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Evaluation of an empiric risk screening score to identify acute and early HIV-1 infection among MSM in Coastal Kenya

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We evaluated the University of North Carolina–Malawi Risk Screening Score (UMRSS) for detection of acute and early HIV-1 infection (AEHI) in a cohort of Kenyan MSM with approximately 8% annual HIV-1 incidence. Three components of the UMRSS (fever, diarrhea, and discordant rapid HIV tests) were also independent predictors of AEHI in our cohort. The predictive ability (area under the receiver operating characteristic curve, AUC) of the UMRSS was 0.79. A cohort-derived risk score consisting of six characteristics (fever, diarrhea, discordant rapid HIV tests, fatigue, age <30 years, and symptomatic sexually transmitted disease) had a higher AUC of 0.85. Screening for AEHI will have substantial transmission prevention benefits.

MSM have among the highest HIV-1 incidence in sub-Saharan Africa, but targeted interventions for HIV-1 testing of MSM are mostly lacking [1–3]. When HIV-1 is acquired, patients may frequently seek urgent healthcare for symptoms, including fever or unconfirmed ‘malaria’ [4–6], and become extremely infectious during a short period of 3–4 weeks (acute HIV infection; AHI) and highly contagious during the first 6 months (early HIV-1 infection) [7,8]. However, diagnosing acute and early HIV-1 infection (AEHI) remains challenging in resource-limited settings, in part due to a lack of low-cost, point-of-care tests for nucleic acid detection [9]. In Malawi, the UNC Malawi Risk Screening Score (UMRSS) combining discrete clinical and behavioral characteristics has been developed to identify AHI among sexually transmitted diseases (STDs) clinic patients [10]. In this study, STD patients who were HIV-1 negative or had discordant rapid HIV tests received a score of 1 for fever, body ache, and more than one partner; 2 for diarrhea and genital ulcer disease (GUD); and 4 for discordant rapid tests. Using this algorithm, Powers *et al.* [10] could identify 95% of the AHI cases identified by targeted testing of only patients with a score of 2 or greater (40% of the population studied). As MSM frequently present with an STD, we wanted to validate this UMRSS in our MSM cohort in Coastal Kenya, and compare it to a

cohort-derived risk screening score (CDRSS) using our own data and similar methodology.

Since 2005, we have enrolled HIV-seronegative MSM in a cohort study of HIV-1 acquisition, as previously described [1]. Men made either monthly or quarterly scheduled visits at which risk reduction counseling was provided and a medical history and physical examination was performed. HIV-1 seroconversion was diagnosed using two rapid test kits (Determine, Abbott Laboratories, Abbott Park, Illinois, USA; Unigold, Trinity Biotech plc, Bray, Ireland) in parallel. Patients with discordant rapid HIV-1 test results were retested until discordancy was resolved. All seronegative and discordant samples were tested for p24 antigen (Vironostika HIV-1 p24 ELISA, Biomérieux, Ltd, Marcy l'Etoile, France). Up to 1 January 2012, preseroconversion and postseroconversion plasma samples were tested for HIV-1 RNA level (Amplicor Monitor, version 1.5; Roche, Branchburg, New Jersey, USA) with a positive result defined as more than 400 copies/ml [1]. All HIV diagnoses were confirmed by a positive RNA level ($n=67$) or by follow-up until both rapid tests were positive ($n=6$).

An AEHI visit was defined as a visit with an antibody seroconversion (determined by two positive rapid HIV tests), serodiscordant rapid HIV tests (one rapid test positive, one rapid test negative), or positive p24 antigen test. Eighteen (90%) of 20 patients with a positive p24 antigen test were clinically evaluated within 1 week of the test result [1].

HIV-1 incidence was estimated at 7.5% (95% confidence interval 6.0–9.5) per 100 person years during the study period. The median number of days from estimated date of HIV-1 infection to evaluation was 39 (interquartile range 19–59). At their AEHI visit, 42 patients had a rapid antibody seroconversion (after a documented seronegative result at the last study visit), 11 had a serodiscordant rapid HIV test, and 20 had a positive p24 antigen test. Characteristics reported (including symptoms experienced since the last study visit) at 73 AEHI visits were compared with characteristics reported at 6458 scheduled cohort visits (Table 1).

Cohort-derived risk screening score

To identify predictors of AEHI in our MSM cohort, we calculated unadjusted prevalence odds ratios for

Table 1. Comparison of clinical and behavior characteristics in MSM at acute and early HIV-1 infection and seronegative clinic visits, Coastal Kenya, 2005–2012.

