THE LANCET
Global Health

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Brenner IR, Flanagan CF, Penazzato M, et al. Cost-effectiveness of viral load testing for transitioning antiretroviral therapy-experienced children to dolutegravir in South Africa: a modelling analysis. *Lancet Glob Health* 2024; **12:** e2068–79.

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

Supplemental Appendix

Isaac Ravi Brenner, BA

et al.

Contents

Supplemental Methods

Cohort characteristics and starting regimens

Using the CEPAC-Pediatric model, we simulated a cohort of children known to have HIV from a user-specified age to death. In the base case, we assumed all children entering the model were 8 years old and currently prescribed abacavir-lamivudine-efavirenz in South Africa. We varied starting age in sensitivity analyses, examining children with HIV aged 2 and 5 years at model start. We simulated children aged 2 years at model start to have abacavir-lamivudine-ritonavir-boosted lopinavir as their starting regimen; in the no dolutegravir strategy, they transitioned to abacavir-lamivudine-efavirenz at 3 years.[1]

Some children aged 8 years may be on ritonavir-boosted lopinavir at time of transition,[1] however the regimen at the time of transition is unlikely to substantially impact current virologic suppression rates, rates of clinically significant nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) resistance, or subsequent response to dolutegravir. Children face similar probabilities of suppression, independent of being prescribed ritonavir-boosted lopinavir or efavirenz at model start.[2,3] Children experiencing virological failure on ritonavir-boosted lopinavir are less likely to develop NRTI resistance while waiting for a dolutegravir-based regimen than are children with virological failure on efavirenz.[4] The NADIA trial demonstrated noninferiority of dolutegravir when switching antiretroviral therapy regimens.[5,6] The clinical benefits of this strategy in children remain uncertain due to the use of efavirenz and ritonavir-boosted lopinavir as available options for children. To be conservative regarding the impact of initial suppression rates for dolutegravir and NRTI resistance, we chose efavirenz as the starting regimen in the base case. We used observational and trial data in children to inform our assumptions on initial suppression rates for dolutegravir,[7,8] however, we varied these inputs in sensitivity analyses to account for uncertainty regarding the impact of starting regimen and paediatric NRTI options.

Cost inputs

Antiretroviral therapy costs, found in manuscript Table 1 and Supplemental Table 1, varied by regimen, age, and weight, and were derived from the Clinton Health Access Initiative and World Health Organization weight-based dosing.[9,10] CD4 and viral load test costs were derived from a South African study.[11] We calculated HIV-related care costs by multiplying resources used by unit costs from published data sources.[12–15]

Overview of the CEPAC-Pediatric model

The CEPAC-Pediatric model is a Monte Carlo microsimulation model of HIV infection, diagnosis, and disease progression that runs on a monthly time cycle. Additional details regarding model structure, derivation of data about disease progression of untreated HIV, and model calibration and validation, are described in prior work.[16–21] For further details regarding the mathematical formulas used in the model, model flowcharts, and opportunities for collaboration, we direct readers to the CEPAC website: https://mpec.massgeneral.org/cepac-model/.

Model initiation and patient characteristics

Children enter the model at a user-specified age and are simulated until death; they undergo monthly transitions from one health state to another, reflecting the natural history of illness and

the impact of antiretroviral therapy on disease progression. At model start, children are randomly assigned to a health state drawn from distributions of HIV RNA and CD4 percentage (for children < 5 years old) and absolute CD4 count (for children aged 5 years and above).

In previous work, we validated the CEPAC-Pediatric model output for both untreated[16,21] and treated[19] children with HIV over time. Although CEPAC can generate validated cohort characteristics of children at age 8 when simulated from birth, these projections depend substantially on assumptions about availability and type of HIV testing and antiretroviral therapy in previous years, which are uncertain. For this analysis, we therefore chose to assign cohort characteristics of children on antiretroviral therapy at age 8 based on clinical data from the International epidemiology Databases to Evaluate AIDS (IeDEA) cohort and other cohorts.

Untreated HIV infection
Current age and CD4%/count in each month determine the risks of disease progression, including development of acute opportunistic infections (OIs) and death. Without effective antiretroviral therapy, CD4%/count declines monthly. The model tracks true CD4%/count and HIV viral load, although clinical decisions are made based on observed information, such as symptomatic illness or observed CD4%/count or viral loads.

Treated HIV infection
All children with HIV in this analysis are on antiretroviral therapy at model start. For each line of antiretroviral therapy, we specify "antiretroviral therapy efficacy," defined as the probability of suppressing HIV viral load to <400 copies/mL (c/mL) by 6 months. Children with suppressed viral load experience CD4%/count gains each month. Individuals who initially achieve virological suppression by 6 months then face a subsequent monthly risk of virological failure ("late failure"). Following virological failure, HIV viral load gradually rises to a "set point" that is determined as a function of HIV viral load at initial infection. After virological failure, there is a 12-month delay until CD4%/count begins to decline at pre-antiretroviral therapy rates, leading to increased monthly risks of OIs and death unless virologic suppression is achieved again. If children are observed to experience virological failure, they receive a one-time probability of resuppressing on the same line of antiretroviral therapy. If an HIV viral load test performed on two consecutive occasions over one year demonstrates an HIV viral load >1,000 c/mL, then the individual is switched to the next line of antiretroviral therapy.[22] We also incorporate a reduction in mortality and OI risks for individuals on antiretroviral therapy, independent of CD4 level and HIV RNA suppression.

Viral load and CD4 are modeled as continuous trajectories over time, reflecting disease progression in the absence of antiretroviral therapy and the response to sequential antiretroviral therapy regimens. Individual resistance mutations are not modeled, but the model incorporates the risk of acquiring or developing resistant virus through the impact of these events on the effectiveness of subsequent regimens (Figure 1, Table 1).

