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RESEARCH ARTICLE

Optimizing HIV retesting during pregnancy and postpartum in four countries: a cost-effectiveness analysis

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Abstract

Introduction: HIV retesting during late pregnancy and breastfeeding can help detect new maternal infections and prevent mother-to-child HIV transmission (MTCT), but the optimal timing and cost-effectiveness of maternal retesting remain uncertain.

Methods: We constructed deterministic models to assess the health and economic impact of maternal HIV retesting on a hypothetical population of pregnant women, following initial testing in pregnancy, on MTCT in four countries: South Africa and Kenya (high/intermediate HIV prevalence), and Colombia and Ukraine (low HIV prevalence). We evaluated six scenarios with varying retesting frequencies from late in antenatal care (ANC) through nine months postpartum. We compared strategies using incremental cost-effectiveness ratios (ICERs) over a 20-year time horizon using country-specific thresholds.

Results: We found maternal retesting once in late ANC with catch-up testing through six weeks postpartum was cost-effective in Kenya (ICER = $166 per DALY averted) and South Africa (ICER=$289 per DALY averted). This strategy prevented 19% (Kenya) and 12% (South Africa) of infant HIV infections. Adding one or two additional retests postpartum provided smaller benefits (1 to 2 percentage point increase in infections averted versus one retest). Adding three retests during the postpartum period averted additional infections (1 to 3 percentage point increase in infections averted versus one retest) but ICERs ($7639 and in Kenya and $11 985 in South Africa) greatly exceeded the cost-effectiveness thresholds. In Colombia and Ukraine, all retesting strategies exceeded the cost-effectiveness threshold and prevented few infant infections (up to 31 and 5 infections, respectively).

Conclusions: In high HIV burden settings with MTCT rates similar to those seen in Kenya and South Africa, HIV retesting once in late ANC, with subsequent intervention, is the most cost-effective strategy for preventing infant HIV infections. In these settings, two HIV retests postpartum marginally reduced MTCT and were less costly than adding three retests. Retesting in low-burden settings with MTCT rates similar to Colombia and Ukraine was not cost-effective at any time point due to very low HIV prevalence and limited breastfeeding.

Keywords: maternal HIV retesting; elimination of maternal-to-child HIV transmission; EMTCT; prevention of maternal-to-child HIV transmission; PMTCT; cost-effectiveness analysis; maternal and child health

Additional information may be found under the Supporting Information tab for this article.

1 | INTRODUCTION

Despite successful scale-up of prevention of mother-to-child HIV transmission (PMTCT) programmes, an estimated 160 000 children worldwide became infected with HIV in 2018, with approximately 30% of these infections attributable to incident maternal infections occurring after the first antenatal care (ANC) visit [1-4]. Compared to established infection, incident HIV infections acquired during pregnancy or postpartum increase the risk of mother-to-child HIV transmission (MTCT) nearly 10-fold, due to both high viral load and the missed opportunity to detect these infections (and implement interventions to prevent MTCT) if initial testing occurs prior to transmission or seroconversion [5]. Identifying

and treating maternal HIV infections is vital to achieving the UNAIDS 95-95-95 fast-track targets for achieving low HIV incidence by 2030 [6].

Universal HIV testing for pregnant women has been found to be highly cost-effective, even in very low HIV prevalence settings [7], and retesting during pregnancy and postpartum is a promising approach to reduce MTCT risk. The World Health Organization (WHO) has recommended retesting in the third trimester or during labour/delivery in high HIV prevalence settings since 2006, and retesting during breastfeeding since 2015 [8,9]. Despite the promise of maternal HIV retesting, health and economic impacts and optimal timing and frequency are not well-characterized [7,10]. Modelling analyses in Uganda, South Africa and India have found retesting in late pregnancy, at delivery, or very early in the postpartum period to be cost-effective [11-13]. However, recent scale-up of ART coverage and HIV prevention interventions limit the relevance of these analyses, and in light of evidence that women in high burden settings have high HIV risk throughout the postpartum period [14,15], postpartum retesting warrants investigation.

The HIV funding gap is projected to increase to US$7.2 billion below that needed to achieve 2030 fast-track targets [16]. As countries strive to achieve the elimination of MTCT (EMTCT), policymakers must allocate limited resources efficiently. To provide guidance to countries deciding whether to implement maternal retesting, and if so the optimal frequency and time(s) to retest, we assessed the cost-effectiveness of various strategies of HIV retesting during pregnancy, labour/delivery and postpartum in four countries representing a range of national HIV prevalence.

2 | METHODS

2.1 | Model structure and retesting strategies

We constructed a deterministic state-transition model using Excel (Microsoft Corporation, Redmond, WA, USA) to reflect HIV disease progression, HIV testing and treatment during pregnancy and postpartum (54 total states: 6 maternal HIV stages stratified on 9 antenatal and postpartum periods) (Appendices S1 and S2). We chose to model four countries (South Africa, Kenya, Colombia and Ukraine) with varying geography and HIV prevalence and adequate data availability. Countries were classified based on WHO criteria as having high (>15%, South Africa), intermediate (5% to 15%, Kenya) and low national HIV prevalence (<5%, Colombia and Ukraine) [7]. We modelled the annual number of pregnant women in each country (or number of births as a proxy) and used weekly time steps from the start of pregnancy to 12 months postpartum. Infant disability-adjusted life years (DALYs) and treatment costs were estimated over a 20-year time horizon. We did not model infants explicitly; all cost and health events occurring after infant infection were estimated from model outputs. We evaluated six retesting scenarios varying the number and timing of retests (Table 1). We selected retest timing based on routine maternal and child health (MCH) visits/immunization schedules and country policies [10]. Current guidelines for retesting are as follows: South Africa – each ANC visit, labour and delivery and every three months while breastfeeding [17]; Kenya – third trimester, labour and

Table 1. Maternal HIV retesting scenarios

Scenario	Late ANC with catch-up testing at delivery and 6 weeks postpartum	14 weeks	6 months (mid)	9 months (late)
1				
2	✔			
3	✔	✔		
4	✔		✔	
5	✔			✔
6	✔		✔	✔
7	✔	✔	✔	✔

Cells containing a ✔ denote a visit where retesting is offered. ANC, antenatal care visit. Catch-up testing refers to testing at delivery for those who did not test in late ANC, and testing at six weeks postpartum for those who did not test at late ANC or delivery.

delivery, six weeks and six months postpartum [18]; Ukraine – during pregnancy and labour and delivery only if high risk or unknown status [19]; Colombia – second and third trimester and labour and delivery [20]. We defined "late ANC" based on each country's ANC visit schedule, median gestational age at ANC initiation and recommended HIV retesting interval. Late ANC corresponds to a gestational age in the third trimester in Kenya and South Africa and late second trimester in Colombia and Ukraine (Table 2a).

