

Acute HIV-1 infection is as common as malaria in young febrile adults seeking care in coastal Kenya

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Background: Febrile adults are usually not tested for acute HIV-1 infection (AHI) in Africa. We assessed a strategy to diagnose AHI among young adult patients seeking care.

Methods: Young adults (<30 years) who met predefined AHI criteria at care seeking, including fever, sexually transmitted disease symptoms, diarrhoea, body pains or multiple partners were referred from five pharmacies and screened at five health facilities. Prevalent HIV-1 was diagnosed by nationally recommended serial rapid HIV-1 testing. Willing HIV-1-negative patients were evaluated for AHI, defined as a positive p24 antigen test, and subsequent seroconversion or RNA detection. Febrile patients evaluated for AHI were also screened for malaria using a rapid test, with PCR confirmation of positives.

Results: In 3602 adults seeking care, overall HIV-1 prevalence was 3.9%: 7.6% (68/897) among patients meeting AHI criteria vs. 2.6% (71/2705) among those who did not ($P < 0.001$). AHI was diagnosed in five of 506 HIV-1-negative or discordant patients who met AHI risk criteria and were completely evaluated [prevalence 1.0%, 95% confidence interval (CI) 0.3–2.3%]. Of these five AHI cases, four were diagnosed among the 241 patients with fever (prevalence 1.7%, 95% CI 0.5–4.2%), vs. one among 265 non-febrile patients (prevalence 0.4%, 95% CI 0.0–2.0%, $P = 0.1$). Malaria was confirmed by PCR in four (1.7%) of the 241 febrile patients.

Conclusion: AHI was as common as confirmed malaria in young febrile adults seeking care. An AHI detection strategy targeting young febrile adults seeking care at pharmacies and health facilities is feasible and should be considered as an HIV-prevention strategy in high-transmission settings.

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Introduction

Individuals with acute HIV-1 infection (AHI), who frequently seek healthcare for symptoms prior to seroconversion [1–3], are highly contagious [4,5], and may account for a large number of new HIV-1 infections [6,7]. Whereas some individuals with AHI remain asymptomatic, most experience an acute ‘malaria-like’ illness approximately 2 weeks following infection [8,9]. In 2010, Bebell *et al.* [10] reported that 1–3% of adults who sought care for suspected malaria in Uganda actually had acute or early HIV infection. Common symptoms of AHI include fever, joint and muscle pains, headache, fatigue, diarrhoea and sometimes rash [3,11].

Diagnosis and prompt initiation of ART for cases with AHI has been identified as a ‘top scientific priority’ for HIV prevention [12]. Indeed, a major obstacle to ‘treatment as prevention’ (TasP) programmes is the difficulty in finding and treating the people at greatest risk for HIV-1 transmission [12]. In view of declining malaria transmission [13,14] and ongoing HIV-1 transmission in coastal Kenya [15], we set out to determine the utility of a clinical algorithm administered in local health facilities and pharmacies to identify AHI in young adult patients seeking care.

Methods

Selection of acute HIV-1 infection criteria for testing

On the basis of an evaluation on the performance of a risk screening algorithm to identify AHI among sexually transmitted infection (STI) patients in Malawi [16,17], we selected age 18–29 years as an a priori criterion. Potentially eligible patients seeking healthcare were then assigned a risk score by summing points based on the following characteristics: 1 for generalized body pains or multiple partners in the past 2 months and 2 for documented fever ($\geq 37.5^{\circ}\text{C}$ axillary), reported diarrhoea, or symptoms compatible with an STI [17]. Final inclusion criteria included age 18–29 years, residency in the study area, a risk score of at least 2, and willingness to be evaluated for HIV-1, including AHI, and for malaria, if febrile.