All children with HIV are modeled to undergo routine CD4 count and viral load monitoring, and subsequent adherence interventions or antiretroviral therapy regimen changes, consistent with South African guidelines.[1] Observed CD4%/count is measured every 12 months while the child is on antiretroviral therapy. Observed viral load is measured at month 6 and month 12 during the

first year on antiretroviral therapy, and then every 12 months thereafter. These time points are consistent with the guidelines from the Republic of South Africa Department of Health.[1]

Zidovudine-induced anaemia

All modeled children with confirmed viremia switch to zidovudine-lamivudine-dolutegravir in the viral load plus dolutegravir strategy. Published observational studies show a significant association between the use of zidovudine and anaemia in children.[23–27] We evaluated the clinical and cost impact of zidovudine-induced anaemia in a sensitivity analysis. We incorporated an increased monthly risk of virological failure (0.6%/month) for zidovudine-lamivudine-dolutegravir to account for anaemia-related complications and hospitalizations. This increased risk represents an overestimation of zidovudine-induced anaemia since some children who acquire anaemia may switch to another NRTI without incurring an additional risk of virological failure. Consistent with World Health Organization guidelines, we modeled haemoglobin testing at 6-month intervals for children on zidovudine-lamivudine-dolutegravir.[28] We derived the cost of haemoglobin testing based on existing literature regarding laboratory haemoglobin testing costs, result return to patient costs, and facility/overhead costs.[29–32] To be conservative with respect to the potential cost-effectiveness of the viral load plus dolutegravir strategy, we used a cost of $3/month for haemoglobin testing for children on zidovudine-lamivudine-dolutegravir. See Table 3 in the manuscript for results.

Additional multivariate sensitivity analyses

We conducted both univariate sensitivity analyses, varying individual model parameters, and multivariate sensitivity analyses, in which we simultaneously varied combinations of parameters that were influential in univariate analyses.

To better understand the impact of dolutegravir-based regimens on children with HIV with viraemia, we simultaneously varied: 1) 24-week virologic suppression for zidovudine-lamivudine-dolutegravir for those with virological failure and resistance (60-90%, base case: 90%) and 2) the monthly late-failure risk beginning 24 weeks after switch to abacavir-lamivudine-dolutegravir in the dolutegravir strategy for all children with virological failure (0.2-0.6%, base case: 0.2%).

We chose not to model a strategy where all children switch to zidovudine-lamivudine-dolutegravir without a viral load test, as this would be clinically inferior to the other strategies and is not consistent with current guidelines.

Supplemental Table 1. Extended model input parameters

Parameter	Base-case value	Range	Reference
Baseline cohort characteristics			
Initial CD4 count, cells/μL			
Virological suppression, mean (SD)	689 (229)		[33]
Virological failure, mean (SD)	563 (266)		[33]
Initial CD4%			
Virological suppression, mean (SD)	38 (7.40)		[34,35]
Virological failure, mean (SD)	20 (8.92)		[34,35]
Antiretroviral therapy inputs			
24-week suppression, PI-based regimen, %	82		[36,37]
Post-24-week failure, monthly risk, %			
Abacavir-lamivudine-ritonavir-boosted lopinavir	0·9		[3,38,39]
Abacavir-lamivudine-efavirenz	0·7		[37]
Abacavir-lamivudine-dolutegravir	0·2		[40,41]
Zidovudine-lamivudine-dolutegravir	0·2	0·2-0·6	[5,42–45]
Tenofovir disoproxil-lamivudine-dolutegravir	0·2		[41,46–50]
Protease-inhibitor-based regimen	0·7	0·7-0·9	[37]
Costs, 2020 US$			
CD4 test	7		[11]
Viral load test	25	0·5x-2x	[11]
Monthly costs, 2020 US$			
Routine HIV care*	20·00-155·00		[12–15]
Abacavir-lamivudine-ritonavir-boosted lopinavir	18·00		[9]
Abacavir-lamivudine-efavirenz†	11·00-12·00		[9]
Abacavir-lamivudine-dolutegravir†	12·00-13·00	0·5x-2x	[9]
Zidovudine-lamivudine-dolutegravir†	8·00-9·00	0·5x-2x	[9]
Tenofovir disoproxil-lamivudine-dolutegravir	5·00		[9]
Protease-inhibitor-based regimen†	19·00-24·00		[9]

[*] Range by CD4; [†] Range by age.

SD: Standard deviation.

Supplemental Table 2. Scenario analysis: All children with HIV in the no dolutegravir strategy are eligible for tenofovir disoproxil-lamivudine-dolutegravir as a salvage regimen

Strategy	LE, y (Undisc)	Costs, USD (Undisc)	LE, y (Discounted)	Costs, USD (Discounted)	ICER ($/LYS)
Viral load plus dolutegravir	39·72	24,600	21·24	12,610	*Comparator*†
Dolutegravir	39·62	24,650	21·21	12,660	Less effective, more expensive
No dolutegravir	39·59	25,840	21·20	13,310	Less effective, more expensive

Strategies are arranged by increasing discounted costs. Undiscounted and discounted life expectancies are rounded to the nearest hundredth. Costs are rounded to the nearest tenth and are presented in 2020 USD. Discounted values are discounted at 3% per year. Incremental cost-effectiveness ratios (ICERs) are calculated using unrounded discounted life expectancy and discounted costs. The preferred strategy was the strategy that was the most 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 ($2,828/LYS) when compared to the next strategy.

ICER: incremental cost-effectiveness ratio; **LE:** life expectancy; **LYS:** life-years saved; **Undisc:** undiscounted; **USD:** US dollars; **viral load:** viral load; **y:** years.

† Indicates the preferred strategy.

Supplemental Table 3. Sensitivity analysis: Viral load test result-return time

Viral load test result-return time value	Strategy	LE, y (Undisc)	Costs, USD (Undisc)	LE, y (Discounted)	Costs, USD (Discounted)	ICER ($/LYS)
0 months	*Viral load plus dolutegravir*	39·69	24,610	21·23	12,610	*Comparator*†
	Dolutegravir	39·62	24,650	21·21	12,660	Less effective, more expensive
	No dolutegravir	34·49	26,480	19·82	14,300	Less effective, more expensive
1 month	*Viral load plus dolutegravir*	39·69	24,610	21·23	12,610	*Comparator*†
	Dolutegravir	39·62	24,650	21·21	12,660	Less effective, more expensive
	No dolutegravir	34·49	26,480	19·82	14,300	Less effective, more expensive
2 months	*Viral load plus dolutegravir*	39·71	24,610	21·23	12,610	*Comparator*†
	Dolutegravir	39·62	24,650	21·21	12,660	Less effective, more expensive
	No dolutegravir	34·49	26,480	19·82	14,300	Less effective, more expensive

Supplemental Table 3. Sensitivity analysis: Viral load test result-return time (cont.)

