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Performance of the Integrated Management of Childhood Illness (IMCI) Algorithm for Diagnosis of HIV-1 Infection among Kenyan Infants

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Abstract

Objectives—Early infant HIV-1 diagnosis and treatment substantially improve survival. Where virologic HIV-1 testing is unavailable, Integrated Management of Childhood Illness (IMCI) clinical algorithms may be used for infant HIV-1 screening. We evaluated the performance of the 2008 WHO IMCI HIV algorithm in a cohort of HIV-exposed Kenyan infants.

Methods—From 1999–2003, 444 infants had monthly clinical assessments and quarterly virologic HIV-1 testing. Using archived clinical data, IMCI sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated using virologic testing as a gold standard. Linear regression and survival analyses were used to determine the effect of age on IMCI performance and timing of diagnosis.

Results—Overall IMCI sensitivity, specificity, PPV, and NPV value were 58%, 87%, 52%, and 90%, respectively. Sensitivity (1.4%) and PPV (14%) were lowest at 1 month of age, when 81% of HIV-infections already had occurred. Sensitivity increased with age ($p < 0.0001$), but remained low throughout infancy (range=1.4–35%). Specificity (range=97–100%) was high at each time point and was not associated with age. Fifty-eight percent of HIV-1 infected infants (50/86) were eventually diagnosed by IMCI, and use of IMCI was estimated to delay diagnosis in HIV-infected infants by a median of 5.9 months ($p < 0.0001$).

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Conclusions—IMCI had low sensitivity during the first month of life, when the majority of HIV-1 infections had already occurred, and initiation of treatment is most critical. Although sensitivity increased with age, the substantial delay in HIV-1 diagnosis using IMCI limits its utility in early infant HIV-1 diagnosis.

Keywords

IMCI; HIV; infant; Africa; clinical algorithm; pediatric

INTRODUCTION

Integrated Management of Childhood Illness (IMCI) is a set of standardized clinical algorithms used for the diagnosis and management of common illnesses affecting children in settings with limited access to laboratory diagnostics.¹ A validation study for identifying pediatric HIV-1 infection using a clinical algorithm was first reported in 2003.² In 2006 and 2008, the World Health Organization (WHO) reported an updated IMCI algorithm for identification of HIV-1 infection based on the presence of two or more of seven clinical criteria.^{3,4} IMCI could potentially be a valuable tool to identify HIV-infected infants in settings where virologic testing of all exposed infants is unfeasible. Early diagnosis of HIV-1 infection and initiation of antiretroviral therapy (ART) is critical in children under two years of age; in the absence of ART infant mortality rates have reached 55% in some African cohorts.^{5,6} In contrast, empiric start of ART at ten weeks of age reduced mortality risk by 76% in the Children with HIV Early Antiretroviral Therapy (CHER) study.⁷ WHO guidelines currently recommend initiation of ART at the time of diagnosis for children less than two years old.⁸ Screening for HIV-1 in infants whose mothers access prevention of mother-to-child HIV-1 transmission (PMTCT) services should ideally begin at birth, and continue periodically until at least six weeks after weaning.⁹

Sensitivity and specificity estimates of HIV-1 clinical algorithms have ranged from 9–89% and 42–99%, respectively.^{2,8,10–16} This wide range of values may be attributed to factors such as age distribution, health status, HIV-1 prevalence, health worker training, and selection of gold standard diagnostic test.⁸ Longitudinal studies of IMCI performance are timely in light of these highly discordant results, and the pending 2012 review of evidence proposed by WHO for reevaluation of clinical algorithms among highly vulnerable infant populations.⁸ In this report, we utilize a well-characterized longitudinal cohort to describe the effect of age on IMCI performance in Kenyan infants during the first year of life, and we estimate the delay in HIV-1 diagnosis when using IMCI compared to virologic testing.

