MODELING THE PERFORMANCE AND COST OF EARLY INFANT HIV DIAGNOSIS (EID) AT BIRTH

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Background

Untreated HIV-infected children are at highest risk of death in the first year of life. WHO 2010 guidelines recommend early infant diagnosis (EID) using virological testing (VT) from 4-6 weeks of age [1].

While expanding, global EID coverage remains low with only 34% of HIV-exposed children tested within 2 months of birth, and coverage of antiretroviral therapy (ART) in children remains disproportionately low at 36% of those in need in 2012 [2].

Earlier testing at birth was hypothesized to improve EID coverage, enable earlier initiation of ART and reduce mortality. However, VT at birth has poorer sensitivity and there are scarce data on implementation in resource-limited settings.

Objectives

To model the performance, cost and impact of EID testing at birth as compared to current WHO recommendations of testing from 4-6 weeks of age, applied to data from South Africa.

Methods

A decision tree cohort simulation model was applied to infants born in a PMTCT programme setting. Infants enter the model at birth with a risk of in-utero, intra- and post-partum transmission.

Definitions:

- WHO algorithm: HIV-exposed children are routinely tested at 4-8 weeks, 9 and 18 months (Figure 1);
- Birth test algorithm: HIV-exposed children are routinely tested at birth (0-3 days), 12 weeks, 9 and 18 months;
- Both algorithms include an additional test at end of breastfeeding.
- Children <18 months were assumed to be tested using VT and serology thereafter.

The model runs up to 24 months of age. HIV-infected children have a probability of diagnosis, referral for HIV care, initiation of ART or pre-ART death (Table 1). Outcomes of interest were positive predictive value (PPV), negative predictive value (NPV) of VT at 12 weeks (as assume similar PPV and NPV across algorithms thereafter), cost per diagnosis, proportion of HIV-infected children correctly diagnosed, initiated on ART and pre-ART deaths.

