Cost-effectiveness of viral load testing for transitioning antiretroviral therapy-experienced children to dolutegravir in South Africa: a modelling analysis

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Summary

Background For children with HIV on antiretroviral therapy (ART), transitioning to dolutegravir-containing regimens is recommended. The aim of this study was to assess whether introducing viral load testing to inform new nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) for children with HIV and viraemia alongside dolutegravir-based ART is beneficial and of good economic value.

Methods We used the Cost-Effectiveness of Preventing AIDS Complications-Pediatric model to project clinical and cost implications of three strategies among a simulated cohort of South African children aged 8 years with HIV receiving abacavir–lamivudine–efavirenz: (1) continue current ART (no dolutegravir; abacavir–lamivudine–efavirenz); (2) transition all children with HIV to dolutegravir, keeping current NRTIs (dolutegravir; abacavir–lamivudine–dolutegravir); or (3) transition to dolutegravir based on viral load testing (viral load plus dolutegravir), keeping current NRTIs if virologically suppressed (abacavir–lamivudine–dolutegravir, 70% of cohort) or switching abacavir to zidovudine (zidovudine) if viraemic (zidovudine–lamivudine–dolutegravir, 30%). We assumed 50% of children who had viraemia after abacavir–lamivudine exposure had NRTI resistance; with resistance, we assumed zidovudine–lamivudine–dolutegravir was more effective than abacavir–lamivudine–dolutegravir. We designated a strategy as preferred if it was most effective and least costly or had an incremental cost-effectiveness ratio less than half the South African 2020 gross domestic product per capita.

Findings Under base-case assumptions, the viral load plus dolutegravir strategy would be the most effective (projected undiscounted life expectancy of 39·72 life-years) and least costly strategy (US$24 600 per person); the no dolutegravir strategy was the least effective (34·49 life-years) and most expensive ($26 480 per person). In sensitivity analyses, the 24-week virological suppression probability and subsequent monthly virological failure risks (ie, late failure) were most influential on cost-effectiveness. Only with a high late-failure risk for zidovudine–lamivudine–dolutegravir (ie, ≥0·3% per month in the base case or >0·5% per month if abacavir also confers low virological suppression probability in the presence of NRTI resistance [65%]) would the dolutegravir strategy become preferred above the viral load plus dolutegravir strategy.

Interpretation For programmes transitioning to dolutegravir-based regimens, our model predicted that doing so would be more effective and less costly than continuing current ART regimens, regardless of NRTI choice. Whether viral load testing for children with HIV is necessary to inform NRTI choice depends substantially on the comparative outcomes of abacavir and zidovudine after switching to dolutegravir-containing ART.

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Introduction

In 2022, of the estimated 230 000 children aged 0–14 years with HIV in South Africa, only 54% were receiving antiretroviral therapy (ART) and 37% had viral suppression.[1] WHO now recommends dolutegravir-containing ART for all children older than 4 weeks, including switches for children with known or presumed virological failure on their current ART, and transitions for children with known or presumed virological suppression.[2] Dolutegravir-based regimens

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Research in context

Evidence before this study

Only 37% of children with HIV in South Africa had virological suppression on antiretroviral therapy (ART) in 2022. Viraemia and drug resistance are common among children on ART but go undetected due to limited access to viral load testing. WHO recommends dolutegravir for all children older than 4 weeks due to better efficacy, decreased chance of resistance, and lower costs compared with previously widely used ART regimens. Dolutegravir is recommended for all ART-experienced children, regardless of their virological status. Since 2021, studies have shown non-inferiority of retaining current nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) for adults with viraemia upon switching to dolutegravir. However, whether these results can be extrapolated to children is unclear due to differences in NRTI options. To identify existing literature related to the clinical impact and cost-effectiveness of incorporating viral load testing before transitioning children with HIV to dolutegravir, we searched PubMed on March 5, 2024, for articles published in English with no date restrictions using the search terms "cost-effective" AND "pediatric" AND "dolutegravir" AND "drug resistance." Through this search, we identified ten papers focused on the effects of dolutegravir on adults and adolescents. We found one additional analysis that evaluated the cost-effectiveness of different diagnostic-based strategies for children in settings with dolutegravir availability in South Africa, but this analysis did not investigate lifetime projections of clinical benefits and costs or the effect of switching NRTIs for children with detected viraemia.

Added value of this study

Our study evaluates the long-term clinical outcomes and cost-effectiveness of providing a one-time viral load test before transitioning to a dolutegravir-based ART regimen for ART-experienced children in South Africa using the Cost-Effectiveness of Preventing AIDS Complications-Pediatric model. We found that transitioning children to dolutegravir, regardless of viral load test availability, would lead to higher life expectancy and lower lifetime HIV-related costs than continuing children on current ART regimens. Incorporating viral load testing to inform NRTI selection upon switch to dolutegravir further improved clinical and cost-effectiveness outcomes. These conclusions were sensitive to model inputs regarding NRTI selection, thus highlighting the need for more long-term data among ART-experienced children transitioning to dolutegravir.

Implications of all the available evidence

Dolutegravir-based regimens were projected to be more clinically beneficial for ART-experienced children and to decrease costs compared with not switching to dolutegravir. Using viral load testing to inform NRTI selection upon dolutegravir transition could further improve clinical and cost-effectiveness outcomes. The results of this study further support the existing guidance promoting dolutegravir roll-out among paediatric populations. More data on the effect of NRTI resistance on treatment options are needed to better inform switching practices for children with viraemia.

are well tolerated, highly effective with a high barrier to resistance, and inexpensive.[3–8] For children with viral suppression on ART, including on lopinavir–ritonavir-based and efavirenz-based regimens, dolutegravir-based regimens might confer higher durability of viral suppression and reduced toxicity.[3,5,7] Many children in South Africa have already been transitioned to dolutegravir-based regimens, but uptake is not complete.[9] To implement new dolutegravir guidelines, programmes need specific guidance about how to introduce dolutegravir-based regimens for ART-experienced children.[10]

Viraemia and drug resistance are both common among children on ART but go undetected due to limited access to viral load and HIV genotype testing.[2,11–13] Traditional treatment frameworks call for switching nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) when starting a new regimen in people with viraemia—especially if HIV drug resistance information is unavailable—assuming that resistance to the existing NRTI backbone is probable.[14–17] Thus, WHO suggests children with HIV switch NRTIs (eg, from abacavir to zidovudine or vice versa) if switching to dolutegravir-based ART while viraemic.[2] Challenging this framework, the NADIA study in adults with virological failure with a tenofovir-based regimen showed that when switching to dolutegravir-based regimens, continuation of tenofovir was not inferior to switching to zidovudine.[18] Extrapolation of these findings to the paediatric population remains uncertain due to the use of abacavir, rather than tenofovir, as the preferred NRTI for children.

Viral load testing can identify children with virological failure before switching, but challenges include high costs, limited access, and delayed return of results.[12] Viral load testing might be worth the investment if it leads to optimal NRTI selection and improved virological suppression and clinical outcomes without substantially delaying regimen switch. When viral load testing is unavailable, programmes must decide whether to transition to dolutegravir-containing regimens with or without a change in NRTIs. Our goal was to estimate the clinical and economic value of viral load testing to inform NRTI selection and to identify key gaps in current evidence around the effect of changing NRTIs, with or without viral load testing, among children with HIV transitioning to dolutegravir-based ART in South Africa.

Methods

Analytical overview

In this modelling study, we used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-Pediatric

model, a validated Monte Carlo microsimulation model of HIV disease and treatment in children and adolescents,[19] to project the clinical effect and costs of three strategies for children aged 8 years with HIV currently prescribed abacavir–lamivudine–efavirenz in South Africa. These three strategies are: (1) the continuation of current ART (labelled as no dolutegravir), used as a comparator; (2) the transition of all children with HIV to dolutegravir, keeping current NRTIs (labelled as dolutegravir); and (3) a transition to dolutegravir based on a viral load test, keeping current NRTIs if virological suppression is observed and switching abacavir to zidovudine if virological failure is observed (labelled as viral load plus dolutegravir).

