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Abstract

Background: Gaps persist in HIV testing for children who were not tested in prevention of mother-to-child HIV transmission programs. Oral mucosal transudate rapid HIV tests (OMT) have been shown to be highly sensitive in adults but their performance has not been established in children.

Methods: ART-naïve children aged 18 months to 18 years in Kenya and Zimbabwe were tested for HIV using rapid OraQuick ADVANCE Rapid HIV-1/2 Antibody test on oral fluids (OMT) and blood-based rapid diagnostic testing (BBT). BBT followed Kenyan and Zimbabwean national algorithms. Sensitivity and specificity were calculated using the national algorithms as the reference standard.

Results: A total of 1,776 children were enrolled; median age was 7.3 years (IQR: 4.7, 11.6). Among 71 children positive by BBT, 71 were positive by OMT (sensitivity: 100% [97.5%CI: 94.9-100%]). Among the 1,705 children negative by BBT, 1,703 were negative by OMT (specificity: 99.9% [95%CI: 99.6-100.0%]). Due to discrepant BBT and OMT results, 2 children who initially tested BBT negative and

OMT positive were subsequently confirmed positive within 1 week by further tests. Excluding these 2 children, the sensitivity and specificity of OMT compared to BBT were each 100% (97.5%CI: 94.9-100% and 99.8-100%, respectively).

Conclusions: Compared to national algorithms, OMT did not miss any HIV-positive children. These data suggest that OMTs are valid in this age range. Future research should explore the acceptability and uptake of OMT by caregivers and health workers to increase pediatric HIV testing coverage.

Key Words: HIV, children, pediatric, oral HIV testing, diagnostic, saliva HIV testing

Introduction

The HIV pandemic has heavily affected children with over 1.8 million children (<15 years) living with HIV and 180,000 newly infected in 2017¹. Prompt diagnosis and initiation on antiretroviral therapy (ART) is associated with decreased morbidity and mortality^{2,3} and improved developmental outcomes^{4,5}; however, gaps remain in diagnosis, particularly among older children and adolescents⁶.

World Health Organization (WHO) recommendations endorse rapid antibody-based HIV tests for diagnosis of individuals >18 months⁷. Blood-based HIV tests (BBT) are used globally. Additionally oral mucosal transudate rapid HIV tests (OMT) allow for sample collection that is less invasive, are more acceptable to clients, poses fewer risks to healthcare workers (HCW), and may increase testing uptake⁸⁻¹⁰.

The Food and Drug Administration (FDA) approved the OraQuick OMT in 2004 for testing by health providers for individuals >12 years¹¹. In 2016 the OraQuick HIV Self-Test received WHO prequalification and it is now recommended by WHO as a screening test for HIV¹². OMT has high sensitivity and specificity in detecting HIV antibodies in adults and older adolescents^{7,10}. A meta-

analysis comparing OMT with BBT in adults reported a pooled sensitivity of 98.0% and specificity of 99.7% for OMT¹⁰. OMT has not been validated in children.

We evaluated the diagnostic performance of OMT compared to routine BBT in children and adolescents aged 18 months to 18 years in Kenya and Zimbabwe.

METHODS

Setting & Participants:

This analysis includes pooled data from two studies in Kenya and Zimbabwe that include parallel point of care diagnostic OMT and BBT to assess sensitivity and specificity of OMT among children and adolescents. Data was combined to increase precision of sensitivity and specificity estimates, as the number of newly diagnosed HIV-positive children in both settings has reduced with the scale-up of pediatric HIV prevention and treatment programmes.

Zimbabwe: This analysis was nested within the “Bridging the Gap in HIV Testing and Care for Children in Zimbabwe” (B-GAP Project) whose aim is to evaluate index-linked testing for pediatric case detection. Study participants were children and adolescents of unknown HIV status, aged 2-18 years, attending any health services in the participating hospitals and primary healthcare clinics.

Kenya: The “Saliva Testing and Video Information to Expand Uptake of Pediatric HIV Testing” (STEP-UP) study enrolled children aged 18 months to 12 years. Two recruitment streams were used. First, children of HIV-positive adults attending HIV clinics who were tested for HIV within a randomized controlled trial of financial incentives for index case testing (FIT trial; NCT03049917¹³) were recruited after determining HIV status using BBT within the trial. Second, children from outpatient clinics were recruited after HIV testing using BBT within routine testing; here children who tested BBT positive were oversampled.