2.2 | Model assumptions and parameterization

Model parameters (Table 2a; Appendix S3) were derived from published literature (through April 2020), expert opinion, or assumptions if data were not available. As our model simulates a hypothetical population not corresponding to a specific year, for all parameters we used the most up-to-date value available. HIV testing in our model requires visit attendance, tests in stock, test acceptance and receipt of results. In the base case scenario, HIV testing is offered only once at the first ANC, which is assumed to occur at a country-specific gestational age. To reflect a setting in which retesting at delivery or six weeks postpartum would only occur if women had not retested previously, we modelled catch-up retesting at delivery to be conditional on the probability of not retesting at late pregnancy, and retesting at six weeks postpartum to be conditional on the probability of not retesting in late ANC or delivery.

We assumed no retesting between visits, no viral suppression during recent (acute) infection, no repeat or multiple pregnancies and no foetal losses. We assumed all women diagnosed HIV-positive were ART eligible [21] and based ART initiation and viral suppression rates on country-specific estimates. We assumed a constant weekly risk of ART discontinuation resulting in 74% retention by one year postpartum [22]. MTCT depended on pregnancy/postpartum period; maternal disease stage, use of ART and viral load suppression; infant use of antiretroviral prophylaxis (ARVs); and breastfeeding practices (Appendix S3). Infant HIV testing was only reflected in the probability an infected infant received ART,

Table 2a. Model parameters

Parameter	Kenya	South Africa	Colombia	Ukraine
Population of pregnant women	1 631 479 [41]	1 100 699 [42]	346 409[b]	363 946 [19]
HIV risk				
HIV prevalence among pregnant women	6.1% [43]	31% [44]	0.4% [45]	0.7% [46]
Maternal HIV incidence rate (per person-week)				
Prior to first ANC during pregnancy	0.000331 [47]	0.000227 [15]	0.00001	0.000002 [48]
Between first ANC and delivery	0.000331 [47]	0.000739 [15]	0.00002[a]	0.000004 [48]
Delivery to 6 weeks postpartum	0[a]	0[a]	0[a]	0[a]
6 weeks to 12 months postpartum	0.000269 [47]	0.0009 [15]	0.000023[a]	0.000003 [48]
Duration of acute maternal HIV infection (weeks)	9[a]	9[a]	9[a]	9[a]
HIV testing and prevention				
Test kit stock out	5%[a]	5%[a]	0%[a]	0%[a]
Test acceptance	84% [49]	98% [50]	89%[b]	97% [19]
Receive test results	98% [51]	98% [52]	100%[a]	100%[a]
HIV test sensitivity in early infection	67%[a]	67%[a]	67%[a]	67%[a]
HIV test sensitivity in chronic infection	100% [53]	100% [53]	100% [53]	100% [53]
HIV test specificity	98.9% [53]	98.9% [53]	98.9% [53]	98.9%[53]
MTCT rate per week, acute maternal infection	0.005 to 0.029 [54-58]	0.005 to 0.029 [54-58]	0.005 to 0.029 [54-58]	0.005 to 0.029 [54-58]
MTCT rate per week, chronic maternal infection	0.0005 to 0.023 [54-58]	0.0005 to 0.023 [54-58]	0.0005 to 0.023 [54-58]	0.0005 to 0.023 [54-58]
Maternal PrEP use	0%[a]	0%[a]	0%[a]	0%[a]
Health care visits				
Attend first ANC	96% [59]	94% [52]	97%[b]	99% [18]
Attend late ANC	93% [59]	78% [52]	88%[b]	90%[a]
Facility delivery	62% [59]	96% [52]	99%[b]	99% [60]
Attend postnatal MCH visits				
6 weeks	96% [59]	90%[b]	92% [61]	99%[a]
14 weeks	88% [59]	73%[b]	87% [61]	93%[a]
6 months	87% [59]	86%[b]	90% [61]	96%[a]
9 months	85% [59]	62%[b]	89% [61]	95%[a]
First ANC (gestational age in weeks)	22 [23]	18[b]	15[b]	10[a]
Late ANC (gestational age in weeks)	33[a]	36[a]	24[a]	28[a]
Delivery (gestational age in weeks)	39[a]	39[a]	39[a]	39[a]
Early postpartum (weeks)	6[a]	6[a]	6[a]	6[a]
Mid postpartum (weeks)	26[a]	26	26[a]	26[a]
Antiretroviral coverage				
Maternal ART use	91% [4]	87% [4]	88% [62]	95% [46]
Virally suppressed[c]	88% [63]	72% [64]	88% [63]	88% [63]
Weekly risk of ART dropout	0.33% [22]	0.33% [22]	0.33% [22]	0.33% [22]
HIV-exposed infants receiving ARVs	94% [23]	99%[b]	96%[b]	98%[a]
HIV-infected infants receiving ART[d]	61% [43]	63% [78]	57.9% [62]	95% [46]
Breastfeeding practices among HIV infected women				
Not breastfeeding in early postpartum (0 to 6 weeks)	2.5%[b]	34% [66]	95% [62]	95%[a]
Not breastfeeding in mid postpartum (6 weeks to 6 months)	21%[a]	45% [66]	98% [62]	99%[a]
Not breastfeeding in late postpartum (6 to 12 months)	33%[b]	63% [66]	98% [62]	99%[a]

(Continued)

Table 2a. (*Continued*)