For each modelled strategy, we projected the mean life expectancy from age 8 years and mean lifetime HIV-related costs per person, in 2020 US dollars, from the South African health-care system. We calculated incremental cost-effectiveness ratios (ICERs) from discounted (3% per year) life expectancy and costs as the difference in lifetime costs divided by the difference in life-years, with the lowest cost strategy as the comparator.[20] The intervention that projected the highest mean life expectancy with an ICER less than US$2828 per life-year saved (reflecting a threshold of 50% of South Africa's 2020 gross domestic product per capita, based on emerging guidance) was considered cost-effective.[21,22] To account for uncertainty in the lifetime horizon, we also analysed results at 20 years from the model start. This study was approved by the Mass General Brigham Human Research Committee as research that has a minimal risk to humans (protocol 2016P000492); informed consent was not required.

Model structure

Children start the model at a user-specified age, with clinical characteristics drawn from published cohorts of children on ART, and are simulated throughout their lifetimes. Children face monthly age-stratified risks of non-HIV-related mortality, monthly age-stratified and CD4 cell count (age ≥5 years)-stratified or CD4 percentage (<5 years)-stratified risks of opportunistic infections, and opportunistic infection-related and HIV-related mortality. When starting a new ART regimen, modelled children are assigned a one-time probability of reaching initial virological suppression (defined as HIV RNA <400 copies per mL at 24 weeks), with a corresponding increase in the proportion of CD4 cells (in children aged <5 years) or CD4 cell count (in children aged ≥5 years). Children who reach virological suppression are assigned a regimen-specific monthly risk of virological failure after 24 weeks (ie, late failure); after virological failure, CD4 cell percentage or count remains stable for 12 months and then declines, with subsequent increased risk in opportunistic infection incidence and mortality. Additional details of the CEPAC-Pediatric model are in the appendix (pp 3–5) and online.[23]

Population and strategies

For the base-case analysis, we simulated a cohort of children aged 8 years who were currently accessing care and on ART (abacavir–lamivudine–efavirenz) at model start. We chose 8 years as an age at which many children weigh more than 20 kg and become eligible for the 50 mg dose of dolutegravir.[3] We divided the cohort into three subcohorts based on true virological status at the time of a potential transition or switch: viral suppression (70%), virological failure with resistance to NRTIs (15%), and virological failure without resistance (assumed to be due to low ART adherence; 15%).[11,13,24] These subcohorts differed in terms of CD4 cell count and the expected response after transitioning or switching to dolutegravir-based ART (figure 1).

In the no dolutegravir strategy, children with HIV remained on their current ART regimen until diagnosed with virological failure (ie, HIV RNA >1000 copies per mL) via routine viral load monitoring, at which point they switched to a protease inhibitor-based regimen. In the dolutegravir strategy, children transitioned to dolutegravir-based ART at model start, with probabilities of 24-week viral suppression and late failure varying by subcohort (table 1; figure 1). In the viral load plus dolutegravir strategy, children underwent one-time viral load testing at model start, with the result informing ART regimen selection. After a 3-month delay to receive and act upon viral load test results, children with HIV identified to be virologically suppressed through viral load testing transitioned to a dolutegravir-based regimen with unchanged NRTIs (abacavir–lamivudine–dolutegravir), whereas children with HIV diagnosed with virological failure switched to zidovudine–lamivudine–dolutegravir. Across strategies, children with HIV who developed virological failure while on a dolutegravir-based regimen could reach virological suppression again with adherence counselling. If virological failure persisted for children who had not previously received a protease inhibitor, they switched to a protease inhibitor-based second-line ART regimen, as in the WHO-recommended ART sequences.[36] In the dolutegravir and viral load plus dolutegravir strategies, children who reached age 13 years (when most children weigh ≥30 kg) while still on a dolutegravir-based regimen transitioned to the once-daily tenofovir–lamivudine–dolutegravir regimen.[2]

Model input parameters

We used published trials and observational studies to derive cohort characteristics, natural history of untreated HIV, treatment outcomes, and costs for children in South Africa. When data specific to South Africa were unavailable, we used data from other sub-Saharan African settings to inform our inputs (appendix pp 3–7). When paediatric-specific data were unavailable, and for all modelled risks and costs after age 13 years, we used data from adults to inform our inputs. Costs were derived

