

# Viral load versus CD4<sup>+</sup> monitoring and 5-year outcomes of antiretroviral therapy in HIV-positive children in Southern Africa: a cohort-based modelling study

Luisa Salazar-Vizcaya<sup>a</sup>, Olivia Keiser<sup>a</sup>, Karl Technau<sup>b</sup>,  
Mary-Ann Davies<sup>c</sup>, Andreas D. Haas<sup>a</sup>, Nello Blaser<sup>a</sup>, Vivian Cox<sup>d</sup>,  
Brian Eley<sup>e</sup>, Helena Rabie<sup>f</sup>, Harry Moultrie<sup>g</sup>, Janet Giddy<sup>h</sup>,  
Robin Wood<sup>i</sup>, Matthias Egger<sup>a,c</sup> and Janne Estill<sup>a</sup>

**Objectives:** Many paediatric antiretroviral therapy (ART) programmes in Southern Africa rely on CD4<sup>+</sup> to monitor ART. We assessed the benefit of replacing CD4<sup>+</sup> by viral load monitoring.

**Design:** A mathematical modelling study.

**Methods:** A simulation model of HIV progression over 5 years in children on ART, parameterized by data from seven South African cohorts. We simulated treatment programmes with 6-monthly CD4<sup>+</sup> or 6- or 12-monthly viral load 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<sup>+</sup> than with viral load monitoring.

**Results:** About 7% of children were predicted to die within 5 years, independent of the monitoring strategy. Compared with CD4<sup>+</sup> monitoring, 12-monthly viral load 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<sup>+</sup> compared with 12% with viral load monitoring switched to second-line ART. Differences became larger when assuming higher rates of virological failure. When assuming higher virological failure rates with CD4<sup>+</sup> than with viral load monitoring, up to 4.2% of children with CD4<sup>+</sup> compared with 1.5% with viral load monitoring experienced immunological failure; the mean time spent on failing ART was 27.3 months with CD4<sup>+</sup> monitoring and 6.0 months with viral load monitoring.

**Conclusion:** Viral load monitoring did not affect 5-year mortality, but reduced time on failing ART, improved immunological response and increased switching to second-line ART.

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<sup>a</sup>Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland, <sup>b</sup>Rahima Moosa Hospital, University of the Witwatersrand, Johannesburg, <sup>c</sup>School of Public Health & Family Medicine, University of Cape Town, <sup>d</sup>Khayelitsha ART Programme, Médecins Sans Frontières, <sup>e</sup>Red Cross Children's Hospital, University of Cape Town, Cape Town, <sup>f</sup>Tygerberg Academic Hospital, University of Stellenbosch, Stellenbosch, <sup>g</sup>Wits Reproductive Health & HIV Institute, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, <sup>h</sup>McCord Hospital, Durban, and <sup>i</sup>Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa.

Correspondence to Luisa Salazar-Vizcaya, Institute of Social and Preventive Medicine, University of Bern, Finkenhubelweg 11, 3012 Bern, Switzerland.

Tel: +41 31 631 38 67; e-mail: lsalazar@ispm.unibe.ch

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## Introduction

HIV viral load is routinely monitored in paediatric antiretroviral therapy (ART) programmes in high-income countries, whereas in sub-Saharan Africa, most programmes rely on CD4<sup>+</sup> 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 viral load 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 randomized controlled trials [9–11] showed that routine viral load monitoring may reduce mortality slightly and substantially increase costs. These results cannot be generalized to children: progression of HIV is faster in children than in adults, the CD4<sup>+</sup> 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 viral load monitoring strategy to be yearly monitoring, along with a first measurement 6 months after treatment start, as recommended by the WHO [1]. The authors estimated that the strategy would entail a three-fold increase in the costs of treatment [17]. A recent randomized trial found that routine CD4<sup>+</sup> and toxicity monitoring conferred minimal benefits when compared with monitoring based on clinical progression and toxicity alone [18].

There is no empirical study that compared viral load and CD4<sup>+</sup> monitoring in children. We developed a mathematical model for HIV progression in children on ART in Southern Africa to address this question.