METHODS

Study Population

Five hundred and ten pregnant, HIV-1 seropositive women were recruited from Nairobi City Council Maternal-Child Health Clinics between July 1999 and November 2002 for a prospective cohort study investigating HIV-1 transmission and infant immunity; details of the cohort and primary analyses are presented elsewhere.^{6,17,18} Maternal inclusion enrollment criteria included gestation ≥ 32 weeks, HIV-1 seropositive, ≥ 18 years of age,

plans to reside in Nairobi for at least a year postpartum, and consent for collection of serial infant blood samples. Women were excluded if study clinicians determined they were too sick to participate. This secondary analysis included infants surviving to at least one month of age, who had a minimum of one virologic test and clinical assessment. We excluded infants with loss to follow-up before one month of age and second born twins.

Infant HIV-1 virologic diagnosis

Study participants were provided with nutritional counseling and elected either breastfeeding or replacement feeding according to personal preference. This study was conducted before antiretroviral therapy (ART) became freely available in Kenya; women were provided with short-course zidovudine¹⁹ from 36 weeks gestation according to contemporaneous Kenyan Guidelines, but otherwise received no ART postpartum. Infants received virologic HIV-1 testing within 48 hours of birth, one month, and then at 3, 6, 9, and 12 months of age. At each of these time points dried blood was collected onto filter paper and used for HIV-1-*gag* PCR as previously described.²⁰ At each time point, HIV-1 viral RNA loads were also measured from cryopreserved plasma specimens using the Gen-Probe assay.²¹ Infants were considered infected on the first of two consecutive positive tests for HIV-1 RNA and/or DNA. The time to HIV-1 infection based on virologic testing was calculated as the midpoint between the last negative and first positive test.

Clinical Data Collection

The data collection methodology has previously been described.^{17,22–24} At each monthly visit, a questionnaire was completed with information regarding nutrition, breastfeeding and intercurrent illness. Physical examinations were conducted by a study pediatrician to assess growth and record clinical findings.

IMCI Clinical Diagnostic Criteria

Since all women were confirmed as HIV-1 seropositive at study enrolment, all infants had known exposure to HIV-1 and did not receive HIV-1 serologic testing. The prospective cohort study did not collect data for the purpose of evaluating IMCI; however, variables assessed were appropriate for a retrospective evaluation of WHO IMCI criteria³: persistent diarrhea, very low weight for age, oral thrush, parotitis, lymphadenopathy, pneumonia, and ear discharge. The WHO criteria were modified to include a diagnosis of *otitis media* or *externa* as a surrogate for ear discharge. Weight for age z-scores were calculated using WHO Anthro software.²⁵ IMCI criteria were evaluated discretely at each study visit; infants were identified as having suspected HIV-1 infection if they met two or more clinical criteria at an individual study visit.

Statistical Analysis

All statistical analyses were performed using STATA version 11.0 (StataCorp, College Station, TX). All tests were two-sided with $\alpha=0.05$. Virologic confirmation of HIV-1 infection was considered the gold standard; IMCI sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated overall (an infant classified at any visit as infected using IMCI criteria) and at each month of age up to twelve

months. Fisher's exact test was used to compare frequencies of clinical diagnoses between HIV-infected and HIV-exposed uninfected infants. A cutoff of two clinical criteria was used to compare sensitivity/specificity between age groups (using each infant's maximum IMCI score). Linear regression was used to test for associations between infant age and sensitivity, specificity, PPV and NPV. For the 86 HIV-infected infants, an incidence rate ratio was calculated using a generalized estimating equation (GEE) regression model with a Poisson link to compare time to HIV-1 diagnosis using virologic testing versus IMCI; an exchangeable working correlation structure with robust standard error was used in this model to account for the correlation between multiple observations per infant. Kaplan-Meier survival analysis and the log rank test for equality were used to estimate and compare the median time to HIV-1 diagnosis using virologic testing versus IMCI.