See Online for appendix

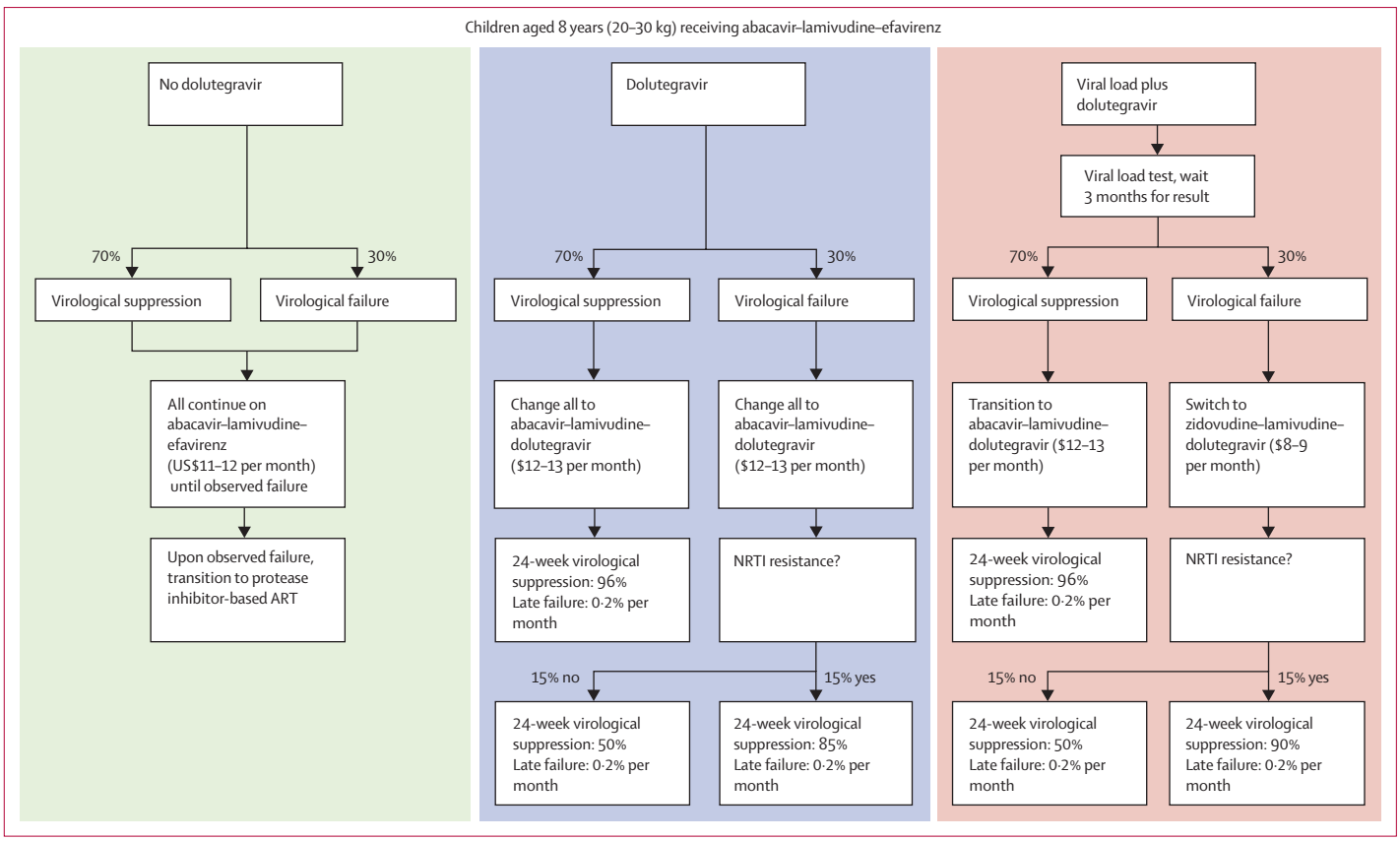

Figure 1: **Flowchart schematic of selected model input data for each modelled subcohort in the three ART strategies**
Costs per person are indicated with a range, which varies by age in the model. In the no dolutegravir strategy, children remain on current ART regimen (abacavir–lamivudine–efavirenz) until observed failure. Upon observed failure, they are switched to a protease inhibitor-based ART. In the dolutegravir strategy, children change to abacavir–lamivudine–dolutegravir regardless of whether they have virological suppression or failure on abacavir–lamivudine–efavirenz. For those suppressed (70% of the cohort), 24-week viral suppression probability on dolutegravir is 96%, with a monthly probability of late failure after 24-week viral suppression of 0·2% per month. For those with virological failure on abacavir–lamivudine–efavirenz, outcomes on dolutegravir differ by reason for failure. For those with virological failure without resistance, 24-week viral suppression is 50%. For those with virological failure due to NRTI resistance, 24-week viral suppression is 85%. In the viral load plus dolutegravir strategy, children are given a viral load test and their subsequent regimen is dependent on the test results. Children with suppression transition to abacavir–lamivudine–dolutegravir, with a 24-week viral suppression rate of 96%. Those with virological failure switch to zidovudine–lamivudine–dolutegravir, with outcomes again differing by reason for failure on the previous regimen. For those with virological failure without resistance, 24-week viral suppression is 50%. For those with virological failure due to NRTI resistance, 24-week viral suppression is 90% (because the NRTIs were changed with the new regimen). In the viral load plus dolutegravir strategy, 24-week viral suppression on zidovudine–lamivudine–dolutegravir is higher than 24-week viral suppression on abacavir–lamivudine–dolutegravir in the dolutegravir strategy for those experiencing virological failure due to resistance. Some children aged 8 years might be on lopinavir–ritonavir at the time of transition;[25] however, the regimen at the time of transition is unlikely to substantially affect current virological suppression rates, rates of clinically effective NRTI resistance, or the subsequent response to dolutegravir (appendix p 3).[26,27] ART=antiretroviral therapy. NRTI=nucleoside or nucleotide reverse transcriptase inhibitor.

from published sources and studies of resource use in South Africa (table 1; appendix p 6).[30–37]

We derived dolutegravir-based ART efficacy data, including 24-week virological suppression and late-failure risk, from published studies.[7,29] We assumed efficacy of dolutegravir-containing regimens in children with virological failure would vary with treatment history, treatment adherence, the presence of NRTI resistance, and the choice of NRTIs used with these regimens. These assumptions were informed by observational and trial data in children[7,29,38] and trial data in adults.[18] Because the efficacy of dolutegravir-based regimens with and without new NRTIs is highly uncertain, we varied these inputs extensively in sensitivity analyses. For the base case, we assumed a 24-week viral suppression probability of 96% on abacavir–lamivudine–dolutegravir for children with previous viral suppression on efavirenz-based ART (table 1; figure 1). We varied this value in the sensitivity analysis.

For children with virological failure without resistance, assumed to reflect low medication adherence, we assumed a 24-week virological suppression probability of 50% after switching to dolutegravir-based ART to reflect a probable continued low adherence after the switch. For children with virological failure and resistance, we assumed a 24-week virological suppression probability of 85% after a switch to abacavir–lamivudine–dolutegravir (in the dolutegravir strategy) and 90% after a switch to zidovudine–lamivudine–dolutegravir (in the viral load plus dolutegravir strategy), reflecting a potential benefit of new NRTIs in children with HIV with high adherence but drug resistance. We varied these 24-week suppression values (60–90%).

	Base-case value	Range	Reference
Baseline cohort characteristics			
Age, years	8	2–8	Assumption
Initial ART regimen	Abacavir–lamivudine–efavirenz	NA	Assumption
Shared cohort characteristics			
Male-to-female ratio	1:1	NA	Assumption
Virological suppression at model start	70%	0–100%	Kadima et al (2018),[11] Teasdale et al (2018),[24] and Segal-Maurer et al (2022)[28]
Virological failure at model start	30%	NA	NA
With resistance	15%	0–100%	Hackett et al (2021)[13]
Without resistance	15%	0–100%	Hackett et al (2021)[13]
ART inputs: 24-week virological suppression*			
Abacavir–lamivudine–dolutegravir			
Previous virological suppression	96%	NA	Bacha et al (2021)[29]
Previous virological failure with resistance	85%	60–90%	Bacha et al (2021)[29]
Previous virological failure without resistance	50%	NA	Bacha et al (2021)[29]
Zidovudine–lamivudine–dolutegravir			
Previous virological failure with resistance	90%	60–90%	Bacha et al (2021)[29]
Previous virological failure without resistance	50%	NA	Bacha et al (2021)[29]
Costs (2020 US dollars)			
Viral load test	$25	0·5–2·0-times base case	Simeon et al (2019)[30]
Routine HIV care, monthly†	$20–155	NA	Menzies et al (2011),[31] Anglaret et al (1999),[32] Holmes et al (2006),[33] and Massyn et al (2020)[34]
Abacavir–lamivudine–dolutegravir, monthly‡	$12–13	0·5–2·0-times base case	Doherty et al (2014)[35]
Zidovudine–lamivudine–dolutegravir, monthly‡	$8–9	0·5–2·0-times base case	Doherty et al (2014)[35]

Values shown in the base-case value column are used deterministically by the model, unless otherwise indicated. Values shown in the range column show the extreme range of the values used for the parameter in sensitivity analysis. Additional inputs can be found in the appendix (pp 6–7). Additional stochastic inputs not specific to this analysis and their distributions are published previously[19] and online.[23] ART=antiretroviral therapy. NA=not applicable. *Stratified by suppression status. †Straified by age and CD4 cell count or percentage. ‡Stratified by age.

Table 1: **Input parameters for a model-based analysis of the cost-effectiveness of viral load testing for transitioning ART-experienced children to dolutegravir in South Africa**

We assumed the late-failure rate to be 0·2% per month for all dolutegravir-containing regimens in the base case. We varied this value in sensitivity analysis (0·2–0·6% per month) for children who switch to zidovudine–lamivudine–dolutegravir in the viral load plus dolutegravir strategy, to reflect the potential effect of zidovudine's twice-daily dosing and mild adverse events on increased virological failure risk over time.[39] For children transitioning to tenofovir–lamivudine–dolutegravir at age 13 years, the modelled late-failure rate was 0·2% per month, regardless of previous NRTIs (appendix pp 6–7).[40]

Scenarios and sensitivity analyses

In univariate analyses, we varied costs of dolutegravir-based ART and viral load testing, return times of viral load test results (from immediate return to 6 months), and the probability of initial virological suppression for children with HIV who transition to each dolutegravir regimen. To reflect concern for zidovudine-induced anaemia, we conducted a scenario analysis in which children switching to zidovudine underwent haemoglobin monitoring every 6 months and had the highest modelled late-failure risk (appendix pp 3–5). Because roll-out of dolutegravir-containing regimens for adults has been more widespread than for children, we also simulated a scenario in which all children with HIV aged 13 years in the no dolutegravir strategy were eligible for tenofovir–lamivudine–dolutegravir as a salvage regimen. Finally, we repeated the base-case analysis for children aged 2 years and 5 years at model start.