Viral load test result-return time value	Strategy	LE, y (Undisc)	Costs, USD (Undisc)	LE, y (Discounted)	Costs, USD (Discounted)	ICER ($/LYS)
3 months (base case)	*Viral load plus dolutegravir*	39·71	24,600	21·23	12,610	*Comparator*†
	Dolutegravir	39·62	24,650	21·21	12,660	Less effective, more expensive
	No dolutegravir	34·49	26,480	19·82	14,300	Less effective, more expensive
4 months	*Viral load plus dolutegravir*	39·70	24,600	21·23	12,610	*Comparator*†
	Dolutegravir	39·62	24,650	21·21	12,660	Less effective, more expensive
	No dolutegravir	34·49	26,480	19·82	14,300	Less effective, more expensive
5 months	*Viral load plus dolutegravir*	39·72	24,640	21·23	12,630	*Comparator*†
	Dolutegravir	39·62	24,650	21·21	12,660	Less effective, more expensive
	No dolutegravir	34·49	26,480	19·82	14,300	Less effective, more expensive

Supplemental Table 3. Sensitivity analysis: Viral load test result-return time (cont.)

Viral load test result-return time value	Strategy	LE, y (Undisc)	Costs, USD (Undisc)	LE, y (Discounted)	Costs, USD (Discounted)	ICER ($/LYS)
6 months	*Viral load plus dolutegravir*	39·74	24,650	21·24	12,640	*Comparator*†
	Dolutegravir	39·62	24,650	21·21	12,660	Less effective, more expensive
	No dolutegravir	34·49	26,480	19·82	14,300	Less effective, more expensive

Strategies are arranged by increasing discounted costs. Undiscounted and discounted life expectancies are rounded to the nearest hundredth. Costs are rounded to the nearest tenth and are presented in 2020 USD. Discounted values are discounted at 3% per year. Incremental cost-effectiveness ratios (ICERs) are calculated using unrounded discounted life expectancy and discounted costs. The preferred strategy was the strategy that was the most 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 ($2,828/LYS) when compared to the next strategy.

ICER: incremental cost-effectiveness ratio; **LE:** life expectancy; **LYS:** life-years saved; **Undisc:** undiscounted; **USD:** US dollars; **y:** years.

† Indicates the preferred strategy.

Supplemental Table 4. Sensitivity analysis: Viral load test costs

Sensitivity analysis	Strategy	LE, y (Undisc)	Costs, USD (Undisc)	LE, y (Discounted)	Costs, USD (Discounted)	ICER ($/LYS)
0·5x viral load test cost	*Viral load plus dolutegravir*	39·72	24,570	21·24	12,580	*Comparator*†
	Dolutegravir	39·62	24,650	21·21	12,660	Less effective, more expensive
	No dolutegravir	34·49	26,480	19·82	14,300	Less effective, more expensive
2x viral load test cost	*Viral load plus dolutegravir*	39·72	24,630	21·24	12,630	*Comparator*†
	Dolutegravir	39·62	24,650	21·21	12,660	Less effective, more expensive
	No dolutegravir	34·49	26,480	19·82	14,300	Less effective, more expensive

Strategies are arranged by increasing discounted costs. Undiscounted and discounted life expectancies are rounded to the nearest hundredth. Costs are rounded to the nearest tenth and are presented in 2020 USD. Discounted values are discounted at 3% per year. Incremental cost-effectiveness ratios (ICERs) are calculated using unrounded discounted life expectancy and discounted costs. The preferred strategy was the strategy that was the most 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 ($2,828/LYS) when compared to the next strategy.

ICER: incremental cost-effectiveness ratio; **LE:** life expectancy; **LYS:** life-years saved; **Undisc:** undiscounted; **USD:** US dollars; **y:** years.

† Indicates the preferred strategy.

Supplemental Table 5. Sensitivity analysis: Antiretroviral therapy costs

Sensitivity analysis	Strategy	LE, y (Undisc)	Costs, USD (Undisc)	LE, y (Discounted)	Costs, USD (Discounted)	ICER ($/LYS)
0·5x 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	1,570[†]
	No dolutegravir	34·49	26,480	19·82	14,300	Less effective, more expensive
2x abacavir-lamivudine-dolutegravir cost	*Viral load plus dolutegravir*	39·72	25,060	21·24	13,030	*Comparator*[†]
	Dolutegravir	39·62	25,320	21·21	13,280	Less effective, more expensive
	No dolutegravir	34·49	26,480	19·82	14,300	Less effective, more expensive
0·5x zidovudine-lamivudine-dolutegravir cost	*Viral load plus dolutegravir*	39·72	24,540	21·24	12,550	*Comparator*[†]
	Dolutegravir	39·62	24,650	21·21	12,660	Less effective, more expensive
	No dolutegravir	34·49	26,480	19·82	14,300	Less effective, more expensive

Supplemental Table 5. Sensitivity analysis: Antiretroviral therapy costs (cont.)

Sensitivity analysis	Strategy	LE, y (Undisc)	Costs, USD (Undisc)	LE, y (Discounted)	Costs, USD (Discounted)	ICER ($/LYS)
2x 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	1,942†
	No dolutegravir	34·49	26,480	19·82	14,300	Less effective, more expensive

Strategies are arranged by increasing discounted costs. Undiscounted and discounted life expectancies are rounded to the nearest hundredth. Costs are rounded to the nearest tenth and are presented in 2020 USD. Discounted values are discounted at 3% per year. Incremental cost-effectiveness ratios (ICERs) are rounded to the nearest dollar and are calculated using unrounded discounted life expectancy and discounted costs. The preferred strategy was the strategy that was the most 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 ($2,828/LYS) when compared to the next strategy.