RESULTS

Cohort characteristics and follow-up

Of the 476 infants delivered, 468 were live, singleton births. Fourteen infants died before one month and ten were lost to follow-up with no visits at or after the first month of age. The 444 infants with at least one follow-up visit between one and twelve months of age were included in this analysis. During the first year of life, infants and their mothers received a median of eleven study visits (IQR= 8–12). Seventy-six percent (336/444) of mothers breastfed for a median duration of 9 months (IQR=4–12).

Eighty-six infants (19%) were diagnosed with HIV-1 infection during the first year of life using virologic testing (Table 1). Twenty-eight (33%) infants were diagnosed at their neonatal visit, 42 (48%) infants by month one, 7 (8%) infants at month three, and the remaining 9 (10%) infants were diagnosed after month three. A total of 30/86 (35%) HIV-infected infants and 20/358 (5.6%) HIV-exposed uninfected infants in this analysis died between one and twelve months. The median age at death was 5.4 months (IQR=4.3–6.9) in HIV-1 infected infants and 3.7 months (IQR=2.5–5.0) in HIV-exposed uninfected infants. Thirty-six (42%) of the infected infants were never identified using IMCI; 14 (39%) died and 5 (14%) were lost to follow-up before twelve months of age. All but one of the 14 deaths were among infants with early acquisition (<1 month) of infection.

Frequency of IMCI clinical criteria detected in HIV-infected and HIV-uninfected infants

Clinical criteria were assessed monthly. Except for parotitis, all indicator conditions were commonly reported, with oral thrush (67%), lymphadenopathy (55%) and pneumonia (55%) being the most commonly identified in HIV-1 infected infants (Table 2). Oral thrush, lymphadenopathy, persistent diarrhea, pneumonia, and very low weight for age were more frequent in HIV-infected infants compared to uninfected infants ($p<0.0001$ for each).

Sensitivity, Specificity and Predictive Power of IMCI for Infant HIV-1 Diagnosis

Of the 444 infants, 86 (19%) were diagnosed with HIV-1 infection by virologic testing and 97 (22%) were identified as having suspected HIV-1 infection using IMCI (Table 3). The overall sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of IMCI compared to virologic testing were 58%, 87%, 52%, and 90%, respectively.

IMCI performance was assessed at discrete monthly study visits during the first year of life (Table 3). At 1 month of age, when 70 infants had already acquired HIV-1 (81% of infections), IMCI correctly identified only 1 of the HIV-infected infants (sensitivity 1.4% (1/70)). Sensitivity was low throughout follow-up, but increased significantly with infant age (Pearson's $r^2=0.79$; $p<0.0001$). Specificity remained high (range 97–100%) at each time point and was not associated with infant age ($r^2=0.06$; $p=0.58$). The PPV ranged from 14–79%, and increased significantly with age ($r^2=0.33$; $p=0.05$). PPV was lowest at one month of age; only 14% of infants who met IMCI criteria were actually HIV-infected, suggesting IMCI would be a poor tool for screening HIV-1 exposed infants at this critical time-point. The NPV ranged from 84–91% and was also significantly associated with infant age ($r^2=0.85$; $p<0.0001$).

Delay in infant HIV-1 diagnosis using IMCI clinical criteria versus virologic testing

Time to HIV-1 diagnosis was compared using IMCI and virologic testing (Figure 1A). Among the cohort of 444 infants, the incidence of HIV-1 detection was 26 per 100 person-years (95% CI=21–33) using virologic testing. Among the 86 truly infected infants, the incidence of HIV-1 detection using IMCI was 15 per 100 person-years (95% CI=11–19). The incidence rate ratio (IRR) for IMCI compared to virologic HIV-1 diagnosis was 0.38 (95% CI=0.26–0.57; $p<0.0001$), indicating IMCI was approximately 62% slower at identifying HIV-1 infection compared to virologic testing.