Parameter	Kenya	South Africa	Colombia	Ukraine
Maternal mortality rate (per person-week)				
During pregnancy	0.0001 [29]	0.0001 [29]	0.00002 [29]	0.00002 [29]
Delivery through 6 weeks postpartum	0.0006 [68]	0.0002 [68]	0.0001 [68]	0.00003 [68]
6 weeks to 12 months postpartum	0.0001 [29]	0.0001 [29]	0.00002 [29]	0.00002 [29]
Neonatal/infant mortality (per person-week) and survival probabilities				
Neonatal mortality, birth-6 weeks	0.0049 [69]	0.0029 [69]	0.0018 [69]	0.0011 [69]
Infant mortality, >6 weeks to 12 months	0.00031 [69]	0.00025 [69]	0.00009 [69]	0.00006 [69]
Survival to 1 year, HIV−	96% [29]	97% [29]	99% [29]	99% [29]
Survival to 1 year, HIV + on ART	96% [29]	97% [29]	99% [29]	99% [29]
Survival to 1 year, HIV + not on ART	65% [30]	65% [30]	65% [30]	65% [30]

ANC, antenatal care; ARV, antiretroviral prophylaxis; ART, antiretroviral therapy; MCH, maternal and child health; MTCT, mother-to-child transmission; PrEP, pre-exposure prophylaxis.
[a]Indicates assumption; [b]indicates in-country source; [c]among women on ART; [d]based on the percent of infants with early infant diagnosis.

taken as the product of the probability of testing and treatment uptake. We assumed no pre-exposure prophylaxis (PrEP) use in the main analyses. The model was validated against estimated MTCT rates from each country [18,23-25] (Appendix S4).

2.3 | Health outcomes

Modelled health outcomes included infant HIV infections, deaths and DALYs. In addition to percent of total infant infections averted by each scenario, we calculated the percent of maximum possible infant infections averted relative to no retesting by excluding infant infections from women diagnosed with HIV prior to pregnancy, as these women would neither be eligible for nor benefit from additional HIV testing.

2.4 | Costs and cost-effectiveness

We estimated costs from a healthcare system perspective, including costs for maternal retesting, maternal ART, infant ARV prophylaxis and infant ART (Table 2b, Appendix S2). Costs and resource utilization were obtained from the published literature, a time-motion study in Kenya (Appendix S5), in-country experts, or assumptions (Table 2b, Appendix S2). Unit costs were applied to testing and treatment/prophylaxis as women transitioned though model states. Costs were adjusted to 2017 USD [26].

Weekly maternal ART costs were applied to women receiving ART and modelled through 12 months postpartum. We modelled PrEP in scenario implementation analyses, with women testing HIV-negative being eligible for PrEP and incurring PrEP-related costs. Costs of infant prophylaxis were applied as a one-time cost to women diagnosed by delivery. Weekly ART costs were applied to HIV-infected infants throughout the 20-year time horizon. Both costs and DALYs were discounted at 3% annually [27].

We converted infant infections and deaths into DALYs [28]. We estimated DALYs through 20 years of life using country-specific WHO life tables and age- and HIV status-specific mortality estimates from published literature (Appendices S2 and

Table 2b. Costs

Parameter	Kenya	South Africa	Colombia	Ukraine
Third generation rapid screening per woman	2.64[a]	7.72[a,b]	6.68[a,b]	3.99[a,b]
True-positive screening tests per woman†	3.68[a]	11.39[a,b]	8.53[a,b]	4.18[a,b]
False-positive screening tests per woman†	26.39[a]	34.17[a,b]	74.83[a,b]	19.80[a,b]
Maternal ART, per week	4.86 [71]	4.79 [72]	18.89[b]	32.84 [73]
Infant ARV prophylaxis (total cost)	2.32 [74]	3.82 [74]	52.10[b]	4.00[b]
Maternal PrEP, per week	6.19 [75]	6.19 [75]	18.89[b]	19.38 [76]
Infant ART, per week (birth to 2 weeks)	6.73 [77]	5.46 [74]	18.89[b,c]	32.84[c]
Infant ART per week (2 weeks to 1 year)	6.73 [77]	5.46 [74]	18.89[c]	32.84[c]

All costs provided in 2017 USD and include labour and supplies. ART, antiretroviral therapy; ARV, antiretrovirals; PrEP, pre-exposure prophylaxis.
[a]Micro-costing estimate; [b]in-country source; [c]assumption.

S3) [29,30]. We choose a time horizon of 20 years for comparability with other HIV cost-effectiveness analyses. We calculated the incremental cost-effectiveness ratio (ICER) as the change in costs divided by the change in health outcomes compared with the next best alternative. Strategies that were more costly and less effective ("strongly dominated") or less costly and less cost-effective ("weakly dominated") than an alternative strategy were considered inefficient [31] and eliminated from the calculations. We used country-specific cost-effectiveness thresholds based on the estimated opportunity cost of health investment foregone. We adopted thresholds of $500 (Kenya) [32,33]; $750 (South Africa), derived in [34] as

in Phillips et al. [35]; $1000 (Ukraine) [36] and $3000 (Colombia) [37] per DALY averted. We followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) in preparing this manuscript [38].

2.5 | Scenario implementation and uncertainty analyses

We estimated the sensitivity of Scenario 2 results in Kenya and South Africa to uncertainty in key parameters by modelling 20% relative increases and decreases (bounded by 0 and 1 for probabilities). We also evaluated the sensitivity of model Scenarios 2 and 3 in each country to reductions in maternal HIV incidence and prevalence, and introduction of PrEP. We modelled PrEP use among 5%, 10% and 15% of all HIV-negative women. We additionally modelled a combination scenario of 15% PrEP use and 20% reduction in both maternal HIV prevalence and incidence. Last, to assess whether the benefits of retesting would change with an optimized HIV care cascade, we estimated the percentage of infections averted with retesting assuming 100% MCH attendance, test coverage, treatment initiation, retention, viral suppression and infant ARV prophylaxis coverage (Appendix S6).

2.6 | Ethical statement

This research involved no identifiable data, and as such does not constitute human subjects research.