Figure 1. Timing of early infant diagnosis in Birth Testing and WHO algorithms

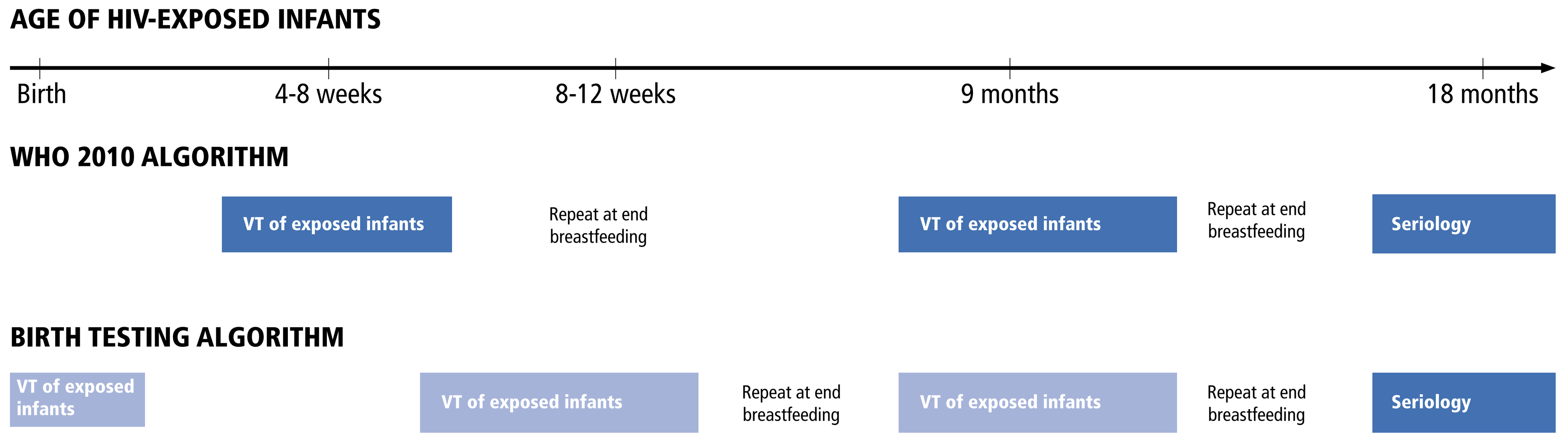


Table 1. Key model assumptions and parameters

Parameters	Estimate	Source
No. HIV-exposed infants born per year	258,000	[3]
Coverage of PMTCT	>95%	[4]
Proportion ever breast-fed and monthly probability of cessation of breast-feeding	70% ever breast-fed; 3.3% end breast-feeding per month at 3-6mo; 2.5% >6mo.	Assumption
MTCT in PMTCT setting (include late presenters /defaulters)	3% in-utero, 1.3% intra partum, 0.2% per month post partum. Cumulative MTCT rate of 7.9%	Assumption on distribution, cumulative rate [5].
Monthly risk of mortality of untreated HIV+ children	5% ≤3months; 1.8% >3 months	Assumption guided by [6]
EID coverage	88% at birth (facility birth rate); 54.7% at <2 mo, assume 50% at 9mo, end of breastfeeding, 30% at 18 mo.	[3],[7]
DNA PCR sensitivity	67% at birth; 98.8% at 6 weeks; 99.2% ≥ 12 weeks	[1, 3, 8]
Time lag between each step of EID cascade (receipt of result, refer for HIV care, start ART)	4 weeks	[5]
Return for test results	Assume 75% for birth test, 60% thereafter	[9] (57% return for results in vaccination clinic)
Referred for ART	82.4% if diagnosed aged<2mo, 77.5% ≥2mo	[10] (Proportion with viral load test pre-ART considered as proxy for referral and start of ART: 67% <2mo, 60%≥2mo)
Initiate ART	82.4% if diagnosed aged <2mo, 77.5% ≥2mo	[10] (Proportion with viral load test pre-ART considered as proxy for referral and start of ART: 67% <2mo, 60%≥2mo)
Cost per HIV test (unit cost of DNA PCR test includes cost of dried blood spots, reagents, infrastructure investment, human resources).	DNA PCR $25 Serology $1	CHAI (personal communication A. Ghadrshenas)

Results

The positive and negative predictive value at 12 weeks was 87.5% and 99.5% in the WHO algorithm and 75.3% and 98.6% in the birth test algorithm, respectively. Cost per HIV-infected diagnosis was US$458 and $823, respectively.

The proportion of HIV+ children correctly diagnosed by 24 months was substantially higher in the birth test vs WHO algorithm at 69% vs 55%, respectively (Fig. 2a). However, the proportions of HIV+ children starting ART was more comparable at 37% vs 31%; and pre-ART deaths at 25% vs 27%, respectively. Furthermore, children start ART at younger ages in the birth test algorithm (Fig.2b)

Figure 2. (a) Proportion of HIV+ children diagnosed, started ART and pre-ART mortality by algorithm (left).
(b) Age at start of ART by algorithm (right)