Procedures:

Zimbabwe: Testing followed the national algorithm¹⁴: first, BBT by Determine (Alere Determine™ HIV-1/2 Ag/Ab Combo – Abbott, Illinois, USA) (4th generation), followed by First Response (First Response HIV-1-2, Premier Medical Corporation Ltd., Kachigam, India) (3rd generation) if Determine was reactive. In the case of two reactive BBTs, the same two BBTs were performed by a different provider to confirm a positive diagnosis. In the case of discordant BBTs, both tests were repeated. If discordance persisted, a third test, CHEMBIO was performed (CHEMBIO HIV 1/2 STAT-PAK Assay, CHEMBIO Diagnostic Systems, Inc., New York, USA). If this third test was positive, the result was reported as inconclusive and a retest conducted in 14 days. OMT was conducted by clinic staff blinded to BBT results.

Kenya: The national algorithm mirrored that in Zimbabwe with the following exceptions: the Determine HIV test was 3rd instead of 4th generation and DNA PCR from dry blood spot specimens was the third test and was considered conclusive¹⁴⁻¹⁶. Additionally, BBT was performed by non-research staff. Research staff performed OMT and were not blinded to BBT results.

The reference standard used for our study was the HIV status as per the national algorithm of each country.

OMT: In Zimbabwe and Kenya, OMT sample collection and processing was performed bedside by qualified HIV testing lay providers who are typically lower than nurse level providers and are responsible for HIV testing in both countries. The qualification for these providers is a standard national training for HIV services conducted over two weeks. Testing was conducted according to manufacturer details (OraQuick ADVANCE Rapid HIV-1/2 Antibody Test - OraSure Technologies Inc., Bethlehem, PA) whereby the research staff collected an oral fluid sample from the participants by running the test device between the lips and outer gums of the client once on top and once on bottom and then place the test device pad directly into the reaction fluid immediately after collection¹⁷. OMT results were read once between 20 and 40 minutes in Zimbabwe, and twice in Kenya at both 20 and 40 minutes to assess

test performance at the lower and upper recommended times. OMT results were not shared with caregivers, as the test was undergoing validation.

Statistical analysis

Data were analyzed using STATA14 (StataCorp, College Station, TX, USA). Sensitivity was calculated by dividing the number of OMT positive children by the number of BBT positive children. Specificity was calculated by dividing the number of OMT negative children by the number of BBT negative children. Positive predictive value (PPV) and negative predictive value (NPV) were calculated in the Zimbabwean cohort by dividing the number with both positive OMT and BBT by all the positive OMT tests (PPV) and by dividing the number with both negative OMT and BBT results by the total negative by OMT (NPV). PPV and NPV were not calculated in the Kenyan cohort because positive children were oversampled. Ninety-five percent (95%) or 97.5% (when the estimate was 100%) confidence intervals (CI) were calculated using a binomial distribution. Stability of the test results using results interpretation pictures from the manufacturer was described in Kenya.

Ethics

Adolescents ≥ 16 gave independent written informed consent without parental/guardian consent. Parents/guardians of children aged 18 months - 15 years provided written consent; adolescents 13-15 years signed a paragraph within the parental consent form to give their assent while children 7-12 signed a separate assent document, which was optional in Kenya. B-GAP received approval from the Biomedical Research and Training Institute, the Medical Research Council of Zimbabwe and institutional review boards at Duke University and the London School of Hygiene and Tropical Medicine. The Kenya study received approval from the Kenyatta National Hospital Ethics and Research Committee and the University of Washington Institutional Review Board.

RESULTS

Demographics

Overall, 1,776 children were enrolled; 1,570 (88%) from Zimbabwe and 206 (12%) from Kenya. The median age was 7.3 years (interquartile range [IQR]: 4.7, 11.6); 2 (0.1%) were 18 months -2 years; 512 (29%) were >2-5 years; 845 (48%) were >5-12 years; 417 (23%) were >12-18 years. Overall, 918 (52%) were female. Among Kenyan children, 169 (82%) were identified via index case testing (ICT) and 37 (18%) in outpatient clinics and inpatient wards.