3 | RESULTS

Model results are presented in Table 3 and Figure 1. In Kenya and South Africa, HIV retesting among women of HIV-negative or unknown status in late ANC, with catch-up testing through six weeks postpartum for women not tested in late ANC, is projected to prevent 19% and 12% of infant infections respectively. In both countries, ICERs associated with this retesting strategy ($166 and $289 per DALY averted for Kenya and South Africa respectively) fell below the cost-effectiveness thresholds. In these countries, adding one or two additional HIV retests postpartum provided only small incremental benefits (1 to 3 percentage point increase in HIV infections averted), and provision of one additional test at 14 weeks postpartum-dominated scenarios in which this test was offered at six, nine, or both six and nine months postpartum. HIV retesting in late ANC and every three months postpartum was the most effective and most costly strategy, exceeding the cost-effectiveness thresholds with ICERs of $7639 per DALY averted in Kenya and $11 985 in South Africa.

In Colombia, HIV retesting in late ANC with early postpartum catch-up averted a similar proportion of HIV infections (17%) as in Kenya and South Africa (19% and 12% respectively), whereas this strategy averted fewer infections in Ukraine (6%). However, due to the low HIV burden, the absolute number of infections prevented was small in both countries (23 in Colombia and 4 in Ukraine). Adding additional HIV retests followed a similar pattern to that of Kenya and South Africa, providing marginal incremental benefits but with substantially higher costs. All HIV retesting scenarios in Colombia

and Ukraine were either dominated or exceeded the cost-effectiveness thresholds.

When restricting our results to women eligible for retesting (those without known HIV infection at the start of pregnancy), retesting in late ANC with early postpartum catch-up testing averted 23% of infections in Kenya, 19% in South Africa, 20% in Colombia and 24% in Ukraine. Consistent with our main results, additional postpartum retests increased the percent of maximum potential infections averted but with diminishing returns.

3.1 | Scenario implementation and uncertainty analyses

In uncertainty analyses, ICERs for HIV retesting in late ANC with catch-up retesting through six weeks postpartum ranged from $102 to $272/DALY averted in Kenya and from $156 to $799 for South Africa (Figure 2). Changes in HIV test coverage, followed by infant ART cost, had the largest impact on ICERs. In all countries, increases in PrEP use, decreases in HIV incidence, and decreases in HIV prevalence resulted in larger ICERs (Figure 3a-h) and fewer HIV infections averted (Figure S1). All scenario analyses of retesting in late ANC in Kenya and South Africa remained below the cost-effectiveness thresholds. Maternal retesting impact on MTCT was lowest when maternal incidence was reduced by 30%. Under an optimized care cascade, retesting in late ANC (with catch-up testing) and every three months postpartum averted 19% to 22% of infections in South Africa and Kenya (Appendix S6).

4 | DISCUSSION

We evaluated the health and economic impact of maternal HIV retesting at varying frequencies and intervals in four countries representing a range of HIV prevalence. In the intermediate- and high-prevalence settings of Kenya and South Africa, our results indicate retesting in late ANC with catch-up testing through early postpartum should be prioritized to capture as many maternal seroconversions occurring during pregnancy as possible. In such settings, retesting later in the postpartum period can capture maternal infections acquired after delivery but should only be considered in addition to retesting earlier in pregnancy/postpartum. As retesting in late ANC with catch-up testing and quarterly postpartum (Scenario 7) most closely aligns with current South African guidelines [17], reducing the frequency of postpartum retesting may be effective in optimizing maternal HIV retesting with limited resources. In the low prevalence settings of Columbia and Ukraine, all HIV retesting strategies were dominated or greatly exceeded cost-effectiveness thresholds. Retesting in late ANC with catch-up testing prevented the largest number of infant HIV infections, but the absolute number was small (<25 infections annually).

Our model results also highlight limits on retesting as a strategy for EMTCT. While one-third of infant infections are attributable to incident maternal infections [4], even with frequent testing throughout pregnancy and postpartum the proportion of infant infections averted due to retesting was only 27% in Kenya and 21% in South Africa after excluding MTCT attributed to women diagnosed with HIV prior to pregnancy.

Table 3. Infant HIV infections, deaths, disability-adjusted life years (DALYs) averted and cost-effectiveness of maternal HIV retesting scenarios vs. base case scenario

Retesting scenario	Infant infections	Total infections averted	% Infections averted[d]	Infant deaths	Total cost	Incremental cost	Total DALYs	Incremental DALYs averted	ICER[e]
KENYA									
1. No retesting	13 484	–	–	61 651	$60 887 865	–	1 405 727	–	–
2. Late ANC[a,b]	10 911	2573	19%	61 226	$63 295 344	$2 407 479	1 391 202	14 525	$166
5. Late ANC + 9 months	10 785	2699	20%	61 205	$66 901 930	–	1 390 493	–	Dom
3. Late ANC + 14 weeks	10 656	2828	21%	61 184	$67 067 821	$3 772 477	1 389 764	1438	$2,623
4. Late ANC + 6 months	10 766	2717	20%	61 202	$67 253 849	–	1 390 387	–	Dom
6. Late ANC + 6 months + 9 months	10 690	2793	21%	61 190	$70 505 634	–	1 389 957	–	Dom
7. Late ANC + every 3 months[c]	10 502	2982	22%	61 158	$73 717 459	$6 649 639	1 388 893	871	$7639
SOUTH AFRICA									
1. No retesting	27 038	–	–	41 077	$144 227 239	–	906 680	–	–
2. Late ANC[a,b]	23 838	3200	12%	40 564	$149 363 142	$5 135 903	888 889	17 792	$289
5. Late ANC + 9 months	23 747	3290	12%	40 550	$153 742 500	—	888 387	–	Dom
3. Late ANC + 14 weeks	23 616	3421	13%	40 529	$154 454 205	$5 091 063	887 657	1232	$4134
4. Late ANC + 6 months	23 703	3334	12%	40 543	$155 719 914	–	888 141	–	Dom
6. Late ANC + 6 months + 9 months	23 650	3387	13%	40 534	$159 530 970	–	887 847	–	Dom
7. Late ANC + every 3 months[c]	23 475	3562	13%	40 506	$163 855 053	$9 400 848	886 873	784	$11 985
COLOMBIA									
1. No retesting	138	–	–	4530	$4 658 472	–	89 810	–	-
2. Late ANC[a,b]	115	23	17%	4525	$7 228 725	$2 570 253	89 648	162	$15 859
3. Late ANC + 14 weeks	111	28	20%	4524	$9 284 324	$2 055 599	89 615	34	$61 080
5. Late ANC + 9 months	112	26	19%	4524	$9 324 935	–	89 626	–	Dom
4. Late ANC + 6 months	113	26	19%	4524	$9 373 546	–	89 629	–	Dom
6. Late ANC + 6 months + 9 months	111	27	20%	4524	$11 433 846	–	89 616	–	Dom
7. Late ANC + every 3 months[c]	107	31	23%	4523	$13 440 069	$4 155 745	89 590	24	$170 418
UKRAINE									
1. No retesting	71	–	–	3101	$8 470 318	–	57 636	–	–
2. Late ANC[a,b]	67	4	6%	3100	$9 960 198	$1 489 880	57 615	22	$69 107
3. Late ANC + 14 weeks	66	5	7%	3100	$11 345 338	$1 385 140	57 610	4	$316 654
5. Late ANC + 9 months	66	5	6%	3100	$11 372 961	–	57 612	–	Dom
4. Late ANC + 6 months	67	5	6%	3100	$11 397 314	–	57 612	–	Dom
6. Late ANC + 6 months + 9 months	66	5	7%	3100	$12 799 222	–	57 611	–	Dom
7. Late ANC + every 3 months[c]	66	5	8%	3100	$14 168 275	$2 822 937	57 608	3	$1 087 274

