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Infant/child rapid serology tests fail to reliably assess HIV exposure among sick hospitalized infants

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Abstract

Background—The WHO guidelines for infant and child HIV diagnosis recommend the use of maternal serology to determine child exposure status in ages 0-18 months, but suggest that infant serology can reliably be used to determine exposure for those less than 4 months. There is little evidence about the performance of these recommendations among hospitalized sick infants and children.

Methods—Within a clinical trial (NCT02063880) in Kenya, among children < 18 months, maternal and child rapid serologic HIV tests were performed in tandem. Dried blood spots were tested using HIV DNA PCR for all children whose mothers were seropositive, irrespective of child serostatus. We characterized the performance of infant/child serology results to detect HIV exposure in 3 age groups: 0-3, 4-9, and 10-18 months.

Results—Among 65 maternal serology positive infants age 0-3 months, 48(74%), 1(2%) and 16(25%) had positive, indeterminate and negative infant serology results respectively. Twelve (25%), 0 and 4(25%) of those with positive, indeterminate and negative infant serology results respectively, were HIV-infected by DNA PCR.

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Among 71 maternal serology positive infants age 4-8 months, 31(44%), 8(11%) and 32(45%) had positive, indeterminate and negative infant serology results respectively. Fourteen (45%), 2(25%) and 7(22%) of infants with positive, indeterminate and negative infant serology results respectively, were HIV-infected.

Among 67 maternal serology positive infants/children age 9-18 months, 40(60%), 2(3%) and 25(37%) had positive, indeterminate and negative infant serology results respectively. Thirty-six (90%), 2(100%) and 2(8%) of infants with positive, indeterminate and negative infant serology results respectively, were HIV-infected.

In the 0-3, 4-8 and 9-18 month age groups, use of maternal serology to define HIV exposure identified 33% (95% CI: 10-65%), 44% (95% CI: 20-70%) and 5% (95% CI: 0.1-18%) more HIV infections, respectively.

Conclusions—Maternal serology should preferentially be used for screening among hospitalized infants of all ages to improve early diagnosis of children with HIV.

Keywords

Paediatrics; HIV diagnostic tests; Africa; Prevention of mother to child transmission / vertical transmission; Seroprevalence; Healthcare; Antiretroviral therapy

Introduction

Pediatric HIV has a more aggressive course than adult disease; without treatment, 50% of children will die by 2 years [1]. Early diagnosis and initiation of antiretroviral treatment (ART) confers a strong survival benefit in infants [2]. However, early diagnosis of infant HIV poses challenges.

Previous World Health Organization (WHO) guidelines recommended the use of either infant or maternal serology during sick child visits to determine HIV exposure, followed by virologic testing for HIV-exposed infants up to 18 months [3]. The 2016 WHO guidelines state a preference for maternal serology in determining infant HIV exposure status at all ages between 0 and 18 months, but also note that infant serology results can reliably assess HIV exposure in infants less than 4 months of age [4].

Within PMTCT programs, maternal HIV status is determined during pregnancy or intrapartum, allowing preferential use of maternal serology to determine infant HIV exposure. However, improved effectiveness of PMTCT interventions means that a growing proportion of new infant infections will occur due to incident maternal HIV infections in the post-partum period, often outside of the PMTCT system. These infant infections may first present at sick child visits or during hospitalization. In this symptomatic population of infants and children, enhanced for recent maternal infection, it is important to determine how well the new WHO guidelines for infant HIV exposure ascertainment perform and note how many infections would be missed with continued use of older guidelines during scale-up of newer guidelines.

In this study of hospitalized children conducted in Kenya, we characterized the performance of infant rapid serology tests to determine HIV exposure status in 3 age groups: 0-3 months, 4-8 months, and 9-18 months. We calculated the proportion of infant or child HIV infections that would have been missed if infant rapid serology tests were used to determine HIV exposure.