Study population and setting

We mapped all health facilities in the coastal towns of Mtwapa and Shanzu (total population: $\sim 100,000$, see supplemental information, <http://links.lww.com/QAD/A497> for map) in 2011 [18]. From a total of 22 pharmacies, 22 private and four government health facilities, five pharmacies and five health facilities were selected, including three private health facilities located centrally in town (i.e. on or nearby the main road) and two government health facilities located peripherally. All

pharmacies were centrally located. Pharmacy staff rarely refer patients for HIV-1 testing, and have not been included in HIV prevention programming supporting the uptake of HIV testing [18,19]. The study area is known for its busy nightlife and hosts the Kenya Medical Research Institute (KEMRI) clinic, which has conducted research with key populations since 2005 [15,20].

Staff at the five pharmacies were requested to give eligible patients a numbered referral coupon and information booklet with study information in Kiswahili or English. Patients were instructed to report to any of the five health facilities for HIV-1 and malaria testing. Pharmacy staff kept a log of coupons distributed. Staff at the five health facilities screened all patients for study eligibility and was supported to offer provider-initiated HIV-1 testing and counselling (PITC) irrespective of study participation. Prior to the study, rates of PITC implementation at private and government health facilities were estimated at 18.4 and 15.4% ($P=0.3$), respectively (Prins *et al.*, in preparation).

After eligible and willing patients provided written informed consent, contact details were collected, a short medical history was obtained, and a symptom-directed physical examination conducted (including measurement of axillary temperature in patients who reported fever). A 5-ml blood sample was collected for on-site HIV-1 testing using two rapid tests in parallel (Determine; Abbott Laboratories, Abbott Park, Illinois, USA; Unigold; Trinity Biotech plc, Bray, Ireland) and for storage. On-site malaria testing was also performed for all febrile participants, using a rapid diagnostic test (RDT; Optimal, Flow Inc., Portland, Oregon, USA). All HIV-1 seronegative or serodiscordant participants were invited for repeat rapid HIV-1 testing 2–4 weeks following enrolment. Study participants received free treatment for minor illnesses, and a 300 Kenyan shilling (approximately \$3.50) transport reimbursement for their enrolment visit.

Laboratory confirmation of acute HIV-1 infection and malaria infection

HIV-1-seronegative or serodiscordant blood samples were transported from the five health facilities to a central laboratory on the day of collection and tested for p24 antigen using miniVidas (Biomérieux, Ltd., France) allowing rapid test results within 2 h [21]. Discordant rapid test results were resolved using a third ELISA test (Vironostika; Biomérieux, Ltd., France) as a tie-breaker. Pooled HIV-1 RNA testing was performed (Hologic; Gen-Probe, San Diego, California, USA) for samples from all participants who did not return for follow-up testing and could not be traced. Pools of 10 samples each were first tested, followed by testing of individual samples included in any positive pool. P24 antigen-positive participants were traced, and repeat HIV-1 testing was conducted until seroconversion was established. Whole blood from participants with a positive RDT was tested

with an in-house PCR to confirm malaria infection [22], except for four participants whose stored plasma was tested by a second RDT (CareStart; Access Bio, New Jersey, USA) to confirm malaria infection.

Data analysis and ethical approvals

Data cleaning and analysis were conducted using Stata 11.0 (StataCorp LP, College Station, Texas, USA). Exact binomial confidence intervals (CIs) were calculated for prevalence estimates. Associations between binary or categorical variables were investigated using chi-square tests. The study was approved by the ethical review committees at the Kenya Medical Research Institute and the University of Oxford.

Results

Between February and July 2013, 3602 young adults were screened for this study (48.5% of all 8013 young adults seeking care; Fig. 1), including 354 (9.8%) referrals from a pharmacy. Overall, 24.9% (95% CI 23.5–26.4%) met screening criteria for AHI risk. When PITC was performed, 3.9% (95% CI 3.2–4.5%) had undiagnosed prevalent HIV-1 infection. Patients with prevalent HIV-1 infection were more likely to meet AHI criteria than HIV-seronegative patients (7.6 vs. 2.6%; $P < 0.001$). Similarly, patients with fever were more likely to be HIV-1-infected than those without fever (9.1 vs. 3.3%; $P < 0.001$). Of the 897 patients meeting AHI criteria, 375 (41.8%) did not enrol (Fig. 1). Patients who met AHI criteria and refused study participation were more likely to be HIV-1-infected than patients who enrolled (18.1 vs. 3.1%; $P = 0.001$). Patients who were not resident of the study area and therefore were excluded from study participation had a borderline increased prevalent HIV-1 infection (7.5 vs. 3.1%; $P = 0.07$). PITC identified 139 patients with previously undiagnosed prevalent HIV-1. Of these patients, 68 (48.9%) met AHI criteria, 36 (25.9%) had never tested for HIV, 100 (71.9%) were previously negative, and three (2.2%) had an unknown status prior to PITC.