ANC, antenatal care; PP, postpartum; DALY, disability-adjusted life-year; Dom, dominated (more costly and less effective than dominating scenario).
[a]Late ANC is between 36 to 39 weeks of gestation; [b]Testing offered in late ANC, or at delivery if not performed at late ANC, or at six week MCH visit if not performed at delivery or late ANC; [c]Approximately every three months PP includes retesting at six weeks, 14 weeks, six months and nine months PP; [d]% infections averted is calculated by dividing total infections averted by the total number of infant infections that occur under Scenario 1 (no retesting); [e]ICER, incremental cost-effectiveness ratio, calculated as incremental costs (in 2017 US$) divided by DALYs averted compared with the next least-costly scenario with dominated and weakly dominated scenarios removed.
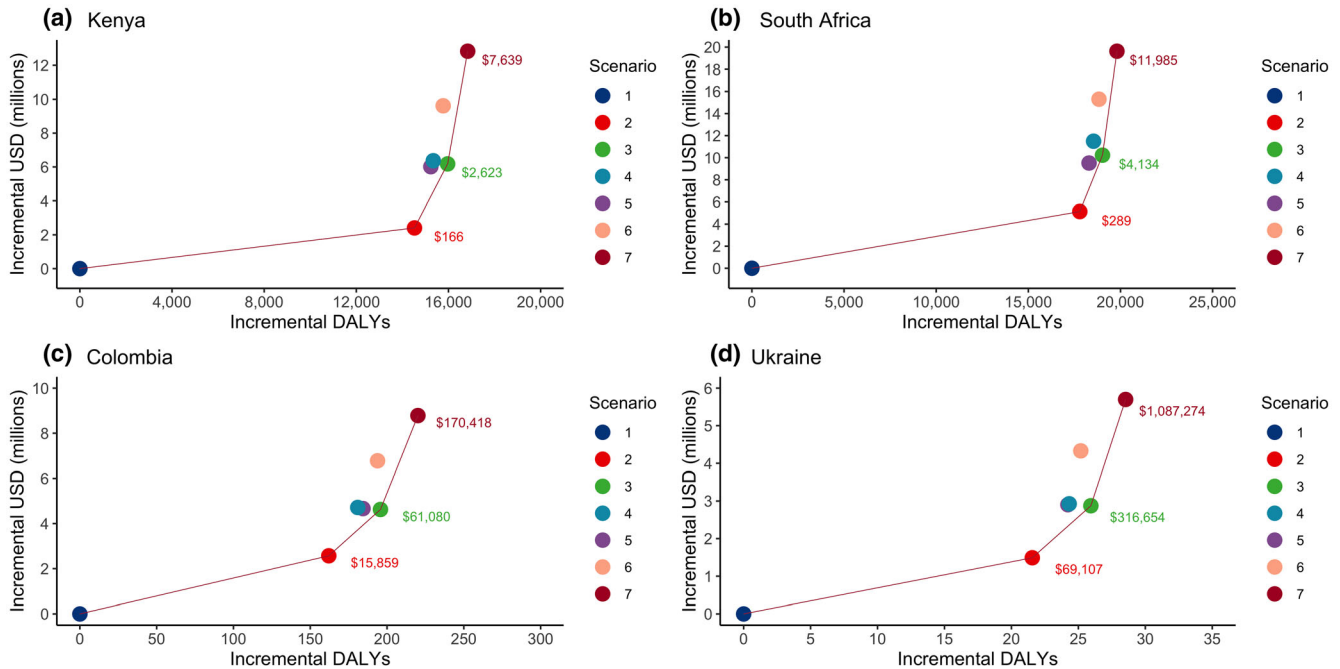
Figure 1. Efficiency frontier. presenting the incremental disability-adjusted life years (DALYs) averted and costs (in 2017 USD) for six retesting scenarios relative to Scenario 1 (no retesting) in (a) Kenya, (b) South Africa, (c) Colombia, (d) Ukraine. The solid line indicates scenarios that are not dominated by other scenarios, where "dominated" indicates a scenario is more costly and less effective. The text indicates incremental cost-effectiveness ratios for the non-dominated scenarios compared to the next least-costly scenario connected by a solid line. Scenario 1: no retesting; Scenario 2: retesting in late ANC/delivery/6 weeks postpartum; Scenario 3: scenario 2 plus retesting at 14 weeks postpartum; Scenario 4: scenario 2 plus retesting at six months postpartum; Scenario 5: scenario 2 plus retesting at nine months postpartum; Scenario 6: scenario 2 plus retesting at both six and nine months postpartum; Scenario 7: scenario 2 plus retesting every three months postpartum.