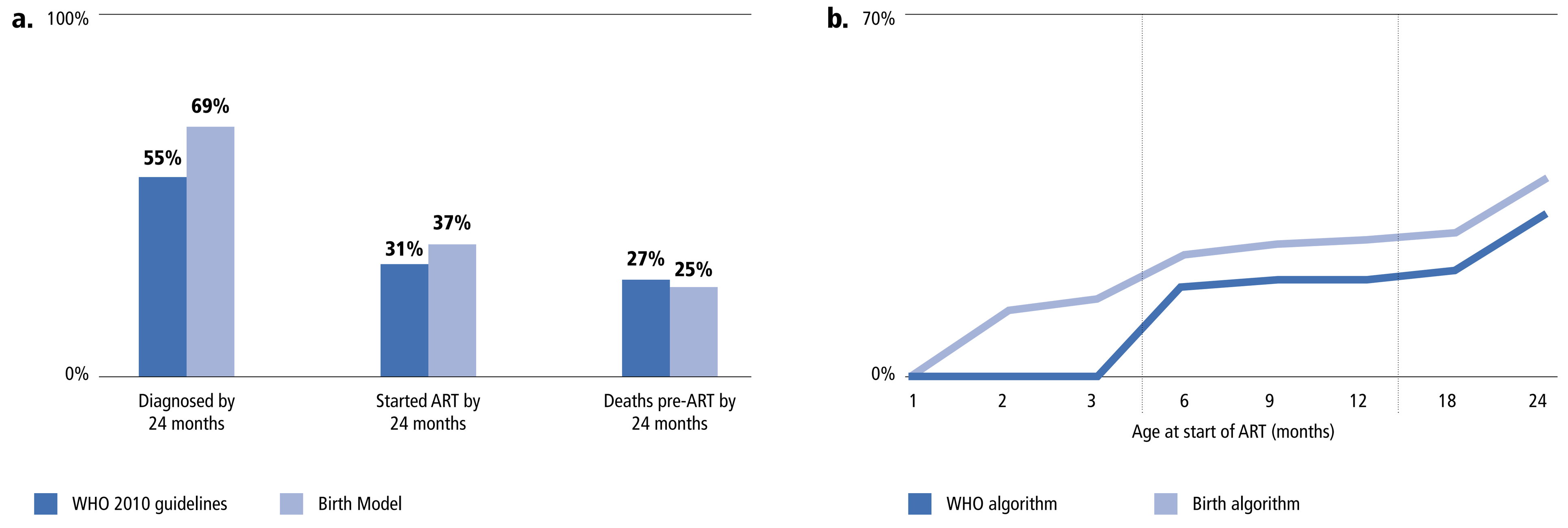
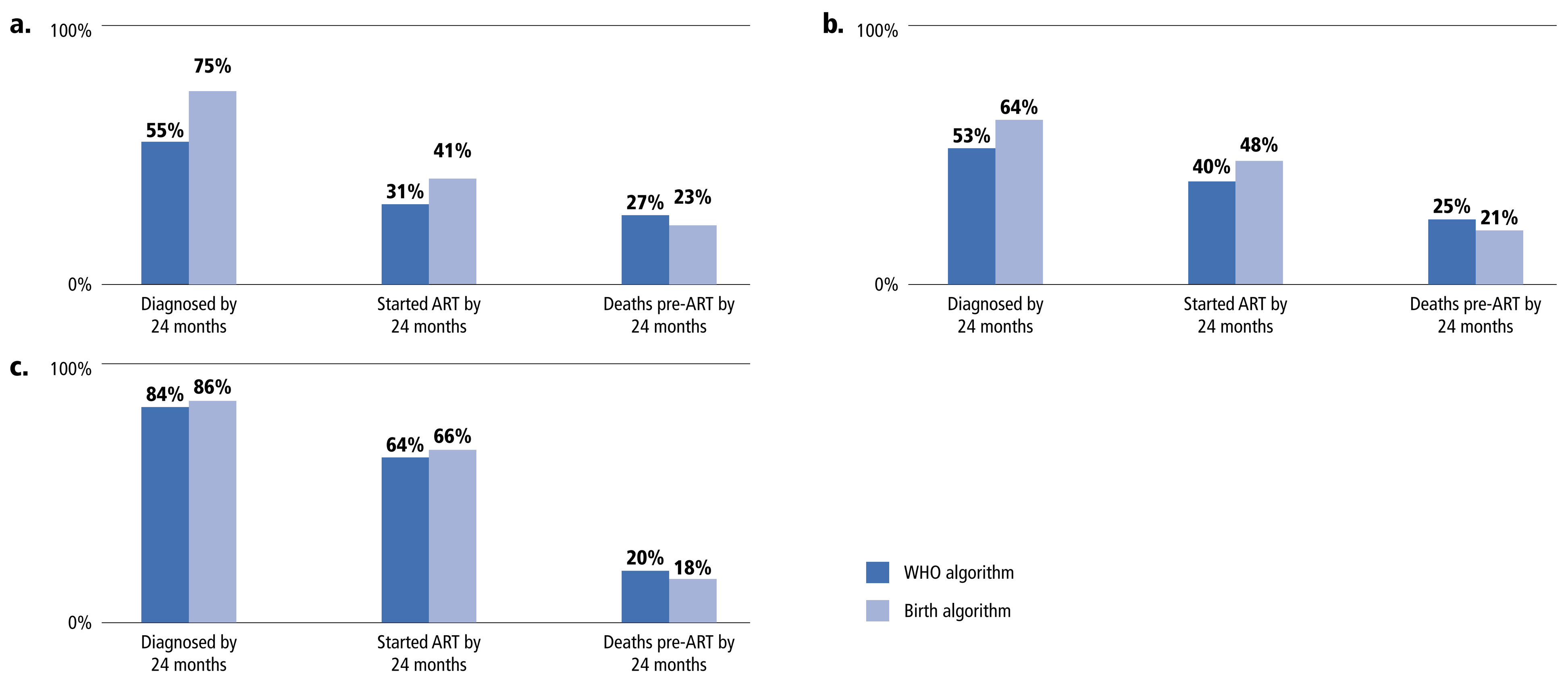


Figure 3. Proportion of HIV+ children diagnosed, started ART and pre-ART by algorithm in scenario analyses assuming:
(a) higher sensitivity (90%)of virological test at birth (top left);
(b) no change in sensitivity but no change in sensitivity but higher referral and retention (90%) of HIV+ children in each point of EID cascade (top right);
(c) higher EID coverage (90% <2mo, 80%≥ 2mo) and high referral and retention (90%) of HIV+ children in EID cascade (bottom left).



Three scenario analyses were conducted, there were limited change in proportion starting ART and pre-ART deaths when assuming higher sensitivity of birth testing (Fig. 3a). However these outcomes improved markedly in both algorithms when assuming higher referral and retention of HIV+ children in the EID cascade (Fig. 3b). The best outcomes were observed in scenario 3, which assumed higher coverage of EID and improved retention/referral of HIV+ children, resulting in the projected proportion of HIV+ children starting ART reaching >60% and the pre-ART deaths falling to ≤20%, with similar results in both algorithms (Fig. 3c).

Importantly, the model assumed birth testing would not change the 4-week time-lag at each step of the EID cascade (return for test results, referral to ART clinic etc). If this time lag was reduced, ie. to same-day results by point of care tests, then the birth test algorithm is likely to have significant benefit on proportions starting ART and reducing early pre-ART mortality.

Conclusion

Virological testing at birth would potentially increase the proportion of HIV+ children diagnosed, but has lower positive predictive value and higher costs. Interventions to improve EID coverage and / or retention and referral for ART initiation offers potentially large benefits in terms of increasing proportions of HIV+ children starting ART and reducing pre-ART mortality, in both algorithms.

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