Predictor	Acute or early HIV-1 infection visits (n = 73) n (%)	HIV-1 negative visits (n = 6458) n (%)	Unadjusted POR ^a (95% CI)	Domain-specific model adjusted POR (95% CI) ^b	Combined model adjusted POR (95% CI) ^c	Final model adjusted POR (95% CI) ^d	Cohort-derived Score ^e	UMRSS score ^f
Sociobehavior and sociodemographic								
>1 Sex partner in the past month	46 (63.0)	4677 (72.4)	0.8 (0.5–1.3)	0.6 (0.4–1.0)	–	–	–	1
Age <30 years ^g	64 (87.7)	4510 (69.8)	3.3 (1.6–6.8)	3.1 (1.5–6.2)	3.0 (1.3–6.9)	3.3 (1.5–7.5)	1	–
Symptoms reported in the past month or since last visit								
Fever ^h	47 (64.4)	1037 (16.1)	9.5 (5.8–15.7)	1.2 (0.6–2.5)	2.3 (1.2–4.6)	2.8 (1.4–5.5)	1	1
Joint or muscle pain	47 (64.4)	1230 (19.1)	7.2 (4.4–11.9)	1.4 (0.7–2.8)	–	–	–	1
Head ache	45 (61.6)	1244 (19.3)	6.7 (4.2–11.1)	1.4 (0.7–2.8)	–	–	–	–
Fatigue	47 (64.4)	939 (14.5)	10.9 (6.6–18.0)	2.2 (1.1–4.6)	3.8 (1.8–7.9)	3.5 (1.8–6.8)	1	–
Loss of appetite	39 (53.4)	700 (10.8)	9.3 (5.8–15.0)	1.6 (0.9–2.9)	–	–	–	–
Night sweats	30 (41.1)	449 (7.0)	9.7 (5.8–16.2)	1.5 (0.8–2.8)	–	–	–	–
Sore throat	26 (35.6)	563 (8.7)	5.9 (3.5–9.8)	1.0 (0.5–2.0)	–	–	–	–
Diarrhea	26 (35.6)	411 (6.4)	8.6 (5.2–14.3)	2.1 (1.2–3.6)	2.7 (1.5–4.9)	2.8 (1.6–4.9)	1	2
Swollen glands	19 (26.0)	328 (5.1)	6.6 (3.7–11.7)	1.2 (0.5–2.6)	–	–	–	–
Vomiting	19 (26.0)	290 (4.5)	6.9 (3.9–12.2)	1.1 (0.6–2.1)	–	–	–	–
Oral ulcers	14 (19.2)	240 (3.7)	6.1 (3.2–11.5)	0.8 (0.4–1.6)	–	–	–	–
Too sick to work	33 (45.2)	345 (5.3)	14.7 (8.9–24.5)	2.6 (1.4–4.7)	–	–	–	–
Urethritis	8 (11.0)	392 (6.1)	1.8 (0.8–3.9)	–	–	–	–	–
Proctitis	13 (17.8)	273 (4.2)	6.5 (3.3–12.6)	–	–	–	–	–
Genital sores	10 (13.7)	186 (2.9)	6.8 (3.2–14.2)	–	–	–	–	–
Any symptomatic STD	21 (28.8)	614 (9.5)	4.2 (2.4–7.3)	1.7 (0.9–3.1)	2.0 (1.1–3.8)	2.3 (1.3–4.0)	1	–
Clinical examination at visit								
Maculopapular rash	4 (6.0)	100 (1.6)	4.1 (1.4–11.8)	2.8 (1.0–7.7)	1.7 (0.5–6.0)	–	–	–
Conjunctivitis	14 (19.2)	349 (5.4)	4.2 (2.2–7.8)	3.1 (1.7–5.9)	1.0 (0.4–2.3)	–	–	–
Genital ulcer	1 (1.5)	40 (0.6)	2.6 (0.3–21.3)	1.4 (0.2–10.2)	–	–	–	2
Genital warts	0	34 (0.6)	–	–	–	–	–	–
Lymph nodes	19 (26.0)	736 (11.4)	2.8 (1.6–4.8)	–	–	–	–	–
Cervical	12 (17.7)	277 (4.3)	5.0 (2.5–9.8)	2.3 (1.1–4.8)	1.3 (0.5–3.0)	–	–	–
Axillar	2 (3.0)	40 (0.6)	5.3 (1.2–23.8)	3.5 (0.8–14.8)	–	–	–	–
Inguinal	15 (22.4)	556 (8.9)	3.1 (1.7–5.6)	1.8 (1.0–3.1)	1.1 (0.5–2.4)	–	–	–
Discordant HIV test results	11 (15.1)	14 (0.22)	73.5 (11.7–462.3)	N/A	53.5 (11.1–258.1)	45.9 (9.2–229.7)	4	4

AEHI, acute and early HIV-1 infection; 95% CI, 95% confidence interval; GEE, generalized estimating equation; POR, prevalence odds ratio; STD, sexually transmitted disease; UMRSS, University of North Carolina-Malawi Risk Screening Score.