## Materials and methods

### Data sources and eligibility criteria

We analysed data on children aged less than 16 years from seven South African cohorts participating in the International epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) collaboration to parameterize 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 2000–2012 with two nucleoside

reverse transcriptase inhibitors (NRTIs) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor. We excluded children who started with ritonavir and NRTIs: this regimen is no longer used [21–23].

All cohorts measure viral load routinely. The 2004 South African guidelines recommended 6-monthly viral load monitoring. Decisions to switch therapy following virological failure were taken after assessing growth, CD4<sup>+</sup> measures and adherence [24]. Since 2010, the guidelines recommend viral load monitoring after 6 months, 12 months and yearly thereafter. If viral load is more than 400 copies/ml, children and caretakers are counselled for adherence [25]. If viral load is more than 1000 copies/ml, it is measured again 3 months later and if confirmed switching to second-line ART is recommended. Children failing a protease inhibitor-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, <http://links.lww.com/QAD/A570> for a list of parameters). We fitted Weibull, exponential and piecewise exponential cumulative distribution functions to time from ART start to virological failure (>1000 copies/ml); drop in CD4<sup>+</sup> percentage to less than 15 and less than 10% in children aged less than 5 years or drop in CD4<sup>+</sup> to less than 200 and less than 100 cells/ $\mu$ l in children aged at least 5 years; and death. We defined a drop below the upper CD4<sup>+</sup> thresholds as immunosuppression. The lower CD4<sup>+</sup> 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<sup>+</sup> 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 viral load, CD4<sup>+</sup> measures and death (see Appendix Text S1 and S2, <http://links.lww.com/QAD/A570>, Figure S1 and S2, <http://links.lww.com/QAD/A570>). We defined two viral load categories (failure and

**Table 1. Parameters for disease progression in the model.**

Event	Threshold	Functional form	Scale (years) Shape	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) Shape	18.9 (17.0–21.0) 1.0 (0.9–1.0)	1.18 (1.03–1.35) 1.28 (1.09–1.51) 1.37 (1.10–1.71)	
Drop in CD4 <sup>+</sup> cell count below threshold <sup>e</sup>						
Before virological failure	200 cells/ $\mu$ l	Exponential	Rate (per 1000 years)	2.7 (2.0–3.6)		1.3 (0.2–9.1)
After virological failure	200 cells/ $\mu$ l			18.7 (12.0–29.0)		1.3 (0.2–9.1)
Before virological failure and CD4 <sup>+</sup> cell count >200 cells/ $\mu$ l	100 cells/ $\mu$ l			1.8 (1.3–2.6)		3.6 (0.3–39.5)
After failure and CD4 <sup>+</sup> cell count >200 cells/ $\mu$ l	100 cells/ $\mu$ l			18.3 (12.0–28.1)		3.6 (0.3–39.5)
Before virological failure and CD4 <sup>+</sup> cell count <200 cells/ $\mu$ l	100 cells/ $\mu$ l			55.0 (32.6–92.8)		3.6 (0.3–39.5)
After virological failure and CD4 <sup>+</sup> cell count <200 cells/ $\mu$ l	100 cells/ $\mu$ l			73.8 (48.1–118.2)		3.6 (0.3–39.5)
Drop in CD4 <sup>+</sup> percentage below threshold <sup>f</sup>						
Before virological failure	15%	Exponential	Rate (per 1000 years)	2.8 (1.9–4.3)	2.04 (0.98–5.30)	4.1 (1.0–16.7)
After virological failure	15%			6.4 (2.7–15.4)	2.04 (0.98–5.30)	4.1 (1.0–16.7)
Before virological failure and CD4% > 15%	10%			1.2 (0.7–2.1)		4.4 (0.8–24.0)
After virological failure and CD4% > 15%	10%			9.0 (4.5–18.1)		4.4 (0.8–24.0)
Before virological failure and CD4% < 15%	10%			31.6 (15.8–63.3)		4.4 (0.8–24.0)
After virological failure and 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 HIV-related mortality rates shown in Appendix Table S1, <http://links.lww.com/QAD/A570>.

<sup>a</sup>Less than 12 months at start of antiretroviral therapy.

<sup>b</sup>Exposure to prevention of mother-to-child transmission (PMTCT) prophylaxis.

<sup>c</sup>Nevirapine (NVP) included in the regimen.

<sup>d</sup>Less than 36 months at start of antiretroviral therapy.