Among the 86 infants with HIV-1 infection, the median time to virologic diagnosis was 0.49 months (IQR=0.03–0.63). Among infected infants, 50 (58%) were eventually identified as having suspected HIV-1 infection by IMCI. Overall, the median time to HIV-1 diagnosis using IMCI was 7.5 months with a median delay of 5.9 months. At six and twelve months, the probability of undetected true HIV-1 infections when using IMCI was 62% (95% CI=0.49–0.72) and 28% (95% CI= 0.18–0.39), respectively.

Among HIV-infected infants, we also compared the median time to diagnosis in infants grouped by timing of HIV-1 acquisition; virologic diagnosis of HIV-1 before 1 month of age were considered “early” acquisition (70/86, 81% of infections; Figure 1B) and virologic diagnosis of HIV-1 after 1 month of age were considered “late breast milk” acquisition (16/86, 19% of infections; Figure 1C). Of the infants with early HIV-1 acquisition 60% (42/70) eventually met IMCI criteria; the median time to diagnosis using IMCI was 6.6 months of age, with a median delay of 6.1 months. Among infants with late HIV-1 acquisition, 50% (8/16) eventually met IMCI criteria; the median time to diagnosis using IMCI was 10.5 months, with a median delay of 4.5 months.

DISCUSSION

In 2010, the WHO reported low quality of evidence yet a strong recommendation for use of clinical algorithms and serologic testing in the absence of virologic testing.⁸ Healthcare workers in low resource settings may rely on IMCI to inform decisions about referral for further HIV-1 testing, early ART initiation, cotrimoxazole prophylaxis, and infant feeding. In this longitudinal study comparing IMCI to HIV viral assays, we found that IMCI performance was very low during infancy, but increased with age. Although many truly

infected infants were eventually identified using IMCI, reliance on IMCI alone would delay identification of the HIV-infected infant for >5 months, an unacceptable delay for infants who are at high risk for opportunistic infections and death in the absence of ART. Our findings support the current push to expand virologic assays for early detection of infant HIV and to foster improved systems to provide these assays to infants.

In this study, IMCI sensitivity increased with age while specificity remained high throughout infancy. Our observation of increasing sensitivity with age is consistent with previous studies^{11,16}, and reflects the increasing incidence of opportunistic infections as HIV-infected infants become immunosuppressed. IMCI performance was poorest at one to two months of age, when identification of infected infants would be most effective for decreasing morbidity and mortality; this is a time when most transmissions (>80%) have already occurred, is the optimal time frame for HAART initiation, and also the time when infants are most likely to visit health clinics (for routine immunizations at six and ten weeks). Although IMCI sensitivity improves with age, this is offset by deaths in infected children, which results in a lower prevalence of HIV-1 in the population. For example, most children attend the nine-month measles vaccination visit, but at this time point, 31% of HIV-infected children have already died (data not shown), and IMCI sensitivity is only 20% (Table 3).

PPV was also lowest at 1 month of age in this cohort, and remained <80% throughout all time-points. This is of particular concern for settings in which IMCI is not used as a screening tool, but is rather employed as a diagnostic test, and may be used to guide initiation of ART. In our cohort of children known to be HIV-exposed, the prevalence of HIV was high, but in populations where maternal HIV status may not be known, PPV may be even lower, meaning a substantial number of children could be misdiagnosed and inappropriately started on ART.