Methods

Recruitment and enrollment

This analysis was nested in the recruitment phase of the PUSH clinical trial (NCT02063880), which was conducted to determine whether urgent antiretroviral therapy (ART) (within 48 hours) would benefit hospitalized, HIV-infected children admitted with a severe co-infection, compared to early ART initiation (7-14 days).

In this analysis, sick, hospitalized children were recruited from 4 hospitals, 2 in Nairobi (Kenyatta National Hospital and Mbagathi District Hospital), and 2 in western Kenya (Jaramogi Oginga Odinga Referral and Teaching Hospital and Kisumu County Hospital) between April 2013 and May 2015. A subset of the children included in this analysis were subsequently enrolled in the clinical trial. Children were eligible for enrollment in the trial if they were HIV-infected, age 0-12 years, ART-naïve other than for PMTCT, did not have a suspected CNS infection, and were living within the study catchment area.

Ethical review

The parent clinical trial was approved by the University of Nairobi/Kenyatta National Hospital Ethics and Research Committee and the University of Washington Institutional Review Board. Caregivers of children provided written consent for HIV testing.

Laboratory

Maternal and infant HIV rapid serologic tests (Determine® or KHB® followed by Unigold® or First response®, per Kenyan guidelines) were performed in tandem through provider initiated testing and counseling (PITC) at hospitalization. HIV-1 deoxyribonucleic acid polymerase chain reaction (HIV-1 DNA PCR) assay was performed on dry blood spots (DBS) samples using an in-house method [5] in Nairobi sites and Abbott Real-Time HIV-1 qualitative assay at the Kenya Medical Research Institute (KEMRI) laboratory in western Kenya sites.

This analysis is restricted to infants whose mothers were HIV positive by rapid serology test. All infants whose mothers were HIV positive had an HIV DNA PCR test performed, irrespective of infant serology results. We characterized the proportion of truly positive infants and children (using HIV DNA PCR as the gold standard) that would have been identified or missed if infant rapid serology tests were used to determine HIV exposure.

For the subset of infants whose maternal serology was positive, infant rapid serology test was negative, and who were categorized as truly HIV-infected by HIV DNA PCR testing, archived DBS samples were retested using 4th generation CBios® HIV 1+2 antibody/antigen (Ag/Ab), a laboratory-based immunoassay kit that detects HIV-1 glycoprotein 41

(gp41), gp120 and HIV-2 gp36 antibodies and HIV-1 protein 24 (p24) antigens (Chemus Bioscience, Inc. www.chemux.com; San Francisco, CA). DBS samples were processed according to the Kania et al protocol [6], with the following differences: whole blood was used instead of serum, DBS sample were stored at ambient room temperature. According to the HIV-1+2 Ag/Ab ELISA test kit criteria, the results were interpreted as positive if the absorbance of the test well were greater than or equal to the cut-off value of the test plate and negative if the absorbance were less than the cut-off value. Additionally, samples with absorbance values lower than but near the cutoff value were interpreted as borderline if the ratio of the sample test well absorbance to the cut-off value of the test plate was between 0.9 and 1.1. Borderline samples were retested in duplicate to confirm initial results. These tests were performed post hoc and were not used to determine infant HIV status.

In this same subset of infants, we reviewed PMTCT history (maternal HIV test history and result during pregnancy, maternal and infant antiretroviral drug prophylaxis or treatment exposure), infant hospitalization history, and 6-month outcomes. Infants enrolled in the clinical trial had available information on viral loads, CD4 percent, WHO clinical staging, and growth parameters (weight for age (WAZ) and height for age (HAZ) z-scores).

Statistical analysis

Descriptive statistics were summarized using proportions, medians and interquartile ranges; 95% confidence intervals (95%CI) were estimated using a binomial distribution. We compared infant rapid serology test results in 3 age groups (0-3 months, 4-8 months and 9-18 months).

We calculated the proportion of infant infections that would have been missed if infant rapid serology tests were used to determine HIV exposure status by dividing the total number of infants positive by HIV DNA PCR by the number of infants who were both positive by HIV DNA PCR and whose rapid serology test results were either positive or indeterminate.