<sup>e</sup>For children aged  $\geq$ 5 years.

<sup>f</sup>For children aged <5 years.

no failure) and three CD4<sup>+</sup> 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 less than 5 and at least 5 years: 6-monthly CD4<sup>+</sup> monitoring, switching according to WHO immunological criteria [1]; 6-monthly viral load monitoring; and viral load monitoring yearly (as well as an additional first measurement 6 months after initiation). For both CD4<sup>+</sup> and viral load 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 protease inhibitor first-line regimen and aged less than 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 protease inhibitor based ART. We report all outcomes at 5 years from ART start.

### Analysis I: Effect of viral load monitoring using cohort parameter values

In a first analysis, we simulated 100 000 children for each monitoring strategy and age group, that is 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 protease inhibitor 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 viral load 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 protease inhibitor based, and a constant virological failure rate over time.

### Analysis III: Effect of viral load monitoring assuming that it improves adherence

We assumed that viral load monitoring prevents virological failure by improving adherence [33]. We calculated the rate ratio between unconfirmed (one viral load measurement >1000 copies/ml) and confirmed failure (two 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 viral load monitoring, mimicking a retrospective study of viral load in stored blood samples in CD4<sup>+</sup> monitoring sites. In sites with routine viral load monitoring, a first high viral load triggers adherence counselling. If the second value is also elevated, the patient is switched and viral load becomes undetectable. Without viral load monitoring, the first elevated viral load value is missed, there is no adherence counselling and we expect viral load to remain high. We used the same range of failure rates for CD4<sup>+</sup> monitoring as in Analysis II and simulated cohorts of 100 000 children for all three monitoring strategies. The virological failure rates with viral load monitoring were calculated by dividing the rate in the CD4<sup>+</sup> monitoring simulation by the rate ratio between unconfirmed and confirmed failure.

### Additional analyses

In additional analyses, on the basis of 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-SA 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, <http://links.lww.com/QAD/A570>). Median age at ART start was 3.6 years [interquartile range (IQR) 1.0–7.5]. Median baseline CD4<sup>+</sup> percentage was 15.6% [interquartile range (IQR) 10.0–22.8] for age less than 5 years, and median baseline CD4<sup>+</sup> 231 cells/μl (IQR 80–424) for age at least 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 8363 (70.3%). A total of 1317 children (11.1%) were lost to follow-up, that is had not been seen in the clinic for at least 1 year. The number of children who had sufficient

measurements to detect and confirm treatment failures was 6484 for viral load and 7036 for CD4<sup>+</sup> monitoring. The median number of months between laboratory measurements was 5.7 (IQR 4.3–7.2) for viral load and 6.1 (IQR 5.3–7.4) for CD4<sup>+</sup>. The majority of children (57%) started with an 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 viral load monitoring using cohort parameter values

With CD4<sup>+</sup> monitoring, about 1.1% of children switched therapy within the first 5 years of follow-up, whereas in both viral load monitoring scenarios, the corresponding proportion was above 12% (Table 2, Fig. 1a). The mean time spent on failing regimens decreased from 6.6 months with CD4<sup>+</sup> monitoring to 3.6 months with 12-monthly and 3.3 months with 6-monthly viral load monitoring (Fig. 1c). The time spent on failing NNRTI-based regimens was reduced by 73%, but the time spent on failing protease inhibitor-based regimens increased slightly when comparing 12-monthly viral load monitoring with CD4<sup>+</sup> monitoring (Appendix Figure S3, <http://links.lww.com/QAD/A570>). With CD4<sup>+</sup> 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 viral load monitoring, the proportion of missed failures dropped to 10% (Table 2).

Viral load monitoring did not reduce mortality. Mortality at 5 years was 7.1% with CD4<sup>+</sup> monitoring and 6.9% with both viral load monitoring strategies (Table 2). The

proportion of children who experienced immunologic failure was 1.6% with CD4<sup>+</sup> monitoring, but 1.0% with viral load monitoring (Fig. 1b), a 40% reduction.