OMT sensitivity and specificity

Among 71 children positive by BBT, 71/71 (sensitivity: 100% [97.5% CI: 94.9-100%]) were positive by OMT. Among 1,705 children negative by BBT, 1,703/1,705 (specificity: 99.9% [95% CI: 99.6-100.0%]) were negative by OMT. In the 1,570 Zimbabwean participants, the PPV was 93.3% (95%CI: 77.9%-99.2%) and the NPV was 100.0% (97.5%CI: 99.8% -100.0%).

In Zimbabwe, two children who initially tested BBT negative and OMT positive were retested within 1 week to confirm HIV status because of suggestive clinical presentation and history; both were confirmed positive. A 9 year old was confirmed positive by ELISA. A 2 year old was confirmed positive by First Response and CHEMBIO. Excluding these 2 children, the sensitivity and specificity of OMT compared to BBT were each 100% (97.5%CI: 94.9-100% and 99.8-100%, respectively) (Table 2).

Stability of visual results (Kenya)

Among 43 children with positive OMT at 20 minutes, 43 (100%) had positive OMT at 40 minutes. Among the 163 children with negative OMT at 20 minutes, 163 (100%) had a negative OMT at 40 minutes. Using results interpretation pictures from the manufacturer, among 43 positive OMT results, 26 (60%) and 29 (67%) were strongly positive at 20 and 40 minutes, respectively. Three reads that were weakly positive at 20 minutes were strongly positive by 40 minutes.

DISCUSSION

In this cross sectional study of children ages 18 months to 18 years, we found that OMT had excellent sensitivity and specificity. When compared to the Kenyan and Zimbabwean national algorithms, OMT did not miss any positive children. These data suggests that OMT is valid for HIV diagnosis in this age range.

As with other antibody tests, OMT is inappropriate as a diagnostic test for children under 18 months due to the presence of maternal antibodies¹⁸. In adults, antibody-based tests have limitations due to a long window period, which may lead to failure in detecting recent HIV infection¹⁹. However, this is less of a concern among older children and younger adolescents who, if infected, are likely to have long-standing HIV acquired perinatally.

Our results provide evidence for wider use of OMT for pediatric testing. Current testing approaches to identify children include index-linked testing, provider-initiated testing and counseling (PITC), targeted testing in health facilities, and community-based testing^{6,7,20-26}. Outpatient PITC can identify children earlier in disease progression²⁷; however, achieving high coverage is challenging²¹ due to high client volume and workload for limited numbers of HCWs²⁸. In resource-limited settings, scaling up testing will require simultaneously increasing coverage and minimizing costly components of testing, including HCW time^{29,30}. The ease and safety of OMT presents a potential opportunity for task-shifting from HCWs to lay providers as was done in this study or to caregivers to overcome human resource constraints. It is also important to note that the time to perform and throughout for OMT is also similar to that required for BBT. Future research is needed to explore the acceptability and feasibility of OMT by caregivers, and HCW in facility and community settings.

A 2012 systematic review comparing OMT with whole blood specimens reported a pooled sensitivity of 98.0% and specificity of 99.7% for OMT¹⁰. Despite this, the concentration of antibodies in oral fluid is lower than in blood and typically wanes during HIV treatment^{31,32}. Prior studies in Zimbabwe have

confirmed that OMT has suboptimal sensitivity in ART-experienced children^{29,33}. WHO has issued warnings, advocating that rapid diagnostic tests not be used among ART-experienced adults; similar warnings appear warranted in children. Therefore, it is critical to avoid use of OMT by ART-experienced patients, either to confirm being “cured” of HIV or when reinitiating HIV care³⁴. Our study included an entirely ART-naïve pediatric population and observed no false negative results. In two cases, children were negative by BBT and positive by OMT and were confirmed HIV-positive upon repeat testing. This suggests slightly better detection by OMT than BBT in our study; it is unclear why we observed this counterintuitive finding.