To our knowledge, the delay in HIV-1 diagnosis when using IMCI has not been described previously. According to the most recent WHO IMCI algorithm, children who met IMCI criteria in our study would have been categorized as “HIV EXPOSED/POSSIBLE HIV;” for this category the WHO IMCI manual recommends confirmation of HIV-1 infection status as soon as possible with the best available test, follow-up in fourteen days, then monthly for three months and then every three months or as per immunization schedule.⁴ The delay from time of infection to presentation of IMCI clinical criteria indicates that reliance on these criteria alone will result in substantial delays before a health worker is prompted to recommend confirmatory testing and/or referral for early initiation of ART.⁸ In settings where receipt of virologic testing results may be delayed up to a period of weeks, or even months, the difference between time to diagnosis for IMCI compared to virologic testing will be smaller. Using either diagnostic tool, the delay to time of infection detection is particularly critical for infants with early HIV-1 acquisition (before one month of age), who demonstrate more rapid onset of morbidity and greater rates of mortality compared to infants with later acquisition.²⁶ The sensitivity observed in this study using two WHO criteria is somewhat lower than reported by Iliff, et al. for infants aged six months (22% versus 44%) and twelve months (34% versus 57%)¹²; however, results are similar to a cross-sectional study of IMCI performance among Kenyan infants (sensitivity of 20% and 26% for infants

less than six months and six to twelve months, respectively).¹⁶ The lower sensitivity and specificity reported here may be related to cohort differences or the retrospective rather than prospective classification of IMCI criteria; clinical assessments in prospective studies of IMCI performance may be more likely to identify IMCI criteria as clinical symptoms during a study visit. In this study, otitis and parotitis were not associated with HIV-infection and their removal from the algorithm should be considered for this population.

Strengths of this study include the prospective, longitudinal cohort, its high power to discern time trends, and its unbiased assessment of IMCI clinical criteria. In this study, sensitivity estimates were undoubtedly reduced by high mortality in HIV-infected infants who were lost to follow-up or died before presenting with IMCI-specific symptoms at clinic visits. Diagnosis of persistent diarrhea relied on maternal recall, and could have led to some misclassification. Reporting of clinical illnesses may have been greater for infected infants since health workers and mothers were sometimes aware of infant HIV status in real time, although the retrospective nature of our IMCI analysis means that clinicians and mothers were not preferentially biased towards looking for or reporting IMCI-specific signs or symptoms. This study relied on a “snapshot” approach assessing clinical criteria available at discrete visits, because in our experience children are often seen by medical officers without access to their previous clinical records. For a provider or clinic with access to a child’s medical history or past records, cumulative observation of IMCI criteria may improve algorithm performance. Differing HIV-1 prevalence, level of health-care worker experience, duration of breastfeeding/HIV-1 exposure and health status of infants should be considered when considering generalizability of this evaluation of IMCI performance.¹²

Although our data demonstrate IMCI performs poorly in this population, the feasibility and cost-effectiveness of infant HIV-1 testing must also be considered when considering EID in resource limited settings.²⁷ Although virologic diagnosis is ideal, PCR-based testing is currently not achievable in many settings. Nucleic acid-based platforms which are affordable, do not require instrumentation, and are available as a point-of-care diagnostic test are urgently needed for infant HIV-1 diagnosis²⁸, and would enable expansion of virologic diagnosis to many more sites. In summary, while IMCI sensitivity increases with age, it is a poor diagnostic/screening test early in infancy when most infections occur and the need for diagnosis and initiation of ART is most urgent. Our findings underscore the critical need for expanded access to virologic-based rapid diagnostic technologies for infant HIV-1 infection in resource-limited settings. Despite its low sensitivity in infants, IMCI may still prove useful in identifying older children with undiagnosed HIV-1 infection, and children who acquire HIV-1 infection through late breast milk transmission.

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GJ-S conceived and obtained funding for the study; LD, JS, KT, and BR developed the analysis plan and analyzed the data; DW, CF, EM-O, and CG developed the clinic sites, cohort, and carried out the clinical portions of the study. JO developed, validated, and executed the virologic assays. The final manuscript was co-written by LD and JS. All authors have contributed edits to this paper, and have approved this final submission. The authors thank Dana DeVange Panteleef and Sandy Emery at the Fred Hutchinson Cancer Research Center, Seattle, Washington for performing viral loads and filter paper PCR analysis, and the Kizazi Working Group who provided feedback during analysis and manuscript development. Most of all, we are grateful to the CTL study clinic and laboratory teams in Nairobi, and the study participants who made this work possible.