ICER: incremental cost-effectiveness ratio; **LE:** life expectancy; **LYS:** life-years saved; **TLD**: tenofovir; **Undisc:** undiscounted; **USD:** US dollars; **y:** years.

† Indicates the preferred strategy.

Supplemental Table 6. Sensitivity analysis: Age at time of dolutegravir transition

Age	Strategy	LE, y (Undisc)	Costs, USD (Undisc)	LE, y (Discounted)	Costs, USD (Discounted)	ICER ($/LYS)
2 years	*Dolutegravir*	31·06	25,880	18·29	14,410	*Comparator*
	Viral load plus dolutegravir	31·17	25,930	18·31	14,430	1,150[†]
	No dolutegravir	23·31	22,930	15·36	14,460	Less effective, more expensive
5 years	*Viral load plus dolutegravir*	40·92	25,680	21·54	13,020	*Comparator*[†]
	Dolutegravir	40·79	25,740	21·50	13,090	Less effective, more expensive
	No dolutegravir	35·21	27,190	20·05	14,550	Less effective, more expensive

Strategies are arranged by increasing discounted costs. Undiscounted and discounted life expectancies are rounded to the nearest hundredth. Costs are rounded to the nearest tenth and are presented in 2020 USD. Discounted values are discounted at 3% per year. Incremental cost-effectiveness ratios (ICERs) are rounded to the nearest dollar and are calculated using unrounded discounted life expectancy and discounted costs. The preferred strategy was the strategy that was the most 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 ($2,828/LYS) when compared to the next strategy.

ICER: incremental cost-effectiveness ratio; **LE:** life expectancy; **LYS:** life-years saved; **Undisc:** undiscounted; **USD:** US dollars; **y:** years.

[†] Indicates the preferred strategy.

Supplemental Figure Legends

Supplemental Figure 1. Bar graph depicting per-person cumulative costs in the base case, by strategy. Costs include direct medical costs (i.e., non-HIV-related healthcare costs, depicted in light blue), routine HIV-related care costs (ranging by CD4 from $20-155/month, depicted in orange), CD4 test costs ($7/test, conducted once yearly while the child is on antiretroviral therapy, depicted in gray), viral load test costs ($25/test, conducted at month 6 and month 12 during the first modeled year, and then every 12 months thereafter, depicted in gold), efavirenz-based antiretroviral therapy costs (ranging by age from $11-12/month, depicted in maroon), dolutegravir-based antiretroviral therapy costs (ranging by age from $5-13/month, depicted in green), and PI-based antiretroviral therapy costs (ranging by age from $19-24/month). The no dolutegravir strategy (on the left) had the highest overall per-person cumulative costs at $26,480. The per-person cumulative costs were very close for the dolutegravir strategy (in the middle) at $24,650 and the viral load plus dolutegravir strategy (on the right) at $24,600. For all strategies, routine HIV-related care costs and direct medical costs comprised the majority component costs, with similar total costs for each component across strategies. After that, the highest component cost was protease-inhibitor-based antiretroviral therapy, ranging from $6,534 total in the no dolutegravir strategy, $3,539 in the dolutegravir strategy, and $3,491 in the viral load plus dolutegravir strategy.

Abbreviations: ART: antiretroviral therapy; DTG: dolutegravir; EFV: efavirenz; PI: protease inhibitor; VL: viral load.

Supplemental Figure 2. Bar graph depicting average per-person time spent on each regimen, by strategy. Time spent (in years) on efavirenz-based antiretroviral therapy is depicted in blue, time spent on dolutegravir-based antiretroviral therapy is depicted in orange, time spent on protease inhibitor-based antiretroviral therapy depicted in gray, and time spent lost to follow-up is depicted in gold. Individuals in the viral load plus dolutegravir (top) and dolutegravir (middle) strategies spent the most time on dolutegravir-based antiretroviral therapy (22.00 years). In the no dolutegravir strategy (bottom), individuals spent the most time on protease inhibitor-based antiretroviral therapy (22.53 years). Overall time is higher in the viral load plus dolutegravir and dolutegravir strategies, reflecting the longer life expectancy of individuals modeled within those strategies.