Optimizing MCH attendance and HIV care cascade parameters had little impact on these results. Antibody-based testing has low sensitivity during acute infection, when transmission risk is highest, making incident infections more difficult to detect. Our results thus suggest that achieving EMTCT will require additional interventions for prevention, such as PrEP, partner testing or diagnostics that facilitate earlier detection of incident infections.

In Colombia and Ukraine, where postnatal risk of maternal HIV acquisition is low, as is subsequent MTCT risk due to low rates of breastfeeding, the impact of postpartum retesting is similar to antenatal retesting. Decisions on implementation of maternal retesting will depend on national priorities (such as EMTCT), programmatic goals and targets, and available resources, and countries with low HIV prevalence may consider retesting women at higher risk of HIV, including key populations (e.g. women who inject drugs, female sex workers) and those in serodiscordant relationships. Risk-based screening tools, such as the one developed for pregnant and postpartum Kenyan women [39], may help identify such women during pregnancy or postpartum in both high and low prevalence settings.

Although our findings suggest maternal retesting is cost-effective in countries with high maternal HIV prevalence, there are several factors that need to be considered when implementing this strategy. First, country guidelines need to provide clear criteria on retesting eligibility and timing [10]. Countries should consider provider capacity to offer retesting given their workload and ensure monitoring and evaluation activities both document testing history and measure impacts of retesting. Providers who offer testing will need training to deliver post-test counselling messages that address HIV risk during pregnancy and breastfeeding and the need for future retesting, in addition to reinforcing HIV prevention messages. Emphasizing the importance of maternal retesting to prevent MTCT may also help providers prioritize retesting during busy ANC or postnatal care/infant immunization visits, including conveying elevated risks of HIV acquisition during pregnancy and breastfeeding and subsequent MTCT. Finally, test kit procurement and supply-chain management must be optimized to ensure test kit availability at facilities and that maternal retesting does not hinder other HIV testing efforts.

We found additional postpartum retesting incurs high costs per DALY averted, thus countries adopting this approach will need innovative and differentiated retesting models to optimize resource use [2]. Because HIV test coverage at first ANC visit is high in most countries, alternative delivery approaches to retesting may increase coverage among women who only attend one ANC visit, deliver at home, and/or do not return for MCH visits for postnatal care/infant immunizations. The WHO recommends self-testing as an additional testing approach [40]; however, to date few programmes have introduced self-tests for maternal retesting. While self-tests are unlikely to replace clinic-based rapid tests, they may play a complementary role in PMTCT programmes to increase access and acceptability of retesting and should be evaluated
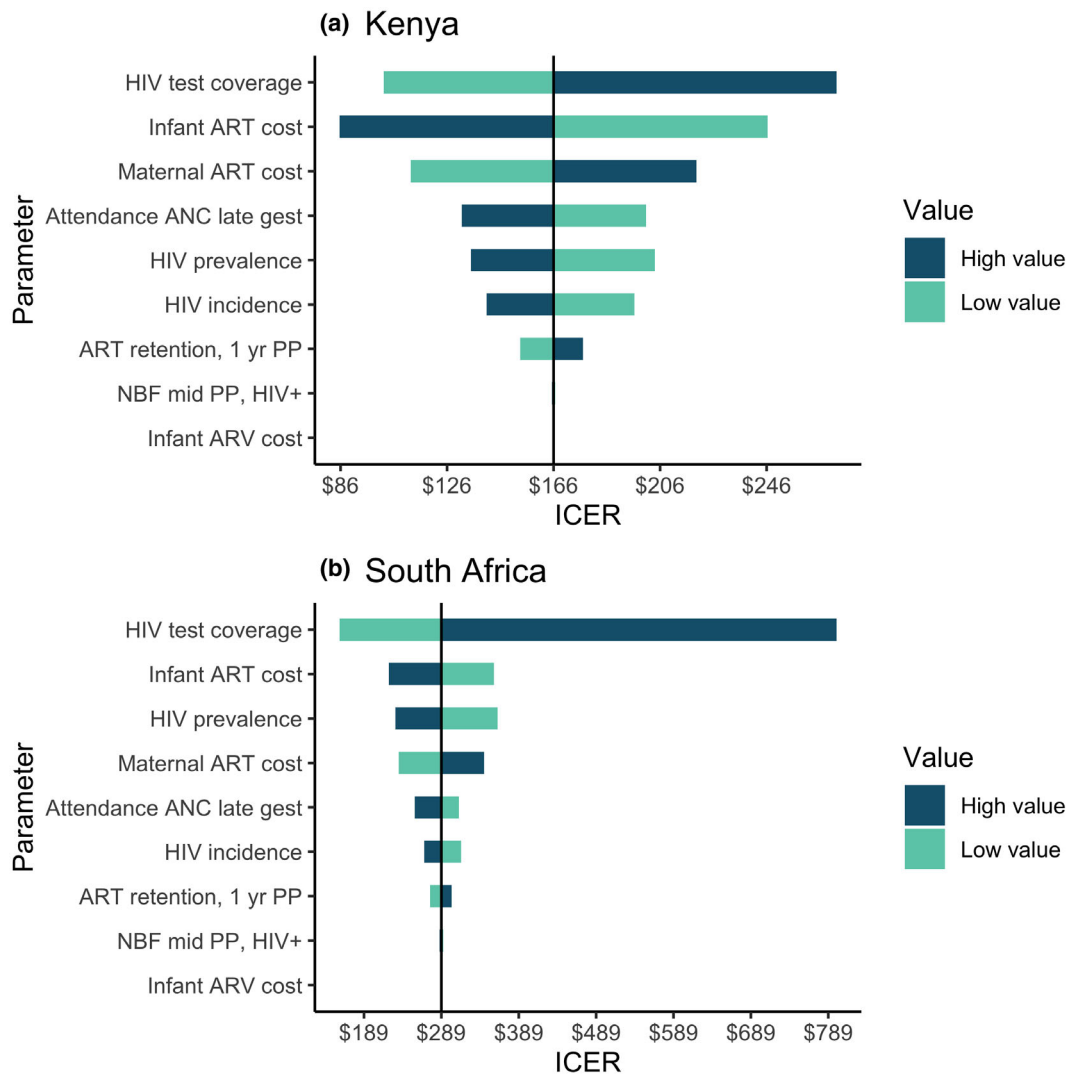
Figure 2. One-way parameter uncertainty analyses in (a) Kenya and (b) South Africa under retesting Scenario 2 (retesting in late ANC/delivery/six weeks postpartum). Models included 20% relative increases and decreases in individual parameters, bounded by 0 and 1 for probabilities. ANC, antenatal care visit; PP, postpartum; ART, antiretroviral therapy; NBF, not breastfeeding; ARV, antiretroviral prophylaxis; HIV+, HIV positive; ICER: incremental cost-effectiveness ratio, calculated as incremental costs (in 2017 US$) per disability-adjusted life year averted. HIV incidence refers to both incidence between onset of pregnancy and first antenatal care (ANC) visit, and incidence between first ANC and delivery, with both parameters varied by 20% for this analysis. HIV test coverage is the product of test acceptance and test kit being in-stock, with the composite parameter (test coverage) varied by 20% for this analysis.