In multivariate analyses, to account for wide-ranging uncertainty in available data, we simultaneously varied 24-week virological suppression for abacavir–lamivudine–dolutegravir for those with virological failure and resistance (60–90%, base case 85%) and the monthly late-failure risk beginning 24 weeks after switch to zidovudine–lamivudine–dolutegravir in the viral load plus dolutegravir strategy (0·2–0·6%, base case 0·2%). Next, we simultaneously varied two characteristics of the starting cohort of children with HIV at the time of possible switch: (1) the proportion with virological suppression on abacavir–lamivudine–efavirenz (0–100%, base case 70%), and (2) the proportion of children with HIV with virological failure and NRTI resistance (0–100%, base case 50%). We also varied 24-week virological suppression for zidovudine–lamivudine–dolutegravir for those with

virological failure and resistance (60–90%, base case 90%) and the monthly late-failure risk after the switch to abacavir–lamivudine–dolutegravir in the dolutegravir strategy for all children with virological failure (0·2–0·6%, base case 0·2%). Finally, we repeated each of these sensitivity analyses, halving the cost of abacavir-based ART and doubling the cost of zidovudine-based ART. We have previously published validation and calibration of the CEPAC-P model, which is coded in C++.[19]

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Results

For the base-case analysis, projected undiscounted life expectancy was 34·49 years for the no dolutegravir strategy (table 2). Both dolutegravir-containing strategies increased projected life expectancy, to 39·62 years for the dolutegravir strategy and 39·72 years for the viral load plus dolutegravir strategy. In the subcohort of children with previous viral suppression, all of whom continued abacavir, projected life expectancy was 40·20 years with the dolutegravir strategy and 40·27 years with the viral load plus dolutegravir strategy. In this group, waiting 3 months to receive results from viral load testing provided a small survival benefit in the model due to added time on suppressive ART before transition to dolutegravir-based regimens. In the subcohort of children with HIV with virological failure due to resistance, projected life expectancy was 39·50 years with the dolutegravir strategy and 39·89 years with the viral load plus dolutegravir strategy; prolonged viraemia caused by waiting for viral load results was offset by the higher rate of 24-week virological suppression with zidovudine in the viral load plus dolutegravir strategy (90%) compared with abacavir-based ART in the dolutegravir strategy (85%; figure 1). In the subcohort of children with HIV with virological failure without resistance, for whom zidovudine and abacavir were assigned identical modelled viral suppression and late-failure risks, the time spent awaiting viral load results decreased life expectancy (37·01 years with the dolutegravir strategy *vs* 36·95 years with the viral load plus dolutegravir strategy).

Projected lifetime undiscounted per-person costs were highest for the no dolutegravir strategy ($26 480) compared with the dolutegravir strategy ($24 650) and the viral load plus dolutegravir strategy ($24 600; table 2). Higher costs for the no dolutegravir strategy were due to more time spent on costly protease inhibitor-based ART; slightly lower lifetime costs of the viral load plus dolutegravir strategy compared with the dolutegravir strategy were due to the lower cost of zidovudine–lamivudine–dolutegravir than abacavir–lamivudine–dolutegravir and the slightly reduced durations of more costly protease inhibitor-based ART (appendix pp 19–20). In the cost-effectiveness analysis with discounted results (table 3), under our base-case assumptions, the viral load plus dolutegravir strategy was the most effective and least costly strategy (21·24 discounted life-years at $12 610 per person), although the dolutegravir strategy led to only a slightly lower life expectancy and slightly greater costs (21·21 discounted years at $12 660 per person). At 20 years from model start, viral load plus dolutegravir remained the most effective (13·73 discounted life-years) and least costly ($10 200) strategy, followed by the dolutegravir strategy (13·72 discounted life-years at $10 260 per person) and the no dolutegravir strategy (13·62 discounted life-years at $12 060 per person).

In univariate sensitivity analyses, the no dolutegravir strategy remained less effective and more costly than either the dolutegravir strategy or the viral load plus dolutegravir strategy, even when the return time of the viral load test results and drug costs were varied widely, whereas the viral load plus dolutegravir strategy remained most effective (table 3). Halving the cost of abacavir–lamivudine–dolutegravir or doubling the cost of zidovudine–lamivudine–dolutegravir made the viral load plus dolutegravir strategy more costly than the dolutegravir strategy; however, the ICER relative to the dolutegravir strategy was lower than the specified threshold for cost-effectiveness ($2828 per life-year saved), so the viral load plus dolutegravir strategy remained economically preferable (table 3). Varying the return time of the viral load test results did not change policy conclusions compared with the base case. If the

	Weight	Life expectancy, years	Costs per person
No dolutegravir			
Viral suppression (abacavir–lamivudine–efavirenz)	0·70	36·61	$26 870
Virological failure with resistance (abacavir–lamivudine–efavirenz)	0·15	29·55	$25 550
Virological failure without resistance (abacavir–lamivudine–efavirenz)	0·15	29·55	$25 550
Strategy weighted for entire cohort	NA	34·49	$26 480
Dolutegravir			
Viral suppression (abacavir–lamivudine–dolutegravir)	0·70	40·20	$24 530
Virological failure with resistance (abacavir–lamivudine–dolutegravir)	0·15	39·50	$24 690
Virological failure without resistance (abacavir–lamivudine–dolutegravir)	0·15	37·01	$25 160
Strategy weighted for entire cohort	NA	39·62	$24 650
Viral load plus dolutegravir			
Viral suppression (abacavir–lamivudine–dolutegravir)	0·70	40·27	$24 550
Virological failure with resistance (zidovudine–lamivudine–dolutegravir)	0·15	39·89	$24 460
Virological failure without resistance (zidovudine–lamivudine–dolutegravir)	0·15	36·95	$25 000
Strategy weighted for entire cohort	NA	39·72	$24 600

Undiscounted life expectancy and cost per person for each subcohort and weighted for each strategy. Costs are presented in 2020 US dollars (undiscounted). ART=antiretroviral therapy. NA=not applicable.

Table 2: **Base-case results per strategy for a model-based analysis of the cost-effectiveness of viral load testing for transitioning ART-experienced children to dolutegravir in South Africa**

	Undiscounted life expectancy, years	Undiscounted costs, per person	Discounted life expectancy, years	Discounted costs, per person	ICER
Base case					
Viral load plus dolutegravir	39·72	$24 600	21·24	$12 610	Comparator*
Dolutegravir	39·62	$24 650	21·21	$12 660	Less effective and more expensive
No dolutegravir	34·49	$26 480	19·82	$14 300	Less effective and more expensive
0·5-times abacavir–lamivudine–dolutegravir cost					
Dolutegravir	39·62	$24 310	21·21	$12 340	Comparator
Viral load plus dolutegravir	39·72	$24 370	21·24	$12 390	$1570 per life-year saved*
No dolutegravir	34·49	$26 480	19·82	$14 300	Less effective and more expensive
2·0-times zidovudine–lamivudine–dolutegravir cost					
Dolutegravir	39·62	$24 650	21·21	$12 660	Comparator
Viral load plus dolutegravir	39·72	$24 720	21·24	$12 720	$1940 per life-year saved*
No dolutegravir	34·49	$26 480	19·82	$14 300	Less effective and more expensive
0 months viral load test return time					
Viral load plus dolutegravir	39·69	$24 610	21·23	$12 610	Comparator*
Dolutegravir	39·62	$24 650	21·21	$12 660	Less effective and more expensive
No dolutegravir	34·49	$26 480	19·82	$14 300	Less effective and more expensive
6 months viral load test return time					
Viral load plus dolutegravir	39·74	$24 650	21·24	$12 640	Comparator*
Dolutegravir	39·62	$24 650	21·21	$12 660	Less effective and more expensive
No dolutegravir	34·49	$26 480	19·82	$14 300	Less effective and more expensive
24-week virological suppression on dolutegravir is 98% for children with previous suppression					
Viral load plus dolutegravir	39·81	$24 590	21·26	$12 580	Comparator*
Dolutegravir	39·72	$24 630	21·23	$12 630	Less effective and more expensive
No dolutegravir	34·49	$26 480	19·82	$14 300	Less effective and more expensive
6-monthly haemoglobin testing and high late-failure risk for zidovudine					
Dolutegravir	39·62	$24 650	21·21	$12 660	Comparator*
Viral load plus dolutegravir	39·14	$24 890	21·10	$12 820	Less effective and more expensive
No dolutegravir	34·49	$26 480	19·82	$14 300	Less effective and more expensive

