mortality was HIV-related mortality during the first few months of ART, which is not influenced by the approach taken to monitoring but driven by immunosuppression at the start of therapy. Virological failure does not directly influence mortality and immunological progression is relatively slow. Indeed, only few children who failed virologically progressed to immunological failure during the 5-year follow-up time. This situation may change with the increase of CD4 cell counts and CD4 percentage at the start of ART: early HIV-related mortality will probably become less important and the type of monitoring more important. Furthermore, in the longer term, children followed up with CD4 monitoring only will increasingly be exposed to virological failure and immunosuppression, which will eventually translate into increased mortality. As could be expected, the differences in mortality were more substantial in the (few) children who failed virologically, i.e. the children who are likely to benefit from a timely switch to second-line ART. Of note, prolonged viraemia may have other sequelae, including, for example, deficits in neurodevelopment [36, 37].

In the South African cohorts, almost half of the children started ART on a PI-based regimen. This proportion was higher in the youngest children: almost 90% of children aged <3 years at ART start started with PI-based first-line regimen. One year of a PI-based regimen can cost more than USD 400, whereas one year of a standard NNRTI-based regimen costs between USD 50 and USD 200 [38]. In South Africa, switching to second-line ART according to WHO recommendations [1] might therefore reduce rather than raise costs. However, switching children from a failing PI-based to NNRTI-based regimens is controversial. Low rates of viral suppression on second-line therapy have been reported in this situation [39] and the risk for PI and NRTI resistance mutations during exposure to unsuccessful PI-based ART may be low [29]. Our model was not designed to account for switches from PI-based regimens to the alternatives that are now becoming available in South Africa. The situation is different in other countries in the region: in the IeDEA cohorts from outside South Africa very few children started with PI-based ART [40].

We did not consider drug resistance explicitly. If VL is not routinely monitored, children failing virologically can spend years on a failing regimen and develop resistance, which will decrease the efficacy of second-line regimens. Drug resistance has often been observed in paediatric cohorts [41–43], related to exposure to PMTCT drugs and poor adherence to ART

[41, 44]. The risk of resistant mutations is higher in settings using NNRTI-based rather than PI-based first-line regimens [29]. An important finding of our study is that across a range of virological failure rates, VL monitoring decreased the time spent on a failing regimen by over 50%. Our study thus supports the notion that VL monitoring may reduce the risk of drug resistance. Nevertheless, other interventions, such as better adherence counselling or improved sequencing of regimens, may be more realistic approaches to prevent drug resistance than VL monitoring [31, 44].

Our study has other limitations. Guidelines and clinical practice in South Africa changed over the study period and the data used to parameterise the model may not reflect current practice. For example, due to the trend to earlier ART initiation, children are now healthier at ART start than previously [45]. Furthermore, because PMTCT coverage has increased, children are more likely to have been exposed to antiretrovirals in utero [16]. The efficacy of drugs and the effectiveness of ART programmes have improved. We did not explicitly model these trends, but incorporated them implicitly by varying virological failure rates. Outcomes were modelled only up to five years after starting ART because of the limited availability of long-term data.

Eleven percent of children in the data were lost to follow-up at 5 years. Censoring patients who are lost to follow-up can lead to programme-level mortality being underestimated because mortality is higher among those lost to follow-up than among patients remaining in care [46, 47]. However, our objective was to model the influence of different monitoring strategies on the outcomes of children remaining in care. It was not our intention to examine programme-level outcomes and include outcomes in children lost to follow-up. Interestingly, our results are closely similar to a recent multiregional analysis of paediatric outcomes of ART in Africa and Asia [48]. Leroy and colleagues used a competing risk model of death and loss to follow-up [48]. They therefore estimated mortality during follow-up only; mortality in patients lost to follow up was not considered. Their estimate at 18 months was 6.2% for Southern Africa, very close to our estimate of about 6.0%. It therefore seems likely that our modelled estimates of mortality reflect mortality among children remaining in care. As expected, our estimates were also compatible with the cumulative mortality and failure observed in the cohort data.

Adherence was also not included explicitly in our model. VL monitoring helps detect poor adherence and identifies children and caretakers who need counselling, which in turn may reduce the risk of virological failure. We examined this scenario in the third analysis but again found that mortality was not reduced, even when assuming lower failure rates with VL monitoring. However, the beneficial effect on immunological outcomes and the reduction in time spent on failing treatments became more pronounced when assuming that the failure rate was higher with CD4 than with VL monitoring. In both the second and third analysis we assumed constant failure rates, which do not reflect the decreasing hazard of virological failure observed in the cohorts. We may thus have underestimated the time a child is exposed to an increased risk of death. However, despite the wide range of virological failure rates assumed in our models, we did not observe differences in mortality between strategies. Mortality is thus unlikely to decrease in the short term with VL monitoring, even if the rate of virological failure is high.