for maternal retesting in future studies. In the context of the COVID-19 response, due to declining and delayed facility visits in many settings, HIV self-tests are increasingly being considered as a way to provide maternal catch-up testing and retesting for programmes and should be considered and evaluated.

Our analysis has several strengths. We model delivery of HIV retesting at routine ANC and MCH visits, mitigating the costs incurred by retesting. A similar strategy could be adopted for HIV testing in conjunction with routine paediatric vaccination past the MCH visits included in our model. We assessed the impact of additional tests during the postnatal period, which is included in comparatively fewer national guidelines than retesting during late pregnancy/delivery [10]. Furthermore, we included countries with different HIV burden

and geographic locations. While countries modelled are currently not implementing PrEP for pregnant and postpartum women at the national level, we assessed the impact of future PrEP scale-up on retesting strategies in sensitivity analyses. We also modelled reductions in maternal HIV incidence that could result from other HIV prevention interventions that may benefit pregnant/lactating women (i.e. condom use, risk reduction, partner HIV testing) [40]. Our conclusions were robust to varying assumptions about HIV prevalence, incidence and PrEP scale-up.

Our analysis also has several limitations. Some parameter values were assumed due to lack of empiric data; however, our estimates of MTCT rates were consistent with published estimates. While we modelled paediatric ART costs through 20 years, we modelled maternal ART costs only through
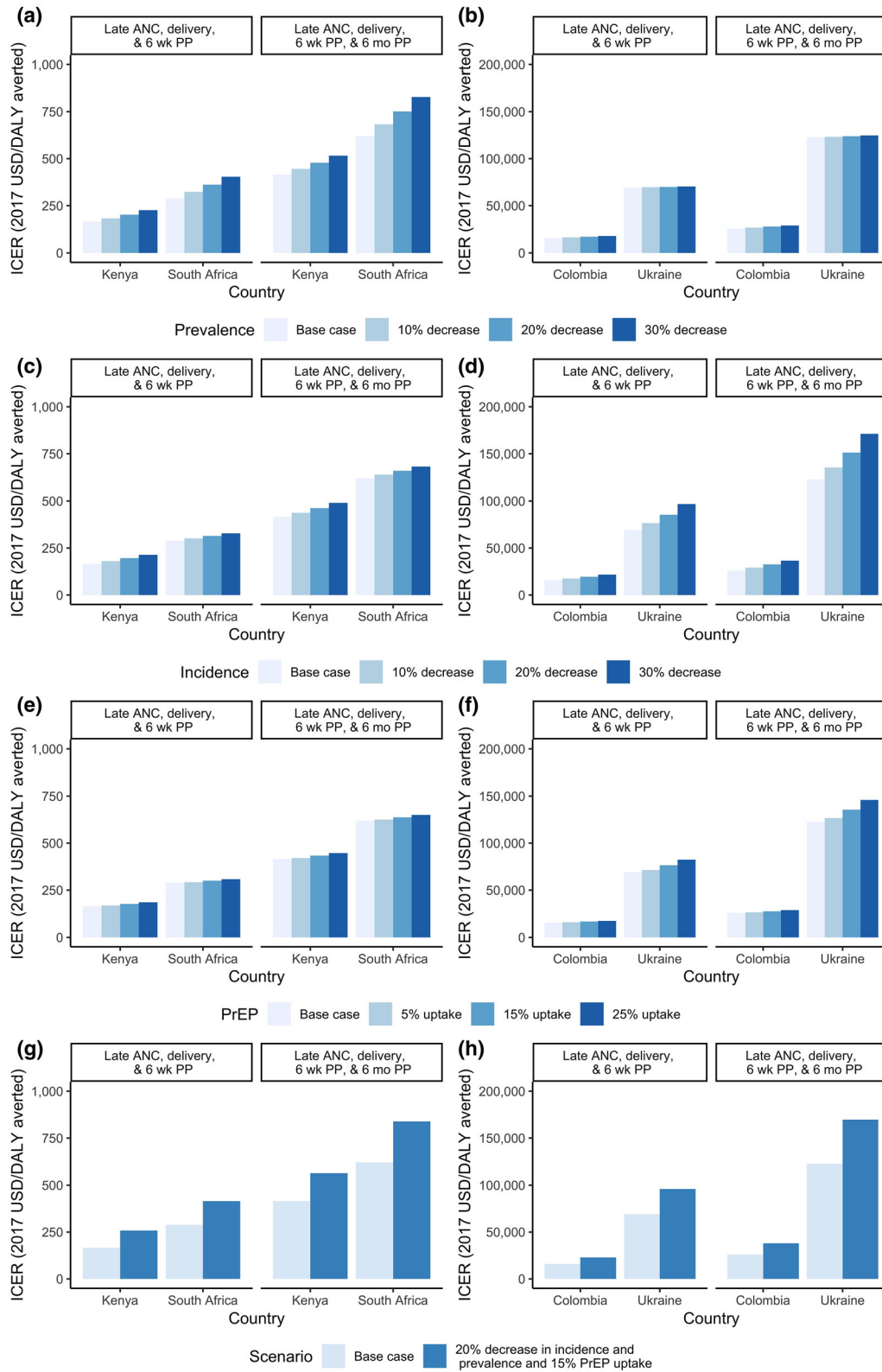
Figure 3. Scenario implementation analysis of maternal HIV retesting. (a) Decreasing HIV prevalence in Kenya and South Africa, (b) Decreasing HIV prevalence in Colombia and Ukraine, (c) Decreasing HIV incidence in Kenya and South Africa, (d) Decreasing HIV incidence in Colombia and Ukraine, (e) Increasing PrEP use in Kenya and South Africa, (f) Increasing PrEP use in Colombia and Ukraine, (g) Decreasing HIV prevalence and incidence, increasing PrEP use in Kenya and South Africa, (h) Decreasing HIV prevalence and incidence, increasing PrEP use in Colombia and Ukraine. ANC, antenatal care; PrEP, pre-exposure prophylaxis; ICER, incremental cost-effectiveness ratio; DALY, Disability-adjusted life year, Maternal HIV retesting Scenarios 2 (retesting in late ANC/delivery/six weeks postpartum) and 3 (retesting in late ANC/delivery/six weeks postpartum and at six months postpartum) modelled. ICERs are calculated with respect to Scenario 1 (no retesting).