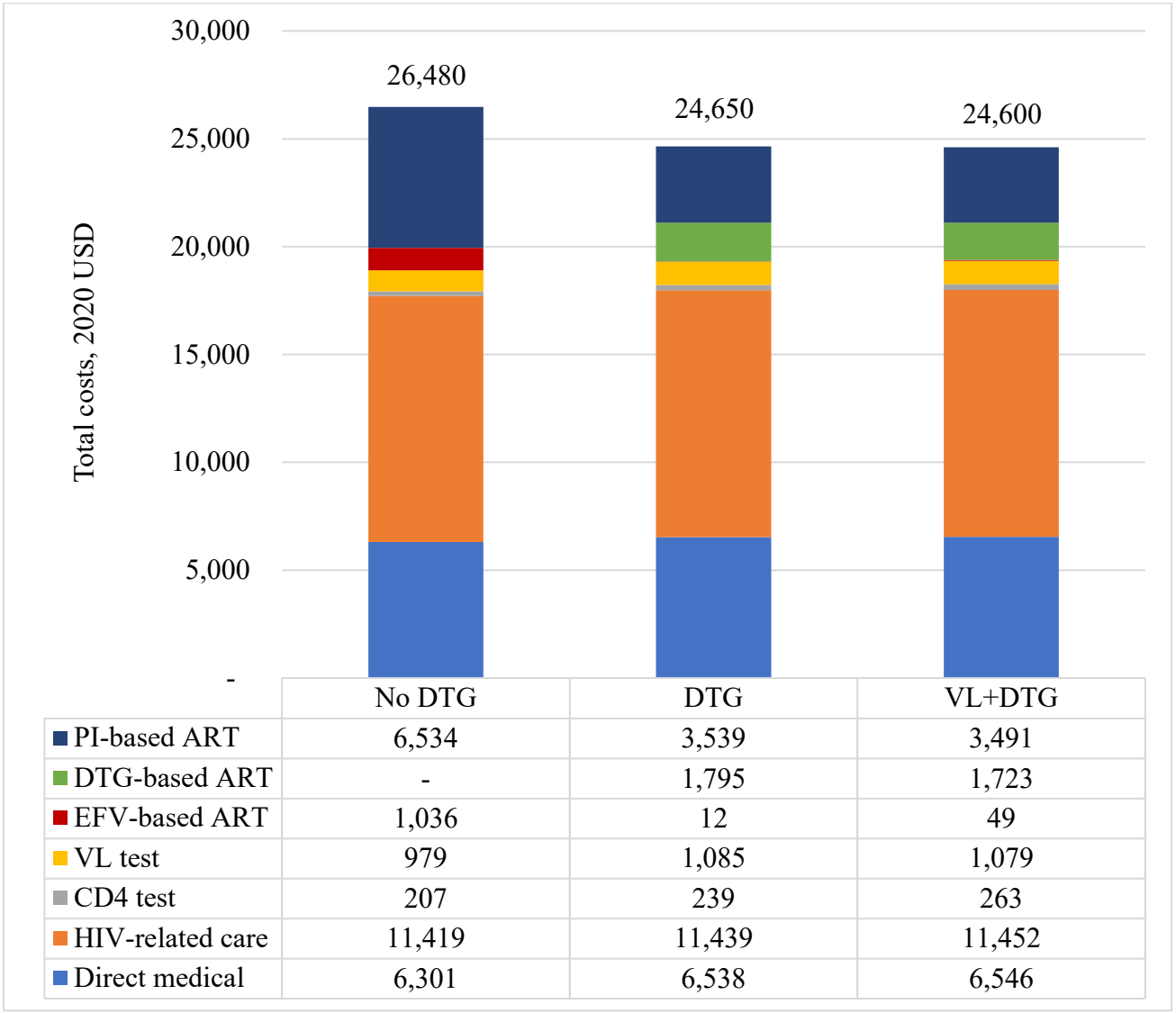
Abbreviations: ART: antiretroviral therapy; DTG: dolutegravir; EFV: efavirenz; LTFU: lost to follow-up; PI: protease inhibitor; VL: viral load.

Supplemental Figure 3. Multivariate sensitivity analysis: Variation in both 24-week virologic suppression on zidovudine-lamivudine-dolutegravir (for children with HIV with virological failure due to resistance on initial regimen) and monthly late-failure risk for those on abacavir-lamivudine-dolutegravir (for children with HIV with virological failure, regardless of resistance, on initial regimen). Results for base-case costs are shown in Panel A. We simulated scenarios in which abacavir-lamivudine-dolutegravir is half the cost of the base case (Panel B) and zidovudine-lamivudine-dolutegravir is double the cost of the base case (Panel C) to model scenarios in which paediatric zidovudine is no longer less expensive than abacavir. For all panels, blue solid cells denote combinations of

parameters where the dolutegravir strategy is cost-effective (ICER <$2,828/life-year saved) compared to the viral load plus dolutegravir strategy, yellow solid cells denote combinations of parameters where the viral load plus dolutegravir strategy is cost-effective compared to the dolutegravir strategy, blue hashed cells show combinations where the viral load plus dolutegravir strategy is more clinically effective than dolutegravir but is not cost-effective (ICER ≥$2,828/life-year saved), making dolutegravir the economically preferred strategy, and yellow hashed cells show combinations where the dolutegravir strategy is more clinically effective than the viral load plus dolutegravir strategy but is not cost-effective (ICER ≥$2,828/life-year saved), making the viral load plus dolutegravir strategy the economically preferred strategy. The vertical axis shows values of 24-week virologic suppression on zidovudine-lamivudine-dolutegravir for children with HIV with virologic resistance. The base-case value is 90%, and the corresponding value for abacavir-lamivudine-dolutegravir (in the viral load plus dolutegravir strategy) is held constant at 85%. The horizontal axis shows values of monthly late-failure risk on abacavir-lamivudine-dolutegravir. The base-case value is 0.2%/month, and the corresponding value for zidovudine-lamivudine-dolutegravir is held constant at 0.2%/month. As 24-week virologic suppression for zidovudine-lamivudine-dolutegravir decreases (moving down within each column), the dolutegravir strategy becomes preferred to the viral load plus dolutegravir strategy for explored late-failure risks <0.4%/month. As late-failure risk increases (moving left-to-right across the figure), the viral load plus dolutegravir strategy becomes preferred to dolutegravir. Even as abacavir became less costly (Panel B) and zidovudine more costly (Panel C), the viral load plus dolutegravir strategy remained the preferred strategy for the base-case values of 24-week suppression on zidovudine and late failure on abacavir.