Strategies are arranged by increasing discounted costs. Life expectancies are rounded to the nearest hundredth. Costs are rounded to the nearest ten and presented in 2020 US dollars. Discounted values are discounted at 3% per year. ICERs are calculated with unrounded discounted life expectancy and discounted costs and rounded to the nearest ten. The preferred strategy is the strategy that was the most clinically effective and least costly or the strategy that offered the greatest increase in overall population life expectancy while still having an ICER less than the cost-effectiveness threshold of $2828 per life-year saved when compared with the next least costly strategy. ART=antiretroviral therapy. ICER=incremental cost-effectiveness ratio. *Economically preferred strategy.

Table 3: **Cost-effectiveness results by strategy for a model-based analysis of the cost-effectiveness of viral load testing for transitioning ART-experienced children to dolutegravir in South Africa**

test result return time was 0 months, life expectancy would increase for children with HIV who were previously having virological failure in the viral load plus dolutegravir strategy due to the immediate dolutegravir switch. These benefits were offset by the smaller life expectancy gains for those who were previously suppressed with efavirenz compared to the base case. Increasing the viral load test result-return time to 6 months would increase the life expectancy in the viral load plus dolutegravir strategy for children with HIV who had previous viral suppression due to additional time on suppressive ART before moving to the next regimen. The increased result-return time would only slightly decrease life expectancy for those with previous virological failure due to additional time on failing ART with risk for disease progression before moving to the next regimen, such that weighted life expectancy for the entire cohort would change only minimally. The viral load plus dolutegravir strategy remained most effective and least costly in both scenarios (table 3; appendix pp 9–11). Increasing the proportion of children with HIV with previous viral suppression who would have viral suppression upon transitioning to dolutegravir resulted in slightly increased life expectancy and decreased costs within the dolutegravir and the viral load plus dolutegravir strategies; policy conclusions remained unchanged. If concerns for zidovudine-induced anaemia led to haemoglobin monitoring every 6 months and high late-failure risks, projected life expectancy would decrease and projected costs would increase within the viral load plus dolutegravir strategy. Under this scenario, the dolutegravir strategy would be preferred (table 3). If all children with HIV were eligible for tenofovir–lamivudine–dolutegravir as a salvage regimen at age

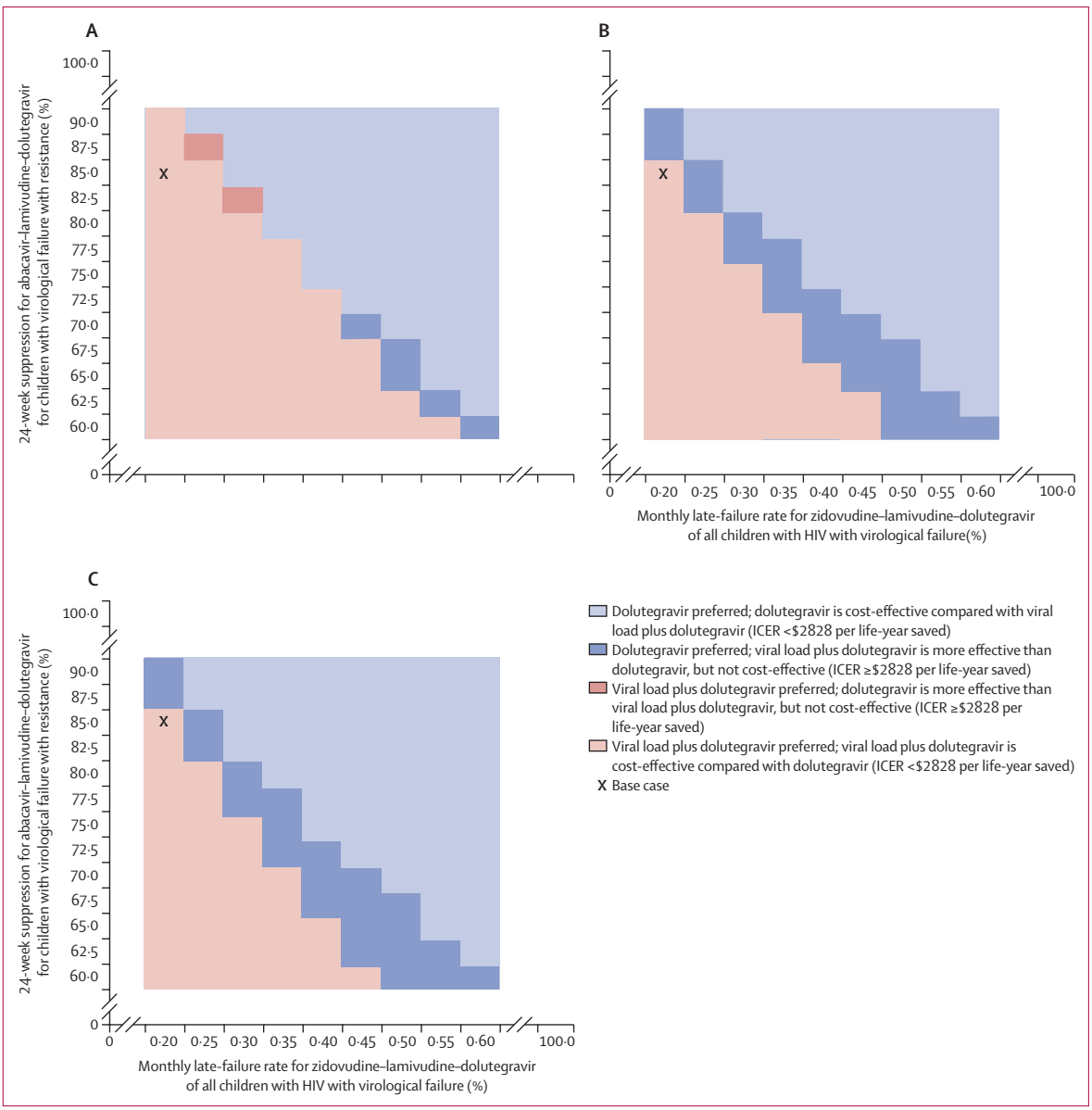

Figure 2: **Multivariate sensitivity analysis**
(A) Base-case ART costs. (B) 0·5-times abacavir–lamivudine–dolutegravir cost. (C) 2·0-times zidovudine–lamivudine–dolutegravir cost. Variation in both 24-week virological suppression on abacavir–lamivudine–dolutegravir (for children with HIV with virological failure due to resistance on their initial regimen) and late-failure risk for those on zidovudine–lamivudine–dolutegravir (for children with HIV with virological failure, regardless of resistance, on their initial regimen). We simulated scenarios in which abacavir–lamivudine–dolutegravir is half the cost of the base case (B) and zidovudine–lamivudine–dolutegravir is double the cost of the base case (C) to model scenarios in which paediatric zidovudine is no longer less expensive than abacavir. The y-axis shows values of 24-week virological suppression on abacavir–lamivudine–dolutegravir for children with HIV with virological resistance. The base-case value is 85%, and the corresponding value for zidovudine–lamivudine–dolutegravir (in the viral load plus dolutegravir strategy) is 90% in all scenarios. The x-axis shows values of monthly late-failure risk on zidovudine–lamivudine–dolutegravir. The base-case value is 0·2% per month, and the corresponding value for abacavir–lamivudine–dolutegravir is held constant at 0·2% per month in all scenarios. ART=antiretroviral therapy. ICER=incremental cost-effectiveness ratio.