12 months postpartum, as maternal outcomes were not the focus of our model and we assume MTCT ceases after 12 months. We did not model any changes in infant ARV and paediatric ART costs over this period, but our results were robust to changes in costs in sensitivity analyses. HIV diagnosis and linkage to care improves maternal health outcomes and may also prevent horizontal transmissions, neither of which are not captured by our model. While our intent was to model retesting in late pregnancy, tests in late ANC capture both incident maternal infections and established infections not detected at first ANC due to late presentation (after the gestational age of first ANC modelled) or absence of testing at first ANC. Furthermore, our model only allows for testing at two antenatal time points, with parameterization corresponding to re-testing in the third trimester in South Africa and Kenya, and in the second trimester in Colombia and Ukraine. As our model did not stratify by demographic or HIV risk factors, our results may not represent the impact of maternal retesting in concentrated epidemics within a country, nor of retesting prioritized for key populations. Our choice of countries was constrained by data availability and may not be generalizable to other settings where key parameters differ substantially from those modelled. We did not explicitly model time since maternal ART initiation and therefore may not have captured more complex temporal patterns in maternal ART use. Our model assumed all HIV-infected infants were equally likely to receive ART regardless of whether their mother's HIV-positive status was known or unknown. As early diagnosis and treatment will avert DALYs even if transmission is not prevented, our results are conservative in this regard. Our results are presented as point estimates without accompanying uncertainty. As several of our model parameters were based on expert elicitation or assumptions, and we expect many are correlated, we felt valid parameterization of a formal probabilistic sensitivity analysis was out of reach. Finally, the cost-effectiveness thresholds used in this analysis are approximate and may not accurately reflect country-specific willingness-to-pay under budget constraints. Affordability constraints may prevent some countries from implementing interventions below these thresholds. Alternatively, in efforts to achieve EMTCT, programmes may consider incurring high costs to implement retesting strategies above the cost-effectiveness thresholds used in this analysis.

5 | CONCLUSIONS

We found retesting women in late ANC followed by catch-up testing though six weeks postpartum is a cost-effective approach to PMTCT in Kenya and South Africa and should be implemented by PMTCT programmes. Universal maternal retesting was not cost-effective in Colombia and Ukraine; these counties may consider retesting if resources are available as retesting does contribute to EMTCT efforts, which would align with their current national retesting guidance. Additional empiric data on implementing maternal retesting guidelines is needed to refine model inputs, to evaluate retesting strategies for key populations at high HIV risk, and to revise retesting guidelines as incidence declines in high-burden countries.

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COMPETING INTEREST

The authors declare they have no competing interests.

AUTHORS' CONTRIBUTIONS

JM, DAR, PR, RB, SE, MSJ, RB, CJ and ALD designed the study and JM, DAR, PR, BG, MBM, AB, AV, AS, GG, SF, SE, CJ and ALD collected data to populate the model. JM, DAR, PR, AD, MSJ, CJ and ALD contributed to the literature search. JM, DAR, PR, MS and ALD were responsible for constructing the model and analysing model results. All authors contributed to writing the manuscript and interpreting the results.

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SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article.

Figure S1. Scenario implementation analysis of maternal HIV retesting on number of infant HIV infections averted. **(a)** Decreasing HIV prevalence in Kenya and South Africa, **(b)** Decreasing HIV prevalence in Colombia and Ukraine, **(c)** Decreasing HIV incidence in Kenya and South Africa, **(d)** Decreasing HIV incidence in Colombia and Ukraine, **(e)** Increasing PrEP use in Kenya and South Africa, **(f)** Increasing PrEP use in Colombia and Ukraine, **(g)** Decreasing HIV prevalence and incidence, increasing PrEP use in Kenya and South Africa, **(h)** Decreasing HIV prevalence and incidence, increasing PrEP use in Colombia and Ukraine. ANC, antenatal care; PrEP, pre-exposure prophylaxis; Maternal HIV retesting Scenarios 2 (retesting in late ANC/delivery/six weeks postpartum) and 3 (retesting in late ANC/delivery/six weeks postpartum and at 6 months postpartum) modelled.

Appendix S1. Model hyperlink: https://github.com/dallenroberts/Maternal-testing

Appendix S2. Model equations.

Appendix S3. Model parameters

Appendix S4. Comparison of model vs published estiamtes of maternal to child transmission

Appendix S5. Microcosting methods

Appendix S6. Infections averted under optimized MCH attendance and HIV care cascade