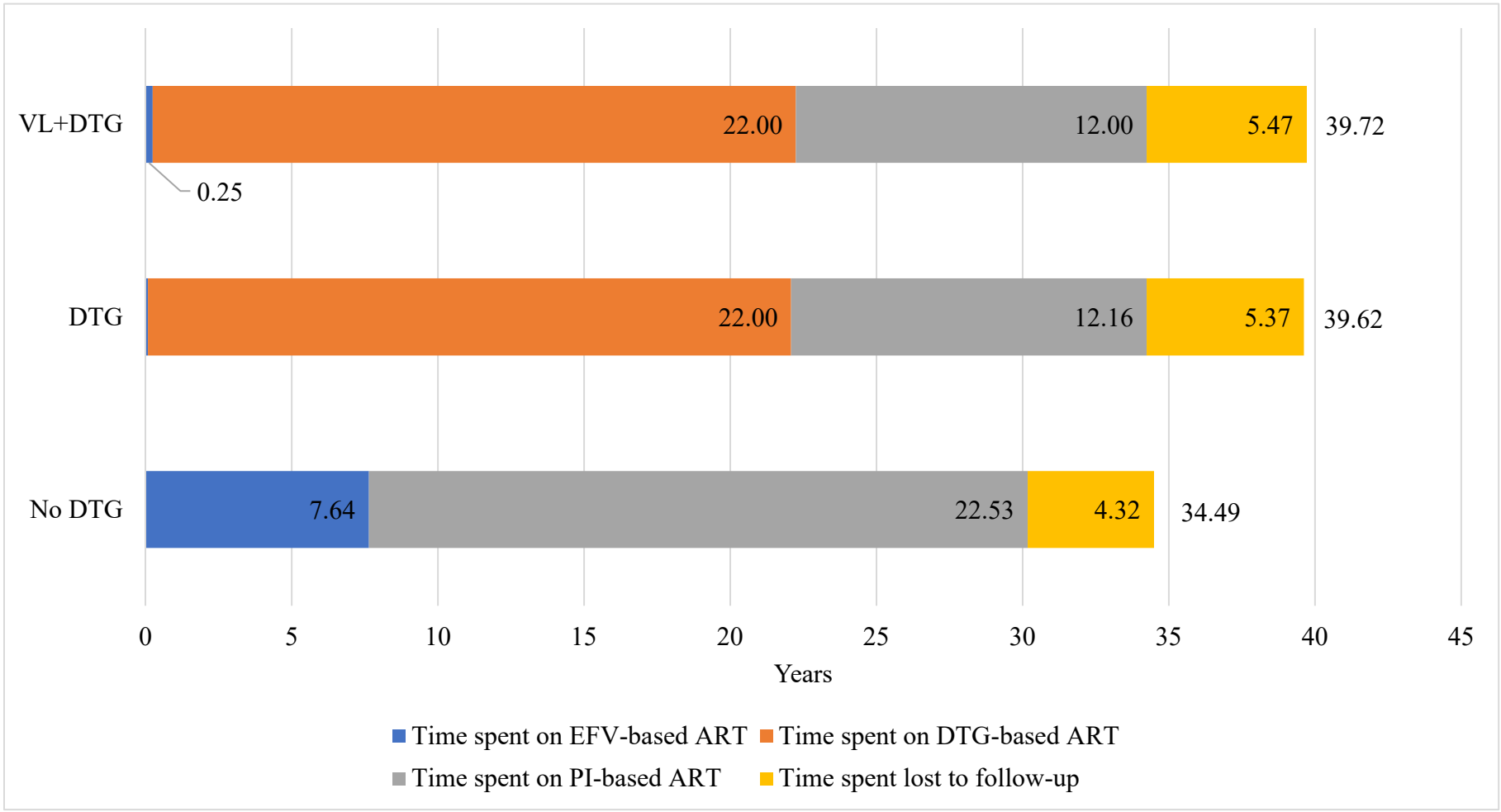
Abbreviations: 3TC: lamivudine; ABC: abacavir; CE: cost-effective; CWH: children with HIV; dolutegravir: dolutegravir; ICER: incremental cost-effectiveness ratio; LYS: life-years saved; VL: viral load; ZDV: zidovudine.

Supplemental Figure 1. Per-person cumulative costs

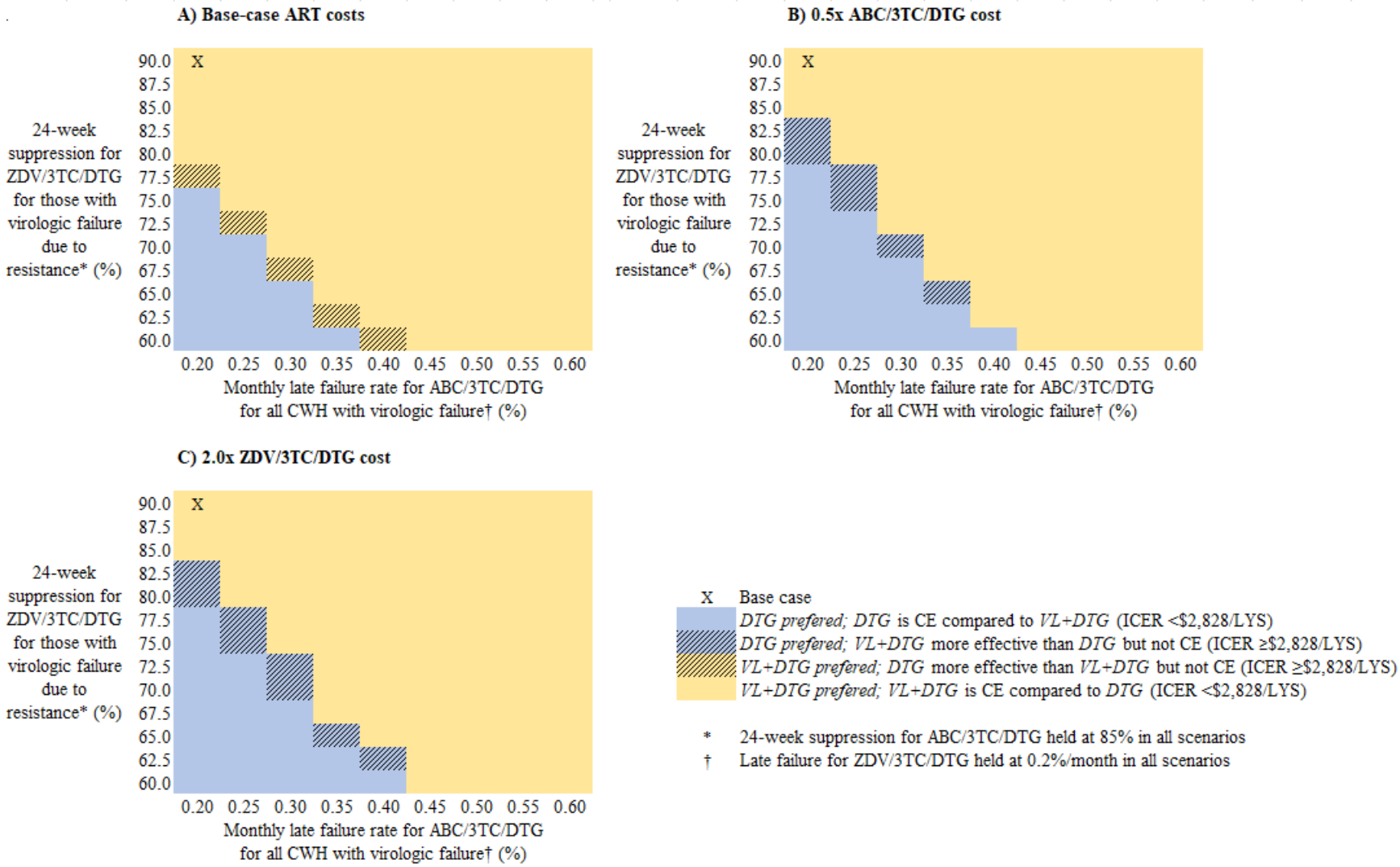


	No DTG	DTG	VL+DTG
PI-based ART	6,534	3,539	3,491
DTG-based ART	-	1,795	1,723
EFV-based ART	1,036	12	49
VL test	979	1,085	1,079
CD4 test	207	239	263
HIV-related care	11,419	11,439	11,452
Direct medical	6,301	6,538	6,546