13 years in the no dolutegravir strategy, the viral load plus dolutegravir strategy would remain most effective and least costly (appendix p 8).

Variations in other model input parameters did not change policy conclusions when compared with the base case; the viral load plus dolutegravir strategy remained the preferred strategy with variations in the costs of one-time viral load tests (0·5–2·0-times base case), the cost of dolutegravir-based ART (0·5–2·0-times base case), and the age of the cohort at time of possible transition (age 2 years or age 5 years; appendix pp 9–16). Throughout the parameter ranges evaluated, the no dolutegravir strategy was never preferred over either the dolutegravir strategy or the viral load plus dolutegravir strategy.

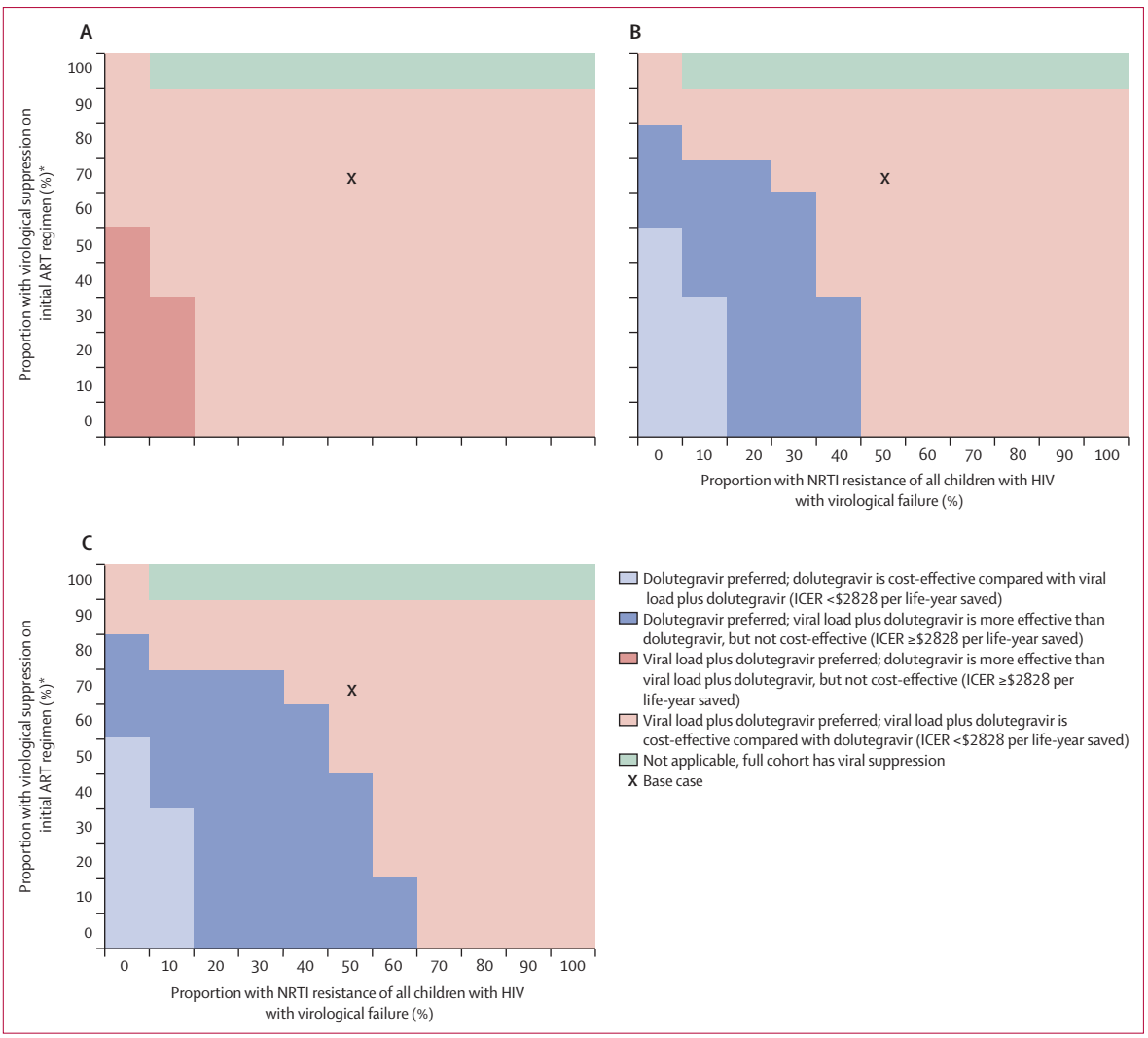

Figure 3: **Multivariate sensitivity analysis**

(A) Base-case antiretroviral therapy costs. (B) 0·5-times abacavir–lamivudine–dolutegravir cost. (C) 2·0-times zidovudine–lamivudine–dolutegravir cost. We modelled scenarios in which paediatric zidovudine is no longer less expensive than abacavir (B and C). We simulated scenarios in which abacavir–lamivudine–dolutegravir is half the cost of the base case (B) and zidovudine–lamivudine–dolutegravir is double the cost of the base case (C) to model when paediatric zidovudine is no longer less expensive than abacavir. The y-axis shows the proportion of children with HIV who have virological suppression at model start (base-case value 70%), with 0% indicating a cohort in which all children have viraemia. The x-axis indicates the proportion of the remaining cohort (ie, children with viraemia) with virological failure due to resistance at model start (base-case value 50%; ie, 15% of the overall cohort). The viral load plus dolutegravir strategy would remain economically preferred at all explored values at base-case antiretroviral therapy costs (A). ICER=incremental cost-effectiveness ratio. NRTI=nucleoside or nucleotide reverse transcriptase inhibitor. *The remainder of the cohort has virological failure.

In multivariate sensitivity analyses, at base-case costs, whether the dolutegravir strategy or the viral load plus dolutegravir strategy emerged as the preferred strategy depended on the trade-offs between the potential benefit of zidovudine over abacavir for children with virological resistance (modelled as 24-week virological suppression) and the potential harms of zidovudine compared with abacavir for all children receiving zidovudine (ie, those with observed virological failure with or without resistance on the viral load plus dolutegravir strategy, modelled as late-failure risk to reflect the possible effect of twice-daily dosing and medication side-effects). Figure 2 shows the simultaneous varying of these two parameters. When the two regimens were modelled with identical parameters (ie, 24-week virological suppression of 90% [the base-case value for zidovudine-based regimens] and a late-failure rate of 0·2% per month; top-left corner of figure 2A), the viral load plus dolutegravir strategy would be preferred given that waiting to switch to dolutegravir-based regimens was slightly beneficial for those with viral suppression and had minimal clinical effect on those with virological failure, and because zidovudine is less costly than abacavir. For any given value of 24-week virological

suppression for abacavir–lamivudine–dolutegravir, as the late-failure rate for zidovudine–lamivudine–dolutegravir increased, the dolutegravir strategy becomes preferred over the viral load plus dolutegravir strategy. For any given late-failure rate value for zidovudine–lamivudine–dolutegravir, as 24-week virological suppression for abacavir–lamivudine–dolutegravir increased, the dolutegravir strategy would be preferable to the viral load plus dolutegravir strategy except at the base-case value of 0·2% per month when viral load plus dolutegravir was the preferred strategy for all explored values of 24-week suppression on abacavir (60–90%; figure 2A). Even as abacavir became less costly (figure 2B) or zidovudine became more costly (figure 2C), the viral load plus dolutegravir strategy remained preferred for the base-case 24-week suppression values on abacavir and late failure on zidovudine. At these varied regimen costs, there were more combinations of abacavir 24-week suppression and zidovudine late failure for which the viral load plus dolutegravir strategy was clinically more effective, but not cost-effective, and thus dolutegravir would be preferred.