All tests were two-sided with alpha 0.05. Data analysis was conducted using STATA 14 (Stata Corporation, College Station, Texas, USA).

Results

There were 203 infants and children ages 0-18 months whose mothers were positive by HIV serology (HIV-exposed infants and children).

Performance of infant rapid serology tests to determine HIV exposure status by age group

Among 65 HIV-exposed infants age 0-3 months, median age was 2.0 months (inter quartile range [IQR]: 0.6-3.1), 32(49%) were male and 16(25%) were HIV-infected. Overall, 48(74%), 1(2%) and 16(25%) had positive, indeterminate, and negative infant rapid serology test results, respectively. Of those who were infant rapid serology test positive, indeterminate, and negative, 12(25%), 0(0%), and 4(25%) were HIV-infected by DNA PCR, respectively. In this age group, 4/16 (25%) infant infections would have been missed had only infant rapid serology tests been used to determine HIV exposure status; 33% (95%CI:

10-65%), more infant infections would have been identified in an algorithm that defined HIV exposure by maternal and not infant serology (16 vs 12, $p=0.39$).

Among 71 HIV-exposed infants age 4-8 months, median age was 6.6 months (IQR: 5.7-7.8), 40(56%) were male and 23(32%) were HIV-infected. Overall, 31(44%), 8(11%) and 32(45%) had positive, indeterminate, and negative infant rapid serology test results, respectively. Of those who were infant rapid serology test positive, indeterminate, and negative, 14(45%), 2(25%), and 7(22%) were HIV-infected by DNA PCR, respectively. In this age group, 7/23 (30%) infant infections would have been missed had only infant rapid serology tests been used to determine HIV exposure status; 44% (95%CI: 20-70%), more infant infections would have been identified in an algorithm that defined HIV exposure by maternal and not infant serology (23 vs 16, $p=0.21$).

Among 67 HIV-exposed infants/children age 9-18 months, median age was 14.2 months (IQR: 11.7-16.9), 33(49%) were male and 38(60%) were HIV-infected. Overall, 40(60%), 2(3%) and 25(37%) had positive, indeterminate, and negative infant/child rapid serology test results, respectively. Of those who were infant/child rapid serology test positive, indeterminate, and negative, 36(90%), 2(100%), and 2(8%) were HIV-infected by DNA PCR, respectively. In this age group, 2/40 (5%) infant/child infections would have been missed had only infant/child rapid serology tests been used to determine HIV exposure status; 5% (95%CI: 0.1-18%), more infant/child infections would have been identified in an algorithm that defined HIV exposure by maternal and not infant/child serology (40 vs 38, $p=0.73$) (Figure 1).

Clinical and care-seeking history and ELISA results of rapid serology test negative, PCR positive infants

Among 13 infants who were infant rapid serology test negative and HIV DNA PCR positive, median age was 5.7 months (range 2.4-11.3). Seven (58%) mothers reported that they tested HIV negative during pregnancy, likely representing incident infections during late pregnancy/postpartum. PMTCT antiretroviral exposure was uncommon with 4/13 mothers reporting having received any PMTCT medications and no infants having received prophylaxis. Seven of these 13 infants enrolled in the clinical trial and had baseline clinical data; most infants were WHO stage III/IV, had high viral loads, low CD4 percentages, and were wasted and stunted (Table 1).

Upon retesting 10 available archived DBS samples by serology using 4th generation CBios® HIV-1+2 antibody/antigen ELISA assay, 9/10 infant samples were identified as HIV positive for either antibody or antigen. By 6 months following diagnosis, 3 infants had died, 6 were known to be alive, and the remaining 4 were either lost to follow-up or not systematically followed, as they were not enrolled in the trial (Table 1).