Supplemental Figure 2. Time spent on each regimen, by strategy



Supplemental Figure 3. Variation in both 24-week virologic suppression on zidovudine-lamivudine-dolutegravir for those with virological failure due to resistance and monthly late-failure risk for all children with HIV with virological failure on abacavir-lamivudine-dolutegravir


A) Base-case ART costs
B) 0.5x ABC/3TC/DTG cost
C) 2.0x ZDV/3TC/DTG cost
24-week suppression for ZDV/3TC/DTG for those with virologic failure due to resistance* (%)
90.0
87.5
85.0
82.5
80.0
77.5
75.0
72.5
70.0
67.5
65.0
62.5
60.0
X
0.20 0.25 0.30 0.35 0.40 0.45 0.50 0.55 0.60
Monthly late failure rate for ABC/3TC/DTG for all CWH with virologic failure† (%)
X Base case
DTG prefered; DTG is CE compared to VL+DTG (ICER <$2,828/LYS)
DTG prefered; VL+DTG more effective than DTG but not CE (ICER ≥$2,828/LYS)
VL+DTG prefered; DTG more effective than VL+DTG but not CE (ICER ≥$2,828/LYS)
VL+DTG prefered; VL+DTG is CE compared to DTG (ICER <$2,828/LYS)
* 24-week suppression for ABC/3TC/DTG held at 85% in all scenarios
† Late failure for ZDV/3TC/DTG held at 0.2%/month in all scenarios

References

1 Republic of South Africa National Department of Health. National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents, and adults. 2015.

2 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.

3 PENPACT-1 (PENTA 9/PACTG 390) Study Team, Babiker A, Castro nee Green H, *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.

4 Hackett S, Teasdale CA, Pals S, *et al.* Drug resistance mutations among South African children living with HIV on WHO-recommended antiretroviral therapy regimens. *Clin Infect Dis* 2021; **73**: e2217–25.

5 Paton NI, Musaazi J, Kityo C, *et al.* Dolutegravir or darunavir in combination with zidovudine or tenofovir to treat HIV. *N Engl J Med* 2021; **385**: 330–41.

6 Paton N, Musaazi J, Kityo C, *et al.* Nucleosides and darunavir/dolutegravir in Africa (NADIA) trial: outcomes at 96 weeks. 2022; published online Feb. https://www.croiconference.org/abstract/nucleosides-and-darunavir-dolutegravir-in-africa-nadia-trial-outcomes-at-96-weeks/ (accessed April 19, 2022).

7 Bacha J, Mayalla B, Jiwa N, Mwita L, Campbell L. The 'dolutegravirs' of dolutegravir for children and adolescents living with HIV (CALHIV): descriptions, trends and gaps of rolling out dolutegravir in CALHIV in Mbeya Tanzania. 2020. https://www.hivpaediatrics2020.com/session-recordings/abstract-session-1-paediatric-hiv-treatment-old-drugs-new-drugs/ (accessed Feb 25, 2021).

8 I.J. Collins, Crichton S, Turkova A, *et al.* Children and adolescents in the UK/ Ireland CHIPS cohort on integrase inhibitors: safety and effectiveness. 2019. https://academicmedicaleducation.com/meeting/international-workshop-hiv-paediatrics-2019/abstract/children-and-adolescents-uk-ireland (accessed April 4, 2022).

9 CHAI. 2018 HIV Market Report. CHAI, 2018 https://3cdmh310dov3470e6x160esb-wpengine.netdna-ssl.com/wp-content/uploads/2018/09/2018-HIV-Market-Report_FINAL.pdf (accessed Jan 11, 2021).

10 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.

11 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**. DOI:10.1371/journal.pone.0223669.

12 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. Cotrimo-CI Study Group. *Lancet Lond Engl* 1999; **353**: 1463–8.

13 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 1999* 2006; **42**: 464–9.

14 Massyn N, Barron P, Day C, Padarath A. District health barometer 2018/19. Durban, South Africa: Health Systems Trust, 2020. https://www.hst.org.za:443/publications/Pages/DISTRICT-HEALTH-BAROMETER-201819.aspx (accessed Oct 11, 2022).

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

16 Ciaranello AL, Morris BL, Walensky RP, *et al.* Validation and calibration of a computer simulation model of paediatric HIV infection. *PLoS ONE* 2013; **8**. DOI:10.1371/journal.pone.0083389.

17 Ciaranello A, Lu Z, Ayaya S, *et al.* Incidence of WHO stage 3 and 4 events, tuberculosis, and mortality in untreated, HIV-infected children enrolling in care before 1 year of age: an IeDEA (International Epidemiologic Databases to Evaluate Aids) East Africa regional analysis. *Pediatr Infect Dis J* 2014; **33**: 623–9.

18 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. *JAIDS J Acquir Immune Defic Syndr* 2006; **42**: 464–9.

19 Ciaranello AL, Doherty K, Penazzato M, *et al.* Cost-effectiveness of first-line antiretroviral therapy for HIV-infected African children less than 3 years of age. *AIDS Lond Engl* 2015; **29**: 1247–59.

20 Frank SC, Cohn J, Dunning L, *et al.* Clinical effect and cost-effectiveness of incorporation of point-of-care assays into early infant HIV diagnosis programmes in Zimbabwe: a modelling study. *Lancet HIV* 2019; **6**: e182–90.