Conclusions

In this modelling study, VL monitoring did not improve survival compared with CD4 monitoring over 5 years of ART but several other benefits of VL monitoring were evident. Provided that appropriate second-line therapy is available, VL monitoring can avert progression to immunosuppression, reduce the time spent on a failing regimen and prevent unnecessary switches to second-line ART. We intend to repeat this analysis in due time to gain insights into the effects of different monitoring strategies on long-term outcomes, and the modifying effect of less advanced immunosuppression at the start of ART. Further research is also needed to gain a better understanding of the causal relationships between adherence, virological failure and drug resistance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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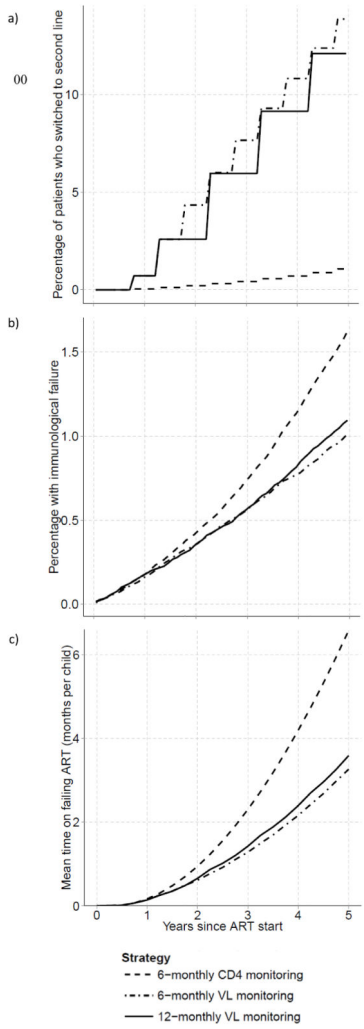

Figure 1. Predicted treatment outcomes over 5 years according to different monitoring strategies (Analysis I)

a) Proportion of children switching to second-line therapy; b) Proportion of children who ever experienced immunological failure; c) Mean time spent on failing ART.

ART: antiretroviral therapy; VL: viral load.

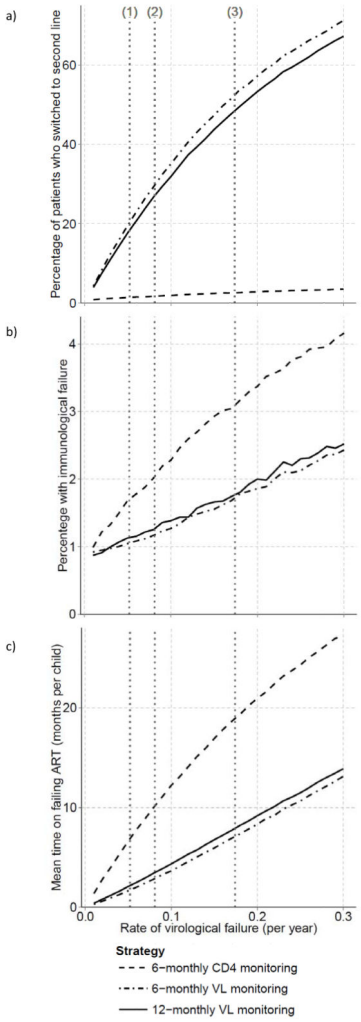

Figure 2. Predicted treatment outcomes over 5 years according to different monitoring strategies for varying virological failure rates (Analysis II)

Failure rates estimated for the ARROW trial [18] **(1)**, Zhao *et al* [35] **(2)**, Janssens *et al* [34] **(3)** are shown with vertical lines. The equivalent constant rate of virological failure for South African IeDEA data is 0.05.

a) Proportion of children switching to second-line therapy; b) Proportion of children who ever experienced immunological failure; c) Mean time spent on failing ART.

ART: antiretroviral therapy; VL: viral load.

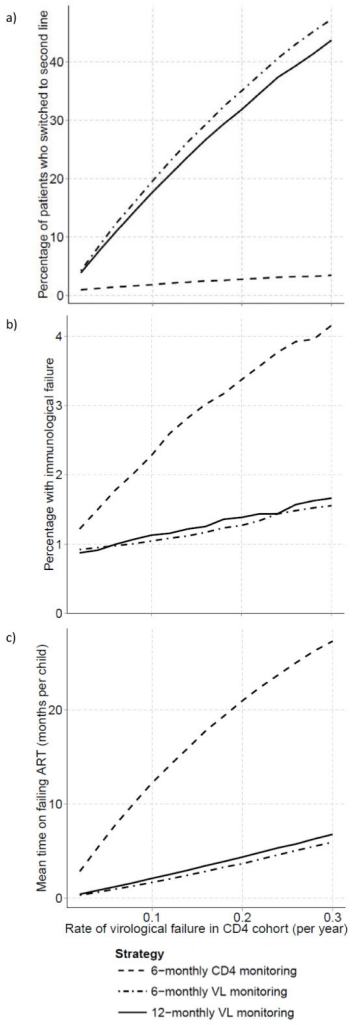

Figure 3. Predicted treatment outcomes over 5 years assuming viral load monitoring reduces the virologic failure (Analysis III)

We assumed that replacing CD4 monitoring by VL monitoring could reduce the rate of virological failure by a factor of 2.08 as estimated from the data (see details in methods). a) Proportion of children switching to second-line therapy; b) Proportion of children who ever experienced immunological failure; c) Mean time spent on failing ART.