### Analysis II: Effect of viral load monitoring for different treatment efficacy scenarios

In Fig. 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 viral load than with CD4<sup>+</sup> monitoring (Fig. 2a), and the difference increased with increasing virological failure rates. The differences in the percentage of children who developed immunological failure (Fig. 2b), and in the time spent on a failing regimen (Fig. 2c) also increased with the rate of virological failure. For the highest virological failure rate assumed (0.30/year), 12-monthly viral load 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<sup>+</sup> monitoring. The mean time spent on a failing protease inhibitor regimen increased from 0.2 months with CD4<sup>+</sup> monitoring to 8.0 months with 12-monthly viral load monitoring. Consistent with Analysis I, mortality was similar for the three monitoring strategies.

### Analysis III: Effect of viral load 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

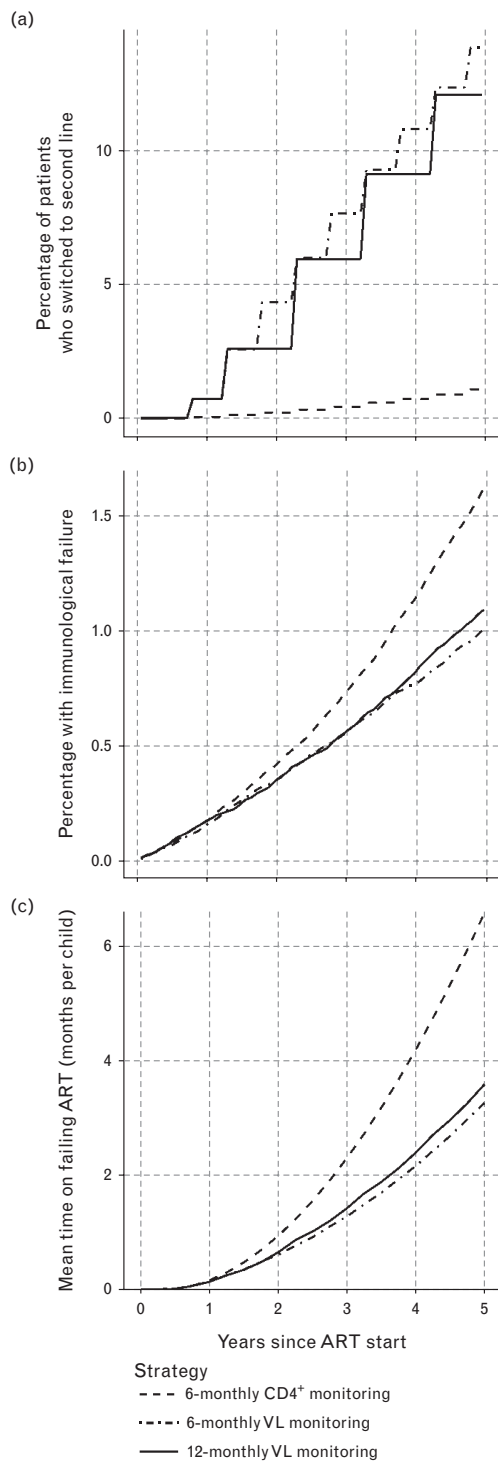
**Table 2. Key model outcomes for different monitoring strategies.**

Type of monitoring	CD4 <sup>+</sup> monitoring	VL monitoring	
		6	12 <sup>b</sup>
Period between measurements (months)	6	6	12 <sup>b</sup>
Children aged <5 years at ART start			
Switched to second line (%)	0.3	6.9	6.0
Switched unnecessarily (%) <sup>a</sup>	41.0	0.0	0.0
Virological 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 (%) <sup>a</sup>	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 (%) <sup>a</sup>	44.1	0.0	0.0
Virological 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