21 McCann NC, Cohn J, Flanagan C, *et al.* Strengthening existing laboratory-based systems vs. investing in point-of-care assays for early infant diagnosis of HIV: a model-based cost-effectiveness analysis. *J Acquir Immune Defic Syndr 1999* 2020; **84 Suppl 1**: S12–21.

22 WHO. Updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring. 2021 https://www.who.int/publications-detail-redirect/9789240022232 (accessed Dec 7, 2022).

23 Shet A, Arumugam K, Rajagopalan N, *et al.* The prevalence and etiology of anaemia among HIV-infected children in India. *Eur J Pediatr* 2012; **171**: 531–40.

24 Renner LA, Dicko F, Kouéta F, *et al.* Anaemia and zidovudine-containing antiretroviral therapy in paediatric antiretroviral programmes in the IeDEA Paediatric West African Database to evaluate AIDS. *J Int AIDS Soc* 2013; **16**: 18024.

25 Teklemariam Z, Mitiku H, Mesfin F. Prevalence of anaemia and nutritional status among HIV-positive children receiving antiretroviral therapy in Harar, eastern Ethiopa. *HIVAIDS - Res Palliat Care* 2015; **7**: 191–6.

26 Techane MA, Anlay DZ, Tesfaye E, Agegnehu CD. Incidence and predictors of anaemia among children on antiretroviral therapy at the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia, 2007-2017: A retrospective follow-up study. *HIVAIDS - Res Palliat Care* 2020; **12**: 951–62.

27 Ejeliogu E, Oguche S, Ebonyi A, SE O. Zidovudine-induced anaemia in Human Immunodeficiency Virus infected children on Highly Active Anti-Retroviral Therapy in Jos, Nigeria. *J Adv Med Pharm Sci* 2014; **1**: 1–10.

28 World Health Organization. Surveillance of antiretroviral toxicity: global HIV, hepatitis and STIs programme: what's new in person-centred HIV patient and antiretroviral drug toxicity monitoring: technical brief. World Health Organization, 2020 https://apps.who.int/iris/handle/10665/333000 (accessed Dec 13, 2022).

29 Amukele TK, Jones R, Elbireer A. Test cost and test accuracy in clinical laboratories in Kampala, Uganda. *Am J Clin Pathol* 2018; **149**: 522–9.

30 Bassett IV, Giddy J, Nkera J, *et al.* Routine voluntary HIV testing in Durban, South Africa: the experience from an outpatient department. *J Acquir Immune Defic Syndr* 2007; **46**: 181–6.

31 Cunnama L, Abrams EJ, Myer L, *et al.* Provider- and patient-level costs associated with providing antiretroviral therapy during the postpartum phase to women living with HIV in South Africa: A cost comparison of three postpartum models of care. *Trop Med Int Health* 2020; **25**: 1553–67.

32 Mvundura M, Lorenson K, Chweya A, *et al.* Estimating the costs of the vaccine supply chain and service delivery for selected districts in Kenya and Tanzania. *Vaccine* 2015; **33**: 2697–703.

33 Chhim K, Mburu G, Tuot S, *et al.* Factors associated with viral non-suppression among adolescents living with HIV in Cambodia: a cross-sectional study. *AIDS Res Ther* 2018; **15**. DOI:10.1186/s12981-018-0205-z.

34 Davies M-A, Moultrie H, Eley B, *et al.* Virologic failure and second-line antiretroviral therapy in children in South Africa - The IeDEA Southern Africa Collaboration. *J Acquir Immune Defic Syndr 1999* 2011; **56**: 270–8.

35 Kuhn L, Schramm DB, Shiau S, *et al.* Young age at start of antiretroviral therapy and negative HIV antibody results in HIV-infected children when suppressed. *AIDS Lond Engl* 2015; **29**: 1053–60.

36 Kadima J, Patterson E, Mburu M, *et al.* Adoption of routine virologic testing and predictors of virological failure among HIV-infected children on antiretroviral treatment in western Kenya. *PLoS ONE* 2018; **13**. DOI:10.1371/journal.pone.0200242.

37 Barth RE, van der Loeff MF, Schuurman R, Hoepelman AI, Wensing AM. Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review. *Lancet Infect Dis* 2010; **10**: 155–66.

38 Violari A, Lindsey JC, Hughes MD, *et al.* Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. *N Engl J Med* 2012; **366**: 2380–9.

39 Palumbo P, Lindsey JC, Hughes MD, *et al.* Antiretroviral treatment for children with peripartum nevirapine exposure. *N Engl J Med* 2010; **363**: 1510–20.

40 Walmsley SL, Antela A, Clumeck N, *et al.* Dolutegravir plus abacavir–lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013; **369**: 1807–18.

41 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 1999* 2015; **70**: 515–9.

42 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.

43 van Elsland SL, Peters RPH, Grobbelaar N, *et al.* Paediatric antiretroviral therapy adherence in South Africa: a comprehensive analysis. *AIDS Behav* 2019; **23**: 475–88.

44 Mulenga V, Musiime V, Kekitiinwa A, *et al.* Abacavir, zidovudine, or stavudine as paediatric tablets for African HIV-infected children (CHAPAS-3): an open-label, parallel-group, randomised controlled trial. *Lancet Infect Dis* 2016; **16**: 169–79.

45 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 Lond Engl* 2007; **21**: 947–55.

46 Raffi F, Rachlis A, Stellbrink H-J, *et al.* Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. *Lancet Lond Engl* 2013; **381**: 735–43.

47 Sax PE, Pozniak A, Montes ML, *et al.* Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet Lond Engl* 2017; **390**: 2073–82.

48 Gallant J, Lazzarin A, Mills A, *et al.* Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet Lond Engl* 2017; **390**: 2063–72.

49 Clotet B, Feinberg J, van Lunzen J, *et al.* Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet Lond Engl* 2014; **383**: 2222–31.

50 Orrell C, Hagins DP, Belonosova E, *et al.* Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. *Lancet HIV* 2017; **4**: e536–46.