Among the 506 HIV-1-seronegative or serodiscordant patients enrolled, including 241 patients with a documented fever (Table 1), AHI was diagnosed in five (prevalence 1.0%, 95% CI 0.3–2.2%), including two patients referred from pharmacies. AHI prevalence was higher among patients with fever (1.7 vs. 0.4%); however, this difference was not statistically significant ($P = 0.1$). All five AHI patients (four women and one man) had a positive p24 antigen test and negative rapid HIV-1 tests at the initial screening visit. Four AHI patients (including one woman and one man who had requested malaria medication at pharmacies) enrolled into comprehensive HIV care. One AHI patient (p24 antigen and RNA-positive) was unwilling to undergo repeat HIV testing and

was lost to follow-up. No additional HIV-1 infections were detected in the 243 patients who reported for repeat HIV testing 2–4 weeks after enrolment. Pooled RNA testing of samples from 258 patients without repeat HIV testing (including one patient with a positive p24 antigen test) revealed no additional infections. Two patients with discordant HIV-1 test results at enrolment were HIV-1-negative upon confirmatory testing. Four (1.7%) of the 241 febrile HIV-1-negative patients had confirmed malaria, none of whom had AHI.

Discussion

This is the first study demonstrating that AHI has become as common as malaria among young febrile adults seeking care at primary care facilities in coastal Kenya. Whereas malaria control is supported by established national programmes that promote prompt malaria diagnosis and treatment in sub-Saharan Africa [23], no HIV-1 prevention policy recommends evaluation for AHI among febrile young adult patients seeking care. Our study confirmed that febrile patients seeking care have a higher HIV-1 prevalence than patients without fever, suggesting that PITC is especially important for this population [24,25]. Our results also suggest that AHI can be best diagnosed among young adults seeking care for fever. Whereas three studies have reported AHI as a cause of fever in adult patients in sub-Saharan Africa [3,10,26], the WHO's guidelines do not mention AHI as a possible cause of fever in adults [25,27] (Prins *et al.*, in preparation).

Targeting patients for HIV-1 testing should start with PITC, but unfortunately the uptake of PITC has been low in sub-Saharan Africa [28]. Frequently mentioned reasons for the low uptake include patient burden, absence of test kits, patients' perceived HIV-1-negative status following a previous HIV-1 test, added costs for patients accessing care at private facilities, and weak health systems in general [28]. Focusing PITC efforts on patients with signs of acute infection (e.g. fever, sexually transmitted diseases, diarrhoea) would greatly reduce the number of patients needed testing, while still allowing the identification of a large number patients with undiagnosed prevalent HIV-1. Community-based HIV counselling and testing targeting the general population or specific risk groups is currently recommended to supplement PITC [19].

Both PITC and community-based testing, however, will miss individuals who have just acquired HIV-1 and are yet seronegative or serodiscordant [29,30]. An AHI detection strategy specifically targeting febrile young adults seeking care at pharmacies and health facilities is feasible and could potentially be used to target TasP programmes, especially since rapid point-of-care p24 antigen and