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Figure 1. IMCI delays HIV-1 diagnosis in infants

Kaplan-Meier curves illustrate the cumulative probability of detecting HIV-1 infection for infants up to twelve months of age using virologic testing (black line) and the IMCI algorithm (gray line) for A) all infected infants, B) infants with early acquisition of HIV-1 infection, and C) infants with late acquisition of HIV-1 infection. P values shown for log-rank test.

Table 1

Participant characteristics.

Infant characteristics (N=444)	Frequency (%), Mean ($\pm$ SD), or Median (IQR)
Months of follow-up	12 (10–12)
Breastfed	336/444 (76%)
Duration of breastfeeding (months)	9 (4–12)
Number of IMCI assessments	11 (8–12)
Number of virologic assessments	4.0 (3–5)
Cumulative infants diagnosed with HIV-1 by virologic testing	86 (19%)
Infants infected with HIV-1 before 1 month of age	70 (81%)
Deaths among HIV-infected infants	30 (35%)
Deaths among uninfected infants	20 (5.6%)
Age at death for HIV-1 infected infants (months)	5.4 (4.3–6.9)
Age at death for uninfected infants (months)	3.7 (2.5–5.0)

Table 2
Prevalence of IMCI clinical criteria among HIV-1 infected and uninfected Kenyan infants.

IMCI indicator ^a	HIV-infected infants (n=86)		HIV-uninfected infants (n=358)		Odds ratio (95% CI; p-value)
	Cases	(%)	Cases	(%)	
Oral thrush	58	67%	114	32%	4.7 (2.7–8.1; p<0.0001)
Lymphadenopathy	47	55%	46	13%	8.6 (4.9–15; p<0.0001)
Persistent diarrhea ^b	15	17%	24	6.7%	3.4 (1.6–7.0; p=0.0002)
Pneumonia	47	55%	107	30%	3.1 (1.9–5.2; p=<0.0001)
Very low weight (z-score < -3)	27	31%	30	8.4%	5.0 (2.6–9.4; p=<0.0001)
Otitis (media or externa)	23	27%	97	27%	1.0 (0.59–1.8; p=0.88)
Parotitis	0	0%	2	0.6%	0 (p=0.49)

^a Presence of clinical criterion for an infant identified at any monthly scheduled visit.

^b Infant diarrhea lasting 14 or more days, self-reported by mothers.

Table 3

Sensitivity, specificity, positive (PPV) and negative predictive (NPV) values of the WHO IMCI algorithm for HIV-1 diagnosis of infants at monthly scheduled visits.

Age (months)	N	HIV-infected infants at visit ^a	IMCI positive infants at visit	IMCI positive among HIV-infected infants at visit	IMCI Sensitivity (%)	IMCI Specificity (%)	IMCI PPV (%)	IMCI NPV (%)
1	441	70	7	1	1.4	98	14	84
2	420	62	4	3	4.5	100	75	85
3	407	67	23	14	21	97	61	86
4	382	60	17	8	13	97	47	86
5	355	53	13	8	15	98	62	86
6	365	53	16	12	22	99	75	88
7	336	42	15	11	26	99	73	90
8	322	40	19	12	28	98	63	90
9	332	46	13	9	20	99	69	88
10	295	40	18	14	35	98	78	91
11	282	36	18	11	29	97	61	90
12	319	44	19	15	34	99	79	90
Total ^b	444	86	97	50	58	87	52	90

Notes. N=total infants assessed at visit. Time points at which Kenyan infants visit health clinics for recommended immunizations are shaded.

^aCumulative virologic-confirmed HIV-infected infants remaining at visit; number declines due to mortality and loss to follow-up.

^bOverall sensitivity, specificity, PPV, and NPV reflect cumulative data (infant IMCI positive at any one visit).