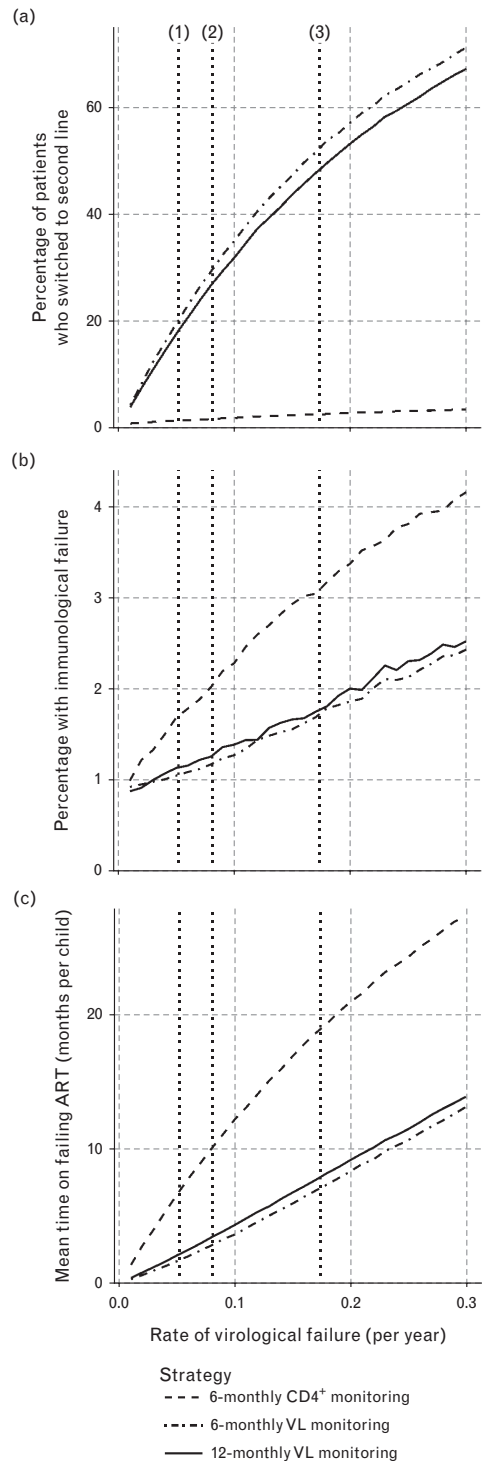
All results refer to Analysis I. Percentages refer to the proportion after 5 years of follow-up. ART, antiretroviral therapy; VL, viral load.

<sup>a</sup>Proportion of all children who switched to second-line who switched without virological failure. By definition, VL monitoring does not lead to unnecessary switches.

<sup>b</sup>As recommended by the WHO [1].



**Fig. 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.



**Fig. 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.

the South African cohort data. We therefore assumed that with CD4<sup>+</sup> monitoring, the virological failure rate was 2.08-fold higher than with viral load monitoring. With the highest failure rates (0.30/year for CD4<sup>+</sup> monitoring, 0.14/year with viral load 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 viral load and CD4<sup>+</sup> monitoring was smaller than in Analysis II (Fig. 3a). The percentage of children who experienced immunological failure was 4.2% with CD4<sup>+</sup> and 1.5% with 12-monthly viral load monitoring (Fig. 3b), and the mean time spent on failing ART was 27.3 months (27.1 on NNRTI, 0.2 on protease inhibitor) with CD4<sup>+</sup> and 6.0 months (3.0 on NNRTI, 3.0 on protease inhibitor) with viral load monitoring (Fig. 3c). Compared with CD4<sup>+</sup> monitoring, viral load monitoring thus prevented 63% of immunological failures and decreased the average time spent on a failing regimen by 21 months (a 78% relative reduction).