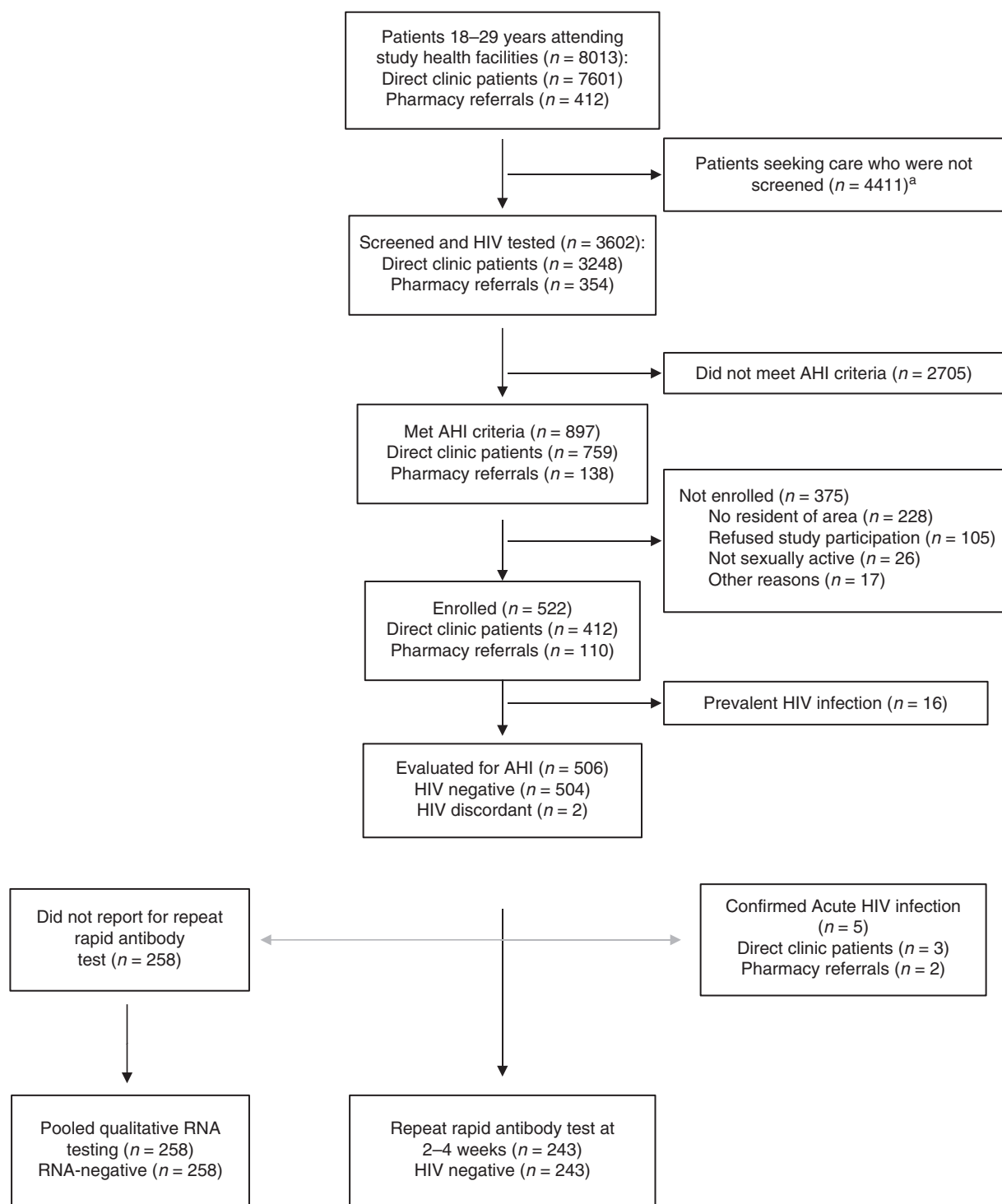


Fig. 1. Patient flow, clinical screening, HIV-1 testing, and acute HIV-1 infection evaluation. ^aNumber of adults aged 18–29 years registered at clinic (i.e. obtained from clinic registry) minus number of adults 18–29 years who were tested for HIV and screened for AHI.