When varying the virological status of the modelled cohort, the viral load plus dolutegravir strategy would remain economically preferred for all explored values at base-case ART costs (figure 3A). If 100% of the cohort had virological suppression at model start, all children would transition to dolutegravir with abacavir–lamivudine with the viral load plus dolutegravir strategy, which would be a more effective strategy than the dolutegravir strategy solely due to the added time spent on suppressive ART before regimen change and would be cost-effective (ICER $280 per life-year saved). If zidovudine was more expensive than abacavir (figure 3B, C), the dolutegravir strategy would become preferred if the proportion of children with virological suppression at model start decreased or if the proportion of children with viraemia and NRTI resistance (of all children with viraemia) decreased. Additional multivariate sensitivity analyses did not change policy conclusions (appendix pp 8–15).

Discussion

We estimated the cost-effectiveness of alternative approaches to dolutegravir-based ART roll-out for children with HIV living in South Africa. There were three key findings of our study: first, projected life expectancy was lowest for the no dolutegravir strategy, in which current efavirenz-based regimens were continued until treatment failure was observed. Dolutegravir-based ART was predicted to be more clinically effective than continuing current ART and also decreased costs. Although the cost difference between efavirenz-containing and dolutegravir-containing regimens is small, the superior efficacy of dolutegravir-containing regimens was predicted to result in lower costs relating to health care, less treatment failure, and less time spent on more costly protease inhibitor-based ART later in life.

Second, we found that the value of viral load testing to inform NRTI choice was primarily influenced by the comparative clinical effectiveness of abacavir versus zidovudine after starting dolutegravir, not by the timing or cost of the viral load test. Our base-case inputs for 24-week viral suppression and late failure for dolutegravir-containing regimens were derived from the best available data, but remain uncertain. The use of a viral load test provided additional benefit because children with virological failure and resistance were switched to a regimen to which they were not resistant. However, if adherence is more challenging with zidovudine-containing regimens (eg, due to its twice-daily dosing or adverse effects), and thus leads to more virological failure and serious toxicity over time compared with abacavir, the slight benefit from initial treatment success would be outweighed by subsequent virological failure, and a single viral load test to select NRTIs would not be valuable.

Conversely, if 24-week viral suppression rates were much higher with zidovudine–lamivudine–dolutegravir than with abacavir–lamivudine–dolutegravir for children with NRTI resistance on their current regimen, the use of viral load testing to inform NRTI choice would be beneficial and cost-effective. This scenario would be consistent with the classic paradigm in HIV care that at least two new antiretroviral agents are needed when adjusting a failing regimen.[14–16,41] However, the NADIA trial showed the high efficacy of switching adults with virological failure on a tenofovir-based regimen to dolutegravir-based regimens with either zidovudine or tenofovir,[18] suggesting that a viral load test would not substantially matter when selecting NRTIs. However, NADIA results might not apply to children because tenofovir is not recommended for young children.[36] Children who develop NRTI resistance on abacavir before switching to dolutegravir might have a virus with increased susceptibility to zidovudine; this scenario might occur with a different frequency than among adults with virological failure with tenofovir-based ART, and the relative benefit of switching to zidovudine might differ when compared with abacavir-based ART.[42] Further research examining virological outcomes after switching to zidovudine and abacavir for children with virological failure before switching will help inform the value of viral load testing before starting dolutegravir-based ART.

Third, we found that the cost of viral load testing is not influential when transitioning children to dolutegravir-containing regimens; viral load testing for all children with HIV would be cost-effective, even if the costs of viral load tests were as much as $50. The cost of a single viral load test at the time of transition is very small compared with the long-term costs of ART regimens and routine care.

This study has important limitations. First, there are few data on long-term virological outcomes for children with HIV on dolutegravir-based ART. Second, data on the

risks and costs of specific adverse events, such as anaemia for children on zidovudine, are also scarce; we simulated a worst-case scenario to identify potential upper bounds of the impact of this toxic effect. Third, we did not model resistance to multiple NRTIs; both prevalence and the effect of resistance are uncertain in the context of dolutegravir-based regimens. Fourth, although we modelled currently available ART, the development of regimens that could improve outcomes and reduce barriers to adherence for children with HIV is very likely.[28] We did not directly model the effect of potential future therapies or technologies, such as point-of-care resistance testing. Last, these analyses were conducted with currently available costs and clinical data for South Africa. Although these results cannot be directly extrapolated to other settings, the costs of antiretroviral medications and treatment effectiveness might be similar in other countries.

The global roll-out of paediatric dolutegravir is under way, and in South Africa dolutegravir is now recommended for all ART-experienced children.[25] Our analysis underscores that this roll-out, regardless of the availability of viral load testing, will markedly improve clinical outcomes and decrease costs. Whether viral load testing improves clinical outcomes by informing NRTI choice depends on the comparative outcomes of abacavir and zidovudine after starting dolutegravir rather than on the timeliness or costs of viral load testing. As more countries and programmes transition children with HIV to dolutegravir-based regimens, identifying the effect of NRTI resistance on treatment outcomes is an important priority. Better data on resistance notwithstanding, the dolutegravir roll-out should proceed in a timely way, even where viral load testing is not readily available.

Contributors

IRB, CFF, MP, SBH, EPH, EA, and ALC designed the study. IRB, CFF, SBH, and ALC drafted the manuscript and performed the data analysis. All authors had access to all the data. All authors participated in the interpretation of the results and the critical revision of the manuscript, and all authors approve of the final submission and accept responsibility for the decision to submit.

Declaration of interests

IJC and SC received funding via their institution from ViiV Healthcare and Gilead Sciences, outside of the submitted work. M-AD received funding to her institution from ViiV Healthcare. ALC, EA, EPH, and KAF received funding to their respective institutions from the National Institutes of Health. ALC and EPH received funding from the Massachusetts General Hospital. EPH received royalties from UpToDate. All other authors declare no competing interests.

Data sharing

All data used as model inputs and all model results are available in the manuscript, appendix (pp 3–21), or on the CEPAC website (https://mpec.massgeneral.org/cepac-model/).