Discussion

In this cohort of HIV-exposed, hospitalized infants and children, HIV was common with over a third of infants and children infected. An HIV testing algorithm that relies on infant rapid serology tests to define HIV exposure would have missed 25% and 30% of HIV-

infected infants in the 0-3 and 4-8 month age groups, respectively. Infant rapid serology tests performed better in older children between 9-18 months, missing an estimated 5% of infections. Among the infant rapid serology test negative, DNA PCR positive infants/children, mothers frequently tested HIV negative during antenatal care, likely representing incident maternal infection during late pregnancy/postpartum.

These findings provide evidence to review the performance of the 2016 WHO guidelines among a symptomatic population. For infants 0-3 months, the permissiveness of using infant rapid serology tests to determine exposure status could result in up to a quarter of infant infections being missed. For infants 4-8 months, the recommendation to use maternal serology to determine exposure status is well-warranted, given the large proportion of infants who were HIV-infected by DNA PCR but were negative by infant rapid serology test. For infants and children 9-18 months, the use of maternal serology to determine infant exposure status performed comparably to using infant rapid serology test. Revisions to the guidelines to recommend the preferential use of maternal serology at all ages to determine infant or child exposure status for symptomatic infants and children should be considered.

There are several potential reasons that HIV-exposed, sick infants could be rapid test seronegative but HIV-infected. Rapid serology test negative infants may lack HIV antibodies. Mothers with acute HIV infections during late pregnancy/postpartum may not have produced or transferred antibodies; consequently, infants born to these mothers may be born without maternal antibodies. A majority of rapid test seronegative, HIV-infected infants had mothers who reported testing HIV negative during antenatal care, presumably having acquired HIV during late pregnancy/postpartum. Additionally, infants recently infected with HIV may not yet have mounted their own antibody response [6], and infants may have been identified during the window period when maternal antibodies had waned but prior to the development of a robust infant antibody response [8]. While HIV antibody production is relatively rapid in adults, antibody production is slower in infants [9]. An *in vitro* study of lymphocytes from HIV-infected infants measured infant antibody production and noted that just 59% of samples had detectable levels of infant antibodies by 2 months, and 86% by 6 months of age [6]. It is also possible that sensitivity of rapid antibody tests is impaired during severe illness due to low levels of antibody production [6]. However, this may not explain all undetected infections, as 10% of these infants were negative by both antibody and antigen on repeat testing with a 4th generation ELISA assay.

Regardless of the mechanism, young infant/child rapid serology tests were not reliable in assessing infant HIV exposure in this study. As PMTCT coverage expands, an increasing proportion of HIV-infected infants will be due to acute maternal infections [9]; therefore, algorithms that recommend HIV DNA PCR tests on symptomatic HIV-exposed infants (by maternal serology), regardless of infant serostatus, may enhance timely case detection and ART initiation.

Previous studies have compared rapid HIV tests against PCR. Studies of 18 month olds observed that Determine® identified between 93-100% of HIV-infected children [10-13]. Only one study included hospitalized children. A South African study noted that virologic tests among infants who were symptomatic, regardless of infant rapid serology test results,

improved sensitivity from 96.3% to 98.4% [15]. However, the proportion of infants who were rapid test seronegative and HIV-infected was lower than in our study, possibly because less than 10% of children were acutely ill in hospital.

It is important to acknowledge that while HIV DNA testing enhances diagnostic performance, there are challenges in timely performance and return of results. Delays in turnaround time can result in infant deaths while awaiting diagnosis and interventions to decrease turnaround time are needed [14-16]. Point-of-care virologic tests decrease turnaround time for testing [19]; however, costs, the availability of trained personnel to operate the machinery, and high volumes of patients may challenge widespread adoption of point-of-care technologies. Cost-effectiveness and operations research studies that compare standard laboratory-based with point-of-care based PCR tests are needed for both asymptomatic and symptomatic infants. Additionally, scale up of Option B+ PMTCT regimens may further complicate diagnosis of infant infections due to potentially delayed detection of infant virus and antibodies [20].