Our study’s strengths include a large sample of ART-naïve, HIV-positive children to inform precise estimates of sensitivity. In addition data from Kenya and Zimbabwe provided similar results. OMT results were compared to routine, field-based BBT according to national algorithms, which provides an apt comparison with standard of care tests and provides useful public health information. Limitations include that OMT result interpretation was not blinded in Kenya, which may have influenced result interpretation. National algorithms between the two countries differed slightly, so the “reference standard” was not the same in both countries. However, in both cases, the algorithms are those used for national guidelines. Consequently our findings demonstrate the performance of OMT against the standard of care and are therefore generalizable in these settings. While the BBT in this study were not ELISA or PCR, OMT has previously been compared with these more sensitive lab-based tests to inform FDA approval and WHO endorsement for adults^{11,31}. An additional limitation is that in our study we did not have any inconclusive test results. Procedures on how to report and manage inconclusive test results must be put in place.

CONCLUSION

OMT is highly sensitive and specific in children and adolescents. This is consistent with findings from studies in adult populations. Policymakers and regulators should consider expanding the age in which OMT may be used to include children over 18 months.

TABLES

Table 1: Sociodemographic characteristics

Table 2: Performance of OMT vs BBT for HIV diagnosis

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CDC and INN and ADW developed the first draft of the manuscript and conducted the data analysis.

Zimbabwe: CR developed the study protocol and was assisted by BC who developed data collection tools and standard operating procedures. RAF, HM, GM and KS supervised CR and provided support in the design of the study. TB managed the dataset. GM, CDC, BC and ED supervised field staff.

Kenya: ADW, INN, JN, GJS, JS, DAK and DW developed the protocol. ADW and INN obtained grant funding. ADW, INN and JN developed study material and supervised data collection.

All co-authors revised and approved the final draft of this manuscript.

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TABLES & FIGURES

Table 1: Sociodemographic characteristics

	All N=1776	BBT* HIV- positive n=71	BBT HIV- negative n=1705
Child characteristics	n (%) or median (IQR[#])	n (%) or median (IQR)	n (%) or median (IQR)
Age group 18mths - 2 years	2 (0.1)	1 (1)	1 (0.1)
>2-5 years	512 (29)	21 (30)	491 (29)
>5-12 years	845 (48)	34 (48)	811 (48)
>12-18 years	417 (23)	15 (21)	402 (24)
Female	918 (52)	46 (65)	872 (51)
Recruitment country			
Zimbabwe	1570 (88)	28 (39)	1542 (90)
Kenya	206 (12)	43 (61)	163 (10)
Index case testing	169 (82)	7 (16)	162 (99)
Inpatient/outpatient	37 (18)	36 (84)	1 (1)
PMTCT History (Kenya)	All n=189	BBT* HIV- positive n=43	BBT HIV- negative n=146
Tested positive in pregnancy	8 (4)	5 (12)	3 (2)
Any maternal ARVs	4 (50)	2 (40)	2 (67)
Any infant prophylaxis	4 (50)	2 (40)	2 (67)

*BBT: Blood based
test
#IQR: interquartile
range

Table 2: Performance of OMT vs BBT for HIV diagnosis overall and stratified by site

Panel A: Overall results

		BBT		
		Positive	Negative	N
OMT	Positive	71	2*	73
	Negative	0	1703	1703
	Total	71	1705	1776
<i>*subsequently confirmed as HIV-positive using additional tests within 1 week of initial testing</i>				
Sensitivity		100% (97.5% CI 94.9-100)		
Specificity (including 2 discrepant)		99.9% (95% CI 99.6-100)		
Specificity (excluding 2 discrepant)		100% (97.5% CI 99.8-100)		

Panel B: Zimbabwe

		BBT		
		Positive	Negative	N
OMT	Positive	28	2*	30
	Negative	0	1540	1540
	Total	28	1542	1570
<i>*subsequently confirmed as HIV-positive using additional tests within 1 week of initial testing</i>				
Sensitivity		100% (97.5% CI 87.7-100)		
Specificity (including 2 discrepant)		99.9% (95% CI 99.5-100)		
Specificity (excluding 2 discrepant)		100% (97.5% CI 99.8-100)		

Panel C: Kenya

		BBT		
		Positive	Negative	N
OMT	Positive	43	0	43
	Negative	0	163	163
	Total	43	163	206
Sensitivity		100% (97.5% CI 91.8-100)		
Specificity (excluding 2 discrepant)		100% (97.5% CI 97.8-100)		