ART: antiretroviral therapy; VL: viral load.

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Table 1

Parameters for disease progression in the model.

Event	Threshold	Functional form	Parameters (95% confidence interval)		Hazard ratio (95% confidence interval)		Hazard ratio for HIV-related mortality (95% confidence interval)
Virological failure	1000 copies/ml	Weibull	Scale (years)	18.9 (17.0 – 21.0)	Age*	1.18 (1.03 – 1.35)	
			Shape	1.0 (0.9 – 1.0)	PMTCT**	1.28 (1.09 – 1.51)	
					NVP***	1.37 (1.10 – 1.71)	
Drop in CD4 count below threshold‡		Exponential	Rate (per 1000 years)				
Before virological failure	200 cells/μl			2.7 (2.0 – 3.6)			1.3 (0.2 – 9.1)
After virological failure	200 cells/μl			18.7 (12.0 – 29.0)			1.3 (0.2 – 9.1)
Before virological failure & CD4 >200cells/μl	100 cells/μl			1.8 (1.3 – 2.6)			3.6 (0.3 – 39.5)
After failure & CD4>200 cells/μl	100 cells/μl			18.3 (12.0 – 28.1)			3.6 (0.3 – 39.5)
Before virological failure & CD4 <200 cells/μl	100 cells/μl			55.0 (32.6 – 92.8)			3.6 (0.3 – 39.5)
After virological failure & CD4<200 cells/μl	100 cells/μl			73.8 (48.1 – 118.2)			3.6 (0.3 – 39.5)
Drop in CD4 percentage below threshold‡‡		Exponential	Rate (per 1000 years)				
Before virological failure	15%			2.8 (1.9 – 4.3)	Age****	2.04 (0.98 – 5.30)	4.1 (1.0 – 16.7)
After virological failure	15%			6.4 (2.7 – 15.4)	Age****	2.04 (0.98 – 5.30)	4.1 (1.0 – 16.7)
Before virological failure & CD4 % >15%	10%			1.2 (0.7 – 2.1)			4.4 (0.8 – 24.0)
After virological failure & CD4 % >15%	10%			9.0 (4.5 – 18.1)			4.4 (0.8 – 24.0)
Before virological failure & CD4 % <15%	10%			31.6 (15.8 – 63.3)			4.4 (0.8 – 24.0)
After Virological failure & CD4 % <15%	10%			41.6 (22.6 – 79.9)			4.4 (0.8 – 24.0)

Hazard ratios for HIV-related mortality are applied to children who experience the event in question. The hazard ratios for the HIV-related mortality are multiplied with the background HIV-related mortality rates shown in Appendix Table S1.

* <12 months at start of antiretroviral therapy

** Exposure to prevention of mother-to-child transmission (PMTCT) prophylaxis

*** Nevirapine (NVP) included in the regimen

***** <36 months at ART start

‡ For children aged ≥5 years

‡‡ For children aged <5 years

Table 2

Key model outcomes for different monitoring strategies.

Type of monitoring	CD4 monitoring	VL monitoring	
Period between measurements (months)	**6**	**6**	**12****
Children aged <5 years at ART start			
Switched to second line (%)	0.3%	6.9%	6.0%
Switched unnecessarily (%)*	41.0%	0.0%	0.0%
Failures missed (%)	97.6%	9.3%	19.1%
Mean time spent on failing regimen (months)	6.7	5.1	5.3
Mortality (%)	10.4%	10.1%	10.3%
Children aged 5 to <16 years at ART start			
Switched to second-line ART (%)	1.7%	20.4%	18.1%
Switched unnecessarily (%)*	45.6%	0.0%	0.0%
Failures missed (%)	95.9%	9.5%	19.4%
Mean time spent on failing regimen (months)	6.5	1.6	2.1
Mortality (%)	4.0%	3.9%	3.9%
All children (aged <16 years at ART start)			
Switched to second line (%)	1.1%	13.9%	12.1%
Switched unnecessarily (%)*	44.1%	0.0%	0.0%
Failures missed (%)	96.7%	9.5%	19.6%
Mean time spent on failing regimen (months)	6.6	3.3	3.6
Mortality (%)	7.1%	6.9%	6.9%

All results refer to Analysis I. Percentages refer to the proportion after 5 years of follow-up.

* Proportion of all children who switched to second-line who switched without virological failure. By definition VL monitoring does not lead to unnecessary switches.

** As recommended by the World Health Organization [1]