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References

1 UNAIDS. UNAIDS data 2023. Oct 31, 2023. https://www.unaids.org/en/resources/documents/2023/2023_unaids_data (accessed March 5, 2024).
2 WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. World Health Organization, 2021.
3 Bollen PDJ, Moore CL, Mujuru HA, et al. Simplified dolutegravir dosing for children with HIV weighing 20 kg or more: pharmacokinetic and safety substudies of the multicentre, randomised ODYSSEY trial. *Lancet HIV* 2020; **7:** e533–44.
4 Ruel T, Acosta EP, Singh R, et al. Pharmacokinetic and 4-week safety/efficacy of dolutegravir (S/GSK1349572) dispersible tablets in HIV-infected children aged 4 weeks to <6 years: results from IMPAACT P1093. XXII International AIDS Conference; July 25, 2018 (poster LBPEB023).
5 Viani RM, Ruel T, Alvero C, et al. Long-term safety and efficacy of dolutegravir in treatment-experienced adolescents with human immunodeficiency virus infection: results of the IMPAACT P1093 study. *J Pediatric Infect Dis Soc* 2020; **9:** 159–65.
6 Amuge P. Dolutegravir-based ART is superior to standard of care in young children living with HIV. International Workshop on HIV Pediatrics 2021; July 16–17, 2021 (abstr 124).
7 Turkova A, White E, Mujuru HA, et al. Dolutegravir as first- or second-line treatment for HIV-1 infection in children. *N Engl J Med* 2021; **385:** 2531–43.
8 Waalewijn H, Chan MK, Bollen PDJ, et al. Dolutegravir dosing for children with HIV weighing less than 20 kg: pharmacokinetic and safety substudies nested in the open-label, multicentre, randomised, non-inferiority ODYSSEY trial. *Lancet HIV* 2022; **5:** e341–52.
9 Sorour G, Sipambo N, Archary M. Paediatric antiretroviral update. *South Afr J HIV Med* 2023; **24:** 1506.
10 WHO. Paediatric ARV Drug Optimization 3 review: summary report. April 1, 2018. https://apps.who.int/iris/bitstream/handle/10665/272292/WHO-CDS-HIV-18.8-eng.pdf?ua=1 (accessed Oct 30, 2024).
11 Kadima J, Patterson E, Mburu M, et al. Adoption of routine virologic testing and predictors of virologic failure among HIV-infected children on antiretroviral treatment in western Kenya. *PLoS One* 2018; **13:** e0200242.
12 Lecher S, Williams J, Fonjungo PN, et al. Progress with scale-up of HIV viral load monitoring—seven sub-Saharan African countries, January 2015-June 2016. *MMWR Morb Mortal Wkly Rep* 2016; **65:** 1332–35.
13 Hackett S, Teasdale CA, Pals S, et al. Drug resistance mutations among South African children living with HIV on WHO-recommended ART regimens. *Clin Infect Dis* 2021; **73:** e2217–25.
14 Blanco JL, Marcelin A-G, Katlama C, Martinez E. Dolutegravir resistance mutations: lessons from monotherapy studies. *Curr Opin Infect Dis* 2018; **31:** 237–45.
15 Blanco JL, Rojas J, Paredes R, et al. Dolutegravir-based maintenance monotherapy versus dual therapy with lamivudine: a planned 24 week analysis of the DOLAM randomized clinical trial. *J Antimicrob Chemother* 2018; **73:** 1965–71.
16 Hocqueloux L, Allavena C, Prazuck T. Dolutegravir monotherapy versus dolutegravir/abacavir/lamivudine for HIV-1-infected virologically suppressed patients: results from the randomized non-inferiority MONCAY trial. AIDS 2018; July 23–27, 2018 (abstr TUAB0103).
17 Aboud M, Brites C, H Lu, et al. Dolutegravir versus LPV/r in second line (DAWNING): outcomes by WHO-recommended NRTI backbone. Conference on Retroviruses and Opportunistic Infections; March 4–7, 2018 (abstr 508).

18 Paton N, Musaazi J, Kityo C, et al. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. *Lancet HIV* 2022; **9:** e381–93.

19 Ciaranello AL, Morris BL, Walensky RP, et al. Validation and calibration of a computer simulation model of pediatric HIV infection. *PLoS One* 2013; **8:** e83389.

20 Bilger M. Cost-influenced treatment decisions and cost-effectiveness analysis. In: Quah SR, ed. International encyclopedia of public health, 2nd edn. Academic Press, 2017: 177–80.

21 The World Bank. World development indicators. Jan 20, 2013. https://databank.worldbank.org/source/world-development-indicators (accessed Oct 11, 2022).

22 Pichon-Riviere A, Drummond M, Palacios A, Garcia-Marti S, Augustovski F. Determining the efficiency path to universal health coverage: cost-effectiveness thresholds for 174 countries based on growth in life expectancy and health expenditures. *Lancet Glob Health* 2023; **11:** e833–42.

23 Massachusetts General Hospital. CEPAC model. Sept 17, 2020. https://mpec.massgeneral.org/cepac-model/ (accessed Oct 30, 2024).

24 Teasdale CA, Sogaula N, Yuengling KA, et al. HIV viral suppression and longevity among a cohort of children initiating antiretroviral therapy in Eastern Cape, South Africa. *J Int AIDS Soc* 2018; **21:** e25168.

25 Republic of South Africa National Department of Health. 2023 ART clinical guidelines for the management of HIV in adults, pregnancy and breastfeeding, adolescents, children, infants and neonates. June, 2023. https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf (accessed March 10, 2024).

26 Duong T, Judd A, Collins IJ, et al. Long-term virological outcome in children on antiretroviral therapy in the UK and Ireland. *AIDS* 2014; **28:** 2395–405.

27 Babiker A, Castro nee Green H, Compagnucci A, et al. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. *Lancet Infect Dis* 2011; **11:** 273–83.

28 Segal-Maurer S, DeJesus E, Stellbrink H-J, et al. Capsid inhibition with lenacapavir in multidrug-resistant HIV-1 infection. *N Engl J Med* 2022; **386:** 1793–803.

29 Bacha J, DiNardo A, Mayalla B, et al. The road to success is paved with dolutegravir: dolutegravir treatment success among children and adolescents living with HIV (CALHIV) at the Baylor Tanzania Centres of Excellence. International Workshop on HIV Pediatrics 2021; July 16–17, 2021 (abstr 70).

30 Simeon K, Sharma M, Dorward J, et al. Comparative cost analysis of point-of-care versus laboratory-based testing to initiate and monitor HIV treatment in South Africa. *PLoS One* 2019; **14:** e0223669.

31 Menzies NA, Berruti AA, Berzon R, et al. The cost of providing comprehensive HIV treatment in PEPFAR-supported programs. *AIDS* 2011; **25:** 1753–60.

32 Anglaret X, Chêne G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Côte d'Ivoire: a randomised trial. *Lancet* 1999; **353:** 1463–68.

33 Holmes CB, Wood R, Badri M, et al. CD4 decline and incidence of opportunistic infections in Cape Town, South Africa: implications for prophylaxis and treatment. *J Acquir Immune Defic Syndr* 2006; **42:** 464–69.

34 Massyn N, Barron P, Day C, Padarath A. District health barometer 2018/19. February, 2020. https://www.hst.org.za/publications/District%20Health%20Barometers/District+Health+Barometer+2018-19+Web.pdf (accessed Oct 11, 2022).

35 Doherty K, Essajee S, Penazzato M, Holmes C, Resch S, Ciaranello A. Estimating age-based antiretroviral therapy costs for HIV-infected children in resource-limited settings based on World Health Organization weight-based dosing recommendations. *BMC Health Serv Res* 2014; **14:** 201.

36 WHO. Update of recommendations on first- and second-line antiretroviral regimens. World Health Organization, 2019.

37 Clinton Health Access Initiative. 2018 HIV market report. Sept 12, 2018. https://chai19.wpenginepowered.com/wp-content/uploads/2018/09/2018-HIV-Market-Report_FINAL.pdf (accessed Jan 11, 2021).

38 Collins I, Crichton S, Turkova A, et al. Children and adolescents in the UK/ Ireland CHIPS cohort on integrase inhibitors: safety and effectiveness. International Workshop on HIV Pediatrics 2019; July 19–20, 2021 (abstr 42).

39 Green H, Gibb DM, Walker AS, et al. Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS* 2007; **21:** 947–55.

40 Walmsley S, Baumgarten A, Berenguer J, et al. Brief report: dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. *J Acquir Immune Defic Syndr* 2015; **70:** 515–19.

41 Wijting I, Rokx C, Boucher C, et al. Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised non-inferiority trial. *Lancet HIV* 2017; **4:** e547–54.

42 Dziuban EJ, DeVos J, Ngeno B, et al. High prevalence of abacavir-associated L74V/I mutations in Kenyan children failing antiretroviral therapy. *Pediatr Infect Dis J* 2017; **36:** 758–60.