^aPrevalence odds ratio.

^bFactors associated with AEHI at $P \leq 0.05$ were included in initial multivariable models for two domains: 'symptom' and 'clinical exam' findings.

^cFactors associated with AEHI at $P \leq 0.05$ in the initial domain-specific models were included in a combined model, to which age and discordant HIV test results were added.

^dAll variables in final model associated with AEHI at $P \leq 0.05$.

^ePredictor score is equal to its β coefficient (natural log of the adjusted prevalence odds ratio) from the GEE model, rounded to the nearest integer.

^fUMRSS derived from multivariable analysis of predictors of acute HIV infection [10].

^gAge <30 years. Younger age in MSM was associated with HIV-1 acquisition in unadjusted multivariable analysis in our cohort [1].

^hIncluded patients who had a history of presumptive 'malaria' treatment.

sociodemographic, medical history, and physical examination findings with AEHI as an outcome. We compared characteristics reported at AEHI visits to those reported at all seronegative visits, using generalized estimating equation (GEE) to adjust for intraindividual correlation. We constructed separate models for two specific domains (i.e. symptoms reported in past months and clinical examination findings), similar to the approach of Powers *et al.* [10]. Characteristics associated with AEHI at $P \leq 0.05$ were included in initial multivariable models for two domains: 'symptom' and 'clinical examination' findings. We constructed a full, combined model including discordant rapid test results, age, fever, and the variables from the reduced, domain-specific models. Fever (or a history of having received treatment for unconfirmed 'malaria') was included *a priori* as this was the most significant reason for care seeking prior to seroconversion in our cohort [4]. The final model retained only predictors associated with AEHI at $P \leq 0.05$ in the combined model. Data for men who seroconverted were censored at the AEHI visit.

Comparison of cohort-derived risk screening score with University of North Carolina-Malawi Risk Screening Score

Similar to Powers' approach, we assigned each variable in the final cohort-derived model a predictor score equal to its β coefficient (natural log of the adjusted prevalence odds ratio) from the GEE model, rounded to the nearest integer (Table 1). Independent predictors for HIV-1 acquisition included in the CDRSS and their corresponding predictor scores were 1 for fever, fatigue, any symptomatic STD, diarrhea or age less than 30 years; and 4 for discordant HIV tests. The maximum score possible using the CDRSS was 9. Predictors in the UMRSS are shown in the last column of the Table 1 and can sum to 11 [10]. We selected the CDRSS cut-off point that optimized sensitivity, specificity, and positive predictive values (details in the supplemental figure, <http://links.lww.com/QAD/A356>) and compared our results with UMRSS results. We calculated the AUC for the predictive ability of each score to identify a patient visit at which AEHI was diagnosed.

The UMRSS with a cut-off point at 2 had a sensitivity of 75.3%, specificity of 76.4%, and positive predictive value of 3.5% to identify AEHI correctly in our study population. Corresponding values for the CDRSS with a cut-off point at 2 were 80.8%, 76.0%, and 3.7%, respectively. The AUCs for the UMRSS and the CDRSS were 0.79 and 0.85, respectively ($P < 0.009$). When we restricted the CDRSS to include only age less than 30 years, fever, or any symptomatic STD, the AUC became 0.77 (not different from the UMRSS).

To our knowledge, this is the first time that the UMRSS has been validated outside Malawi. Three of the six UMRSS characteristics (history of fever, diarrhea, and discordant rapid HIV tests) identified AEHI independently in our MSM population, and so were included in the CDRSS. The CDRSS had a better performance when all six predictors of AEHI in our cohort were included (additional characteristics: fatigue, age <30 years, and symptomatic STD). Interestingly, a simplified CDRSS including only three characteristics (age <30 years, fever, and any symptomatic STD) had a similar performance to the UMRSS.

Study limitations include possible ascertainment bias if patients overreported symptoms at their AEHI visit due to a seroconversion diagnosis, and the fact that we derived our validation from a very high-risk MSM population followed in a research setting. Although GUD was a predictor of AEHI in the study by Powers *et al.* [10], GUD was uncommon in this MSM population [1]. Fatigue was not a predictor of AEHI in STD patients in Malawi, but was frequently reported by our population and by men (but not women) in a large study of primary HIV-1 infection [11].