This study had several limitations. Due to the combined antibody/antigen detection of the 4th generation ELISA test used, we were unable to determine whether the 9 infants who were positive by this test had antibodies or antigen present in their sample. We recruited from higher-level county and referral hospitals, which may have a disproportionately high level of symptomatic, undiagnosed HIV infection among infants and children; future studies should sample from a range of high and low level inpatient wards. Self-reported negative maternal HIV status during antenatal care may be over-reported, which would increase the proportion of infant infections inaccurately attributed to incident maternal HIV infection during pregnancy and postpartum. We were unable to include children brought by a caregiver other than their biological mother; however, these children were rare in this age range.

Conclusion

Young infant infections may be missed under current WHO infant and child testing guidelines, which are permissive of using infant rapid serology tests to determine HIV exposure status. These guidelines, which recommend maternal serology preferentially, perform well in older infants and children, but poorly in younger infants, many of whom were infant rapid serology test negative, but HIV-infected. Revisions to the WHO guidelines to remove endorsement of infant rapid serology tests to determine HIV exposure status in the youngest age range for symptomatic children should be considered.

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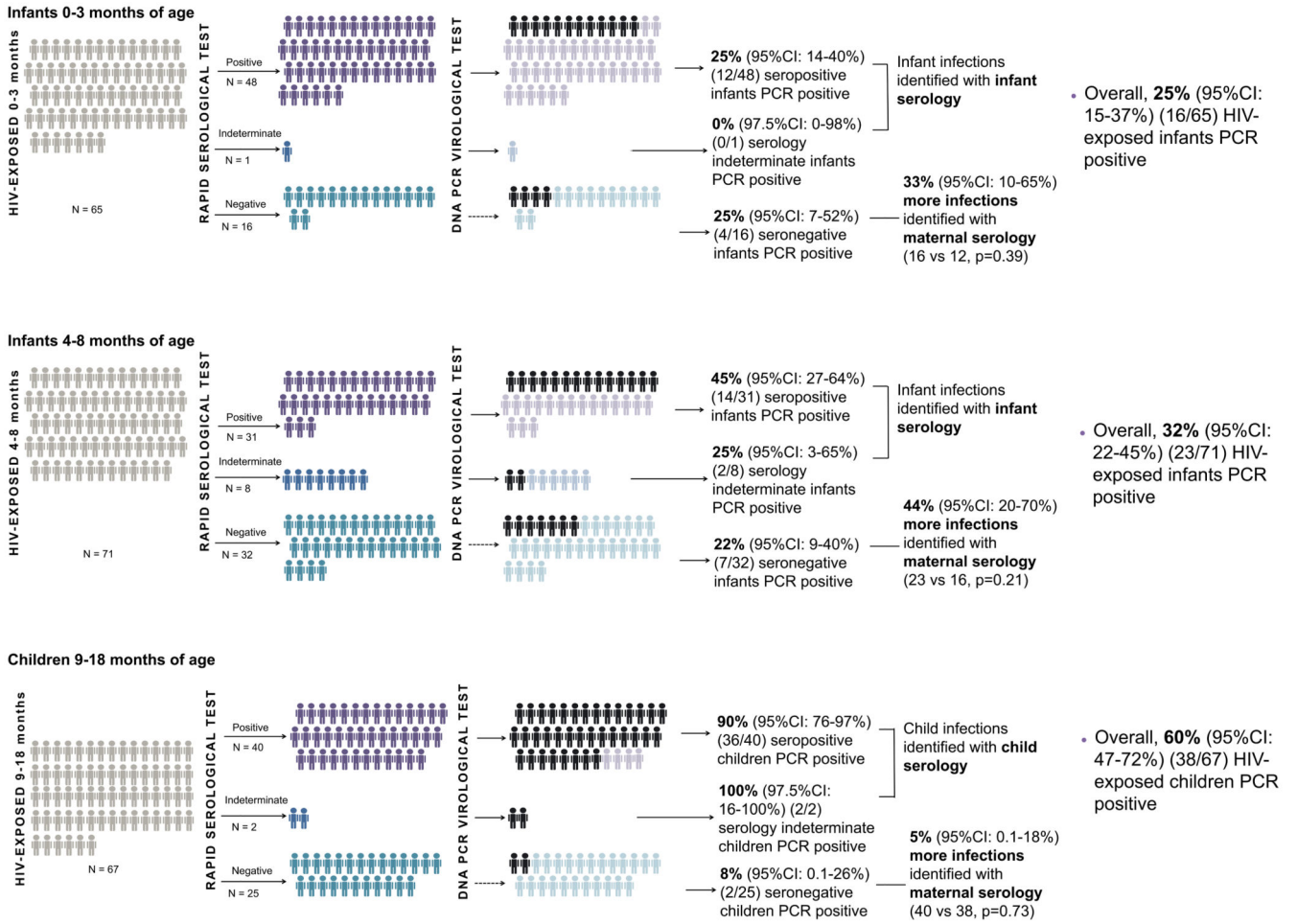