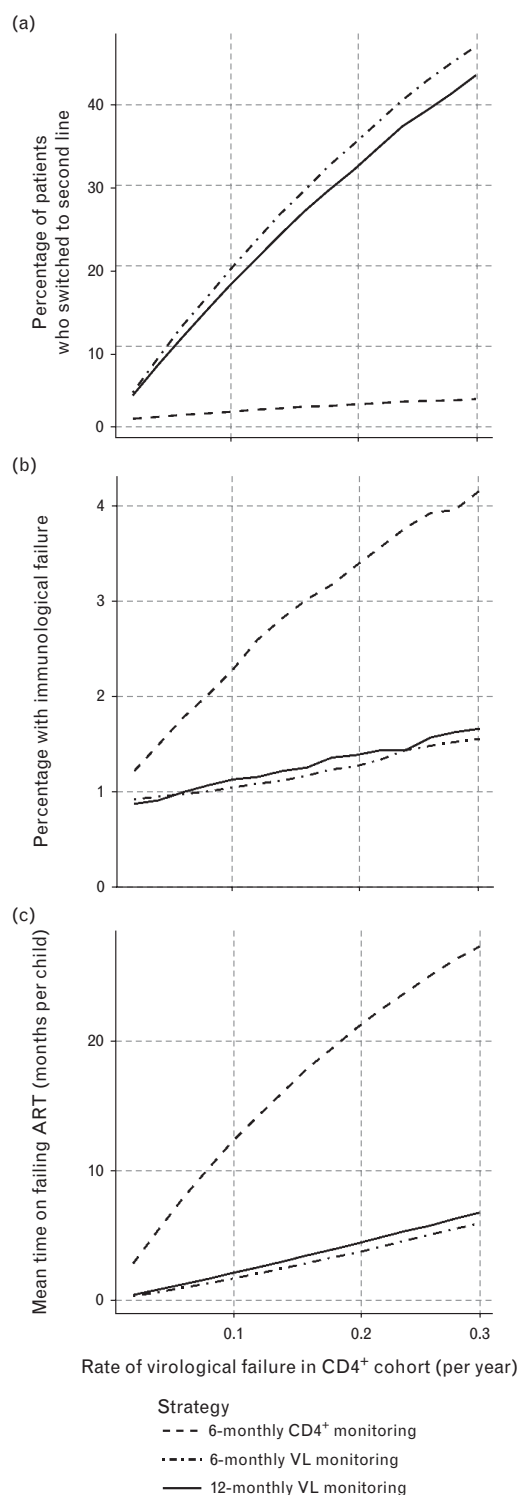
### Additional analyses

As expected, mortality was slightly higher at 5 years with the hypothetical no monitoring and no switching scenario; 7.2 compared with 6.9% with viral load monitoring (Appendix Figure S4, <http://links.lww.com/QAD/A570>). Differences in mortality were more pronounced when restricting the analyses to children who experienced virological failure (Appendix Figure S5, <http://links.lww.com/QAD/A570>). Unsurprisingly, modelled outcomes under the different monitoring strategies were similar to the outcomes observed in the IeDEA-SA cohorts (Appendix Table S3, <http://links.lww.com/QAD/A570>).

## Discussion

This mathematical modelling study showed that routine viral load monitoring does not reduce mortality of children during the first 5 years on ART. However, a clear benefit of viral load monitoring was evident in terms of preventing immunodeficiency through more timely identification of virological failure. Viral load 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 viral load 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 viral load monitoring will improve survival only minimally in the short term. The main



**Fig. 3. Predicted treatment outcomes over 5 years assuming that viral load monitoring reduces the virologic failure rate (Analysis III).** We assumed that replacing CD4<sup>+</sup> 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, antiretroviral therapy; VL, viral load.

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<sup>+</sup> and CD4<sup>+</sup> 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<sup>+</sup> 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, that is 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 protease inhibitor-based regimen. This proportion was higher in the youngest children: almost 90% of children aged less than 3 years at ART start started with protease inhibitor-based first-line regimen. One year of a protease inhibitor-based regimen can cost more than USD 400, whereas 1 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 protease inhibitor-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 protease inhibitor and NRTI resistance mutations during exposure to unsuccessful protease inhibitor-based ART may be low [29]. Our model was not designed to account for switches from protease inhibitor-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-SA cohorts from outside South Africa, very few children started with protease inhibitor-based ART [40].

We did not consider drug resistance explicitly. If viral load 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 protease inhibitor-based first-line regimens [29]. An important finding of our study is

that across a range of virological failure rates, viral load monitoring decreased the time spent on a failing regimen by over 50%. Our study thus supports the notion that viral load 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 viral load 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 parameterize 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 5 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 *et al.* [48] used a competing risk model of death and loss to follow-up. 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. Viral load 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 viral load monitoring. However, the beneficial effect on immunological outcomes and the reduction in time spent on failing treatment became more pronounced when assuming that



the failure rate was higher with CD4<sup>+</sup> than with viral load 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 viral load monitoring, even if the rate of virological failure is high.

## Conclusion

In this modelling study, viral load monitoring did not improve survival compared with CD4<sup>+</sup> monitoring over 5 years of ART, but several other benefits of viral load monitoring were evident. Provided that appropriate second-line therapy is available, viral load 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.

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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.

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## Conflicts of interest

The authors declare no conflicts of interest.

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