HIV-1 RNA tests are being developed [31,32]. P24 antigen may often be detected when patients who acquire HIV-1 first present for care [16,33]. Whereas such an approach will miss individuals who do not seek healthcare, rapid ELISA testing combined with p24

testing can identify approximately 90% of AHI cases in an African setting, without the need for HIV-1 RNA testing [29]. Of note, our study did not show any added value of (pooled) RNA testing. In the absence of a p24 antigen test, repeat HIV-1 testing with readily available rapid tests

Table 1. Young adults evaluated for prevalent and acute HIV-1 infection.

Clinic	Young adults (18–29 years) seeking healthcare at government and private health facilities (A–E)				Study participants evaluated for acute HIV infection		
	No. seen	No. evaluated (% of those seen)	No. meeting AHI criteria ^b (% of those evaluated)	No. with prevalent HIV-1 (% of total evaluated)	No. enrolled ^c	No. with fever (%)	No. with AHI (% of those evaluated)
A	2908	1410 (48.5)	400 (28.4)	62 (4.4)	225	76 (33.8)	1 (0.4)
B ^a	1166	225 (19.3)	117 (52.0)	7 (3.1)	91	56 (61.5)	3 (3.2)
C	1542	555 (36.0)	129 (23.2)	15 (2.7)	78	41 (52.6)	1 (1.3)
D ^a	1380	929 (67.3)	167 (18.0)	34 (3.7)	76	38 (50.0)	0
E ^a	1017	483 (47.5)	84 (17.4)	21 (4.3)	36	30 (83.3)	0
All	8013	3602 (45.0)	897 (24.9)	139 (3.9)	506	241 (47.6)	5 (1.0)

AHI, acute HIV-1 infection.

^aPrivate health facilities

^bAHI criteria: Potentially eligible patients seeking healthcare were assigned a risk score by summing points based on the following characteristics: 1 for generalized body pains or multiple partners in the past 2 months, and 2 for documented fever ($\geq 37.5^{\circ}\text{C}$ axillary), reported diarrhoea, or symptoms compatible with an STI. Patients with a risk score at least 2 met AHI criteria.

^cEligibility criteria: Age 18–29 years, residency in the study area, risk score at least 2, and willingness to be evaluated for HIV-1, including AHI, and for malaria, if febrile. Sixteen HIV-1-positive patients were excluded from AHI evaluation.

will identify seroconversion in most acutely infected individuals 2–4 weeks following symptom onset [8,34].

The study has several limitations, including a geographic bias, as the study area is known for its night life, sex work, and ongoing HIV-1 transmission; non-random selection of study health facilities; selection bias, including exclusion of patients who were not area residents and higher HIV-1 infection in patients who refused study participation; brief duration (only 5 months); and malaria screening only in febrile patients who accepted HIV-1 testing and enrolled in the study.

In summary, we have shown that the prevalence of AHI is similar to that of malaria in young adults presenting with febrile illness to routine health services in coastal Kenya. We propose an AHI evaluation strategy directed at young febrile adult patients seeking care at pharmacies and health facilities that appears feasible and scalable, and recommend that patients identified through this approach be offered immediate ART [35]. Although uptake of immediate ART will confer individual and societal benefits, further evaluation of clinical outcomes, cost-effectiveness, patient counselling and support needs [36], and the added value of partner notification in this setting are needed before routine inclusion of this approach in TasP programmes in areas with ongoing HIV-1 transmission.

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Author contributions: E.J.S. designed the study, performed data analysis and drafted the manuscript.

P.M. contributed to the implementation of the study, conducted field data collections and manuscript editing.

H.A.B.P. contributed to the implementation of the study, conducted field data collections and manuscript editing.

E.W. performed data entry, analysis and quality assurance.

A.N.T. conducted field data collections.

G.M. conducted field data collections.

E.M.vdE. contributed to the design of the study and manuscript editing.

A.O. contributed to the engagement of health facilities and pharmacies.

A.D.S. contributed to the design of the study and manuscript editing.

S.M.G. designed the study and edited the manuscript.

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Conflicts of interest

We declare that we have no conflicts of interest.

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