Figure 1.

Characteristics of 13 serology negative, virologic positive infants

Table 1

Maternal characteristics		Infant PMTCT and hospitalization history		Infant testing characteristics during hospitalization			Infant clinical presentation during hospitalization				Infant outcome by 6 months post diagnosis		
Mother HIV rapid test result during pregnancy	Mother HIV rapid test results during infant hospitalization	Mother ARVs during PMTCT (either prevention or treatment)	Infant ARV prophylaxis in PMTCT	Age in months	Infant HIV rapid test type	Infant HIV rapid test results	Infant DNA PCR test results	Results by 4th generation ELISA***	WHO clinical stage	CD4%	Viral load (RNA PCR)	WAZ	
Negative	Positive	no	no	2.4	Determine	Negative	Positive	Positive	Suspected CNS infection, not enrolled
Positive	Positive	no	no	2.7	KHB	Negative	Positive	Positive	1	20.2%	338,544	-1.04	Alive, on ART
No test	Positive	no	no	3.5	Determine	Negative	Positive	Positive	4	18.5%	1,023,638	1	Alive, on ART
Negative	Positive	no	no	3.9	Determine	Negative	Positive	Positive	Died before enrollment
Negative	Positive	no	no	4.1	Determine	Negative	Positive	Negative	Died before PCR result
Negative	Positive	no	no	4.2	Determine	Negative	Positive	Positive	3	15.6%	.	-4.98	Died before ART initiation
Positive	Positive	yes	no	5.7	Determine	Negative	Positive	Positive	3	0.4%	>10,000,000	-2.13	Alive at 3 months, stopped ART*
Positive	Positive	yes	no	7.2	KHB	Negative	Positive	Positive	4	12.0%	>10,000,000	-2.1	LTFU before ART initiation
Negative	Positive	no	no	7.7	Determine	Negative	Positive	Positive	3	28.0%	48,044	-1.36	Alive, on ART
Negative	Positive	no	no	8.2	Determine	Negative	Positive	Positive	4	27.9%	5,812,749	-3.53	Alive, on ART
Negative	Positive	no	no	8.5	Determine	Negative	Positive	**	LTFU before ART initiation
Positive	Positive	yes	no	9.0	Determine	Negative	Positive	**	LTFU before ART initiation
Positive	Positive	yes	no	11.3	Determine	Negative	Positive	**	Alive, not on ART

* Mother declined continuation of ART at 3 months post-treatment

** No sample available for testing

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*** sensitivity analysis only, not used in determination of infant HIV status

ARVs = antiretrovirals (either prophylaxis or treatment), PMTCT = prevention of mother-to-child transmission of HIV, KHB = KHB Colloidal Gold, PCR = DNA polymerase chain reaction, WHO = World Health Organization, WAZ = weight-for-age z-score, HAZ = height-for-age z-score