In summary, our study confirmed the importance of fever, diarrhea, and discordant HIV test results for the identification of AEHI in African populations, and demonstrated that targeted screening for AEHI in MSM could be performed using a CDRSS consisting of a limited set of characteristics, including age younger than 30 years, fever, diarrhea, fatigue, any symptomatic STD, and discordant HIV test results. Such screening for AEHI, when supported by risk reduction counseling and combination prevention therapy, will have substantial transmission prevention benefits [3].

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Conflicts of interest

There are no conflicts of interest.

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Realtime adherence monitoring of antiretroviral therapy among HIV-infected adults and children in rural Uganda

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A real-time wireless electronic adherence monitor (EAM) and weekly self-report of missed doses via interactive voice response (IVR) and short message service (SMS) queries were used to measure antiretroviral therapy adherence in 49 adults and 46 children in rural Uganda. Median adherence was 89.5% among adults and 92.8% among children by EAM, and 99–100% for both adults and children by IVR/SMS self-report. Loss of viral suppression was significantly associated with adherence by EAM (odds ratio 0.58 for each 10% increase), but not IVR/SMS. Wireless EAM creates an exciting opportunity to monitor and potentially intervene with adherence challenges as they are happening.

Traditional antiretroviral therapy (ART) adherence assessments include self-report, pill counts, electronic monitoring, and drug levels [1]. These measures typically detect adherence challenges after HIV viral suppression has been lost and possibly after drug resistance has developed. Real-time, wireless monitoring strategies could identify adherence challenges before the loss of viral suppression, thus sustaining the effectiveness of first-line regimens [2]. Experience with real-time adherence monitoring in developing settings to date has been limited to proof-of-concept studies [3,4].

This manuscript presents data on the feasibility, validity, and acceptability of real-time adherence monitoring among adults and children in rural Uganda using a wireless electronic adherence monitor (EAM) called Wisepill and self-reported missed doses via interactive voice response (IVR) and short message service (SMS). Ethical approval was obtained from Partners Healthcare, Mbarara University of Science and Technology, and the Uganda National Council for Science and Technology. Participants were enrolled by convenience from two longitudinal, observational cohorts: the Ugandan AIDS Rural Treatment Outcomes Study (NCT01596322) and Children's ART Adherence Study (NCT00868257).

Wisepill wirelessly transmits a date-time stamp with each opening using general packet radio service. Data are stored for later transmission if network access is temporarily unavailable.

Adults and caregivers of children were offered their choice of IVR or SMS for weekly queries of missed doses in their local language. Successful responses required confirmation of a person identification number and receipt of a numeric response. Queries were repeated multiple times, if needed.

Plasma HIV RNA levels were determined at baseline and 6 months (lower detection limit of 400 copies/ml).

After 1 month, adults and caregivers were asked 'How would you describe using the Wisepill medication container?' and 'How do you feel about someone monitoring how you are taking your medicine every day?.'

Associations between loss of viral suppression at 6 months and percentage adherence during the prior month were determined by logistic regression. The 6-month time point was used for both adults and children to ensure uniform exposure to the adherence measures and allow for habituation to monitoring [5]. Given similar findings, data from adults and children were analyzed together, and data for IVR and SMS were analyzed together. Categories of average adherence were compared with loss of viral suppression by Fisher's exact test [6]. Wireless EAM and IVR/SMS-reported adherence were compared by Spearman correlation. Participants with missing data were excluded from analysis.

Forty-nine adults and 46 children were enrolled. Among adults, median age was 37 years [interquartile range (IQR) 32–43]; 77.6% were women. At enrollment, median CD4 cell count was 299 cells/ μ l (IQR 246–392), median duration of ART was 15 months (IQR 11–19), and 43 participants (87.8%) had undetectable HIV RNA. Among children, median age was 7 years (IQR 4–8); 44% were female. At enrollment, median CD4 percentage was 38 (IQR 30–48), median duration of ART was 32 months (IQR 18–48), and 20 (43.4%) had undetectable HIV RNA. All but two participants were taking twice daily nonnucleoside reverse transcriptase inhibitor-based ART.

Adult participants were followed for 53.6 person-years (median 14 months per participant); children were followed for 22.8 person-years (median 6 months per participant). Follow-up periods differed due to distinct funding mechanisms. No participants were lost; one adult died.

Median adherence by wireless EAM was 89.5% (IQR 83.9–92.3%) among adults and 92.8% (IQR 89.2–94.6%) among children.

Five adults (10.2%) and 15 caregivers of children (32.6%) received SMS adherence queries. Median percentage of successful responses was 86.5% (IQR 48.5–87.9%) for adults and 84.5% (IQR 66.5–94.1%) for caregivers. Median self-reported adherence by SMS was 100% (IQR 99.6–100%) for adults and 100% (IQR 99.1–100%) for children.

Thirty-nine adults (79.6%) and 30 caregivers (65.2%) received IVR adherence queries. Median percentage of successful responses was 65.0% (IQR 10.0–94.7%) for adults, and 76.1% (IQR 50.8–88.2%) for caregivers. Median adherence was 99.0% (IQR 96.5–100%) for adults and 100% (99.8–100%) for children.

HIV RNA was missing for four adults and four children. Three adults and three children lost viral suppression (7.0 and 15.0% of participants with baseline viral suppression, respectively). Percentage adherence by wireless EAM was significantly associated with loss of viral suppression (OR 0.58 for each 10% increase in adherence, IQR 0.34–0.98; $P=0.04$). Percentage adherence by IVR/SMS-report was not associated with loss of viral suppression (OR 1.7, 0.2–15.9; $P=0.64$) or adherence by wireless EAM ($r=0.11$, $P=0.35$). Loss of viral suppression was significantly associated with categories of average adherence with wireless EAM ($P=0.02$), but not IVR/SMS-report ($P=0.54$; Fig. 1).

All but two participants (97.9%) reported Wisepill was 'easy/very easy' to use. All stated they 'liked/really liked' being monitored.

Real-time wireless electronic adherence monitoring is feasible, valid, and acceptable for HIV-infected adults and children in a rural African setting. Although IVR was preferred over SMS, self-reported adherence was less feasible by IVR compared with SMS; neither was a valid measure of adherence.

Wireless EAM has several limitations. First, it is currently prohibitively expensive for routine care at \$185 per device. Significant cost reductions, however, could be achieved through mass production. Second, several technical problems were encountered, including failed data transmission and inadequate battery life. Technical limitations at the time of data collection prevented quantification of these problems, which may have affected the adherence assessments. Multiple improvements have since been made, including SMS for back-up data transmission [7] and a daily 'heartbeat' to indicate battery life, device airtime, and signal strength. Third, dedicated data personnel are required to manage this real-time adherence monitoring system, potentially limiting scalability.

The high adherence seen with self-report by IVR and SMS is consistent with traditional forms of self-reported

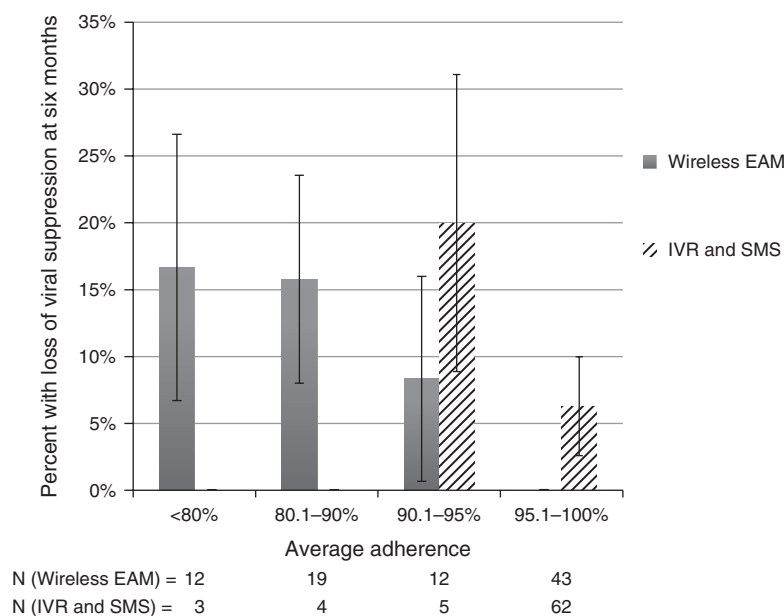


Fig. 1. Loss of viral suppression and adherence. Loss of viral suppression was significantly associated with categories of average adherence by wireless electronic adherence monitor (EAM; $P=0.02$), but not by interactive voice response (IVR) and short message service (SMS; $P=0.54$).

adherence [8]. Although the relative anonymity of technology-assisted adherence reporting could decrease social desirability bias [9] and frequent reporting could decrease recall bias, data in this study do not support using IVR and SMS for adherence assessment.

Real-time wireless adherence monitoring creates a unique and exciting opportunity to potentially intervene with adherence challenges as they are happening and thus prolong the effectiveness of inexpensive and accessible first-line therapies. Such efficiencies are especially important given current economic constraints and consideration of treatment for many, if not all, of the 34 million people living with HIV [10].

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Conflicts of interest

There are no conflicts of interest.

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