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Health-seeking behavior and symptoms associated with early HIV infection: Results from a population-based cohort in southern Malawi

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Abstract

HIV transmission is most likely to occur during the first few months after infection, yet few cases are identified during this period. Using a population-based cohort of young Malawian women, we identify the distinct symptomology and health-seeking behavior marking early HIV infection (EHI) by comparing it to periods of seronegativity and chronic infection. During EHI women are more likely to report malaria-like symptoms and visit clinics for malaria care. In malaria-endemic contexts, where acute HIV symptoms are commonly mistaken for malaria, early diagnostic HIV testing and counseling should be integrated into healthcare settings where people commonly seek treatment for malaria.

Introduction

People with acute HIV infection (AHI), the symptomatic period before antibodies are present, and early HIV infection (EHI), the 6-month period following infection, are likely to transmit HIV due to high HIV-1 RNA levels[1,2]. In sub-Saharan Africa, recent modeling studies estimate that between 20 and 40% of new infections are transmitted during the initial

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Authors' Contribution

SEY designed the study, performed data analysis and drafted the manuscript. RMH contributed to interpreting the data and manuscript editing. AC, SRL and HCN contributed to fieldwork, data collection and data management. AFC contributed to the design of the study. JAT designed the study and edited the manuscript. All authors approved the final draft for submission.

Conflicts of interest

The authors declare no other conflicts of interest.

months of infection[3,4]. People with early HIV infection, however, rarely know their status because they are unlikely to be tested during this period of heightened infectiousness, and because commonly used HIV rapid tests will not detect an acute infection.

Given the broader epidemiological context, recently infected individuals are simultaneously vulnerable to the same array of health conditions that affect the population generally; in Malawi these include malaria, STIs, febrile and diarrheal illnesses, and malnourishment. Given this landscape of co-morbidities, EHI may be confused with other conditions—especially malaria. For example, two cohort studies of female sex workers and men who have sex with men in coastal Kenya found that newly infected individuals frequently had symptoms[5] for which many sought urgent care and were treated for malaria[6]. Recent clinic-based studies from east Africa found high prevalence of AHI among patients presenting with acute clinical issues, including signs and symptoms of malaria and sexually transmitted infections (STI)[7–10].

This article expands current understandings of the EHI period by leveraging a population-based cohort of young women from southern Malawi. Specifically, we contextualize the symptomology and health-seeking behaviors that mark EHI by contrasting them with periods of seronegativity and periods of chronic HIV-1 infection. We further estimate the proportion of young women in this context that sought care at clinics during the EHI period.

Materials and Methods

Tsogolo la Thanzi (TLT) is a prospective cohort study (2009–2011) of 1500 young Malawian women designed to study the social and demographic causes and consequences of HIV[i]. The cohort was drawn using a simple random sample of women aged 15–25 from a complete household listing of all residents within a 7-kilometer radius of the town of Balaka in southern Malawi. Approximately every 4 months for 32 months, respondents came to a central research center, where trained research assistants collected data on life events during the inter-survey period, including: marriage, divorce, pregnancy, sexual behavior, self-reported health, and health-seeking behaviors. Based on an earlier study in Malawi that developed a risk score algorithm for identifying people at high risk of AHI[10], the 16- to 32-month time points included questionnaire items to calculate an AHI risk score. Using a variant of this AHI risk score algorithm that was recently employed in Kenyan clinics[7], we calculated each respondent's risk score at these time points. The following AHI indicators were assigned the points in parentheses: fever (2), diarrhea (2), and body aches (1) in the last month and self-reported STI symptoms (2) and multiple sexual partners (1) within 4 months[ii] of the study visit. The TLT survey included questions about respondents' health-seeking behaviors in the previous 4 months, including where they sought care and for what reason, and whether they believed they had malaria or symptoms of a sexually transmitted infection during the period.

[i]Details about Tsogolo la Thanzi are available online (http://sites.psu.edu/tltc/).
[ii]Two earlier studies from the region that calculated risk scores (Powers et al. 2007; Sanders et al. 2014) used multiple partners in the last 2 months. Since the TLT cohort was interviewed every 4 months, this time period was used to aid recall.

One–third of the cohort was randomly assigned to undergo voluntary HIV testing and counseling (HTC) at every time point[iii]. HIV testing was performed using the serial algorithm employed by the Malawi Ministry of Health at the time: 1) Determine assay (Abbott Laboratories, USA), 2) Unigold (Trinity Biotech, Ireland) for reactive respondents, 3) SD Bioline (Standard Diagnostics Inc., Korea) to confirm discordant tests. For these analyses, we assume that HIV infection occurred at the mid-point between a negative and positive HIV test[6]. We used t-tests and chi-squared tests (Stata, v12.0) to estimate associations between periods of EHI and seronegativity as well as between periods of EHI and chronic HIV infection (defined as >6 months since infection).

Informed consent was obtained at recruitment, before each survey, and separately for HTC. Ethics approval was granted by Penn State University Office for Research Protections and the Malawi National Health Sciences Research Committee.

Setting

Approximately 11% of reproductive age adults in Malawi are estimated to be HIV positive; however, prevalence varies by region and is highest (15%) in the southern region, where TLT is based[11]. 7.3% of female TLT respondents (aged 15–25) tested HIV positive at baseline. Malaria is also a major cause of morbidity and mortality in Malawi. It is estimated that, with a population of 16 million, Malawi experiences approximately 6 million episodes of malaria annually[12].

Results

467 women were tested for HIV at least twice, comprising 2,895 completed study visits, with 14 documented seroconversions. To align our analyses with EHI criteria, we exclude one infection that, due to missed study visits, may have occurred more than 6 months before the first positive HIV test within TLT, therefore representing chronic infection. Another respondent refused testing at the 16-month time point, citing a test the previous month at antenatal care. Based on her reporting of nevirapine use at delivery, we assume seroconversion occurred by the 16-month study visit. Mean time of study visit since infection for the 13 EHI cases was 2.8 months (range: 1.5–6). Compared to individuals who remained HIV negative, women with EHI were more likely to be formerly married (P=0.025) but did not differ by age (Table 1).

Retrospectively identified periods of EHI were distinct in a number of ways from periods of seronegativity and chronic HIV infection. EHI was marked by the presence of body aches (60.0% vs. 27.4% for HIV-uninfected, P=0.024; vs. 27.4% for chronic, P=0.027), more days of work/school missed due to ill health in the last month (2.7 vs. 1.0 days for HIV-uninfected, P=0.014), and multiple sexual partners in the previous four months (7.7% vs. 0.4% for HIV-uninfected, P<0.001). Periods of EHI had a marginally significant increased risk of diarrhea compared to HIV-uninfected periods (20.0% vs. 6.1%, P=0.087). Although 40% of respondents with EHI reported fever within the last month prior to the study visit

[iii]The other 2/3 was randomly assigned to either test at the 16- and 32-month time periods or only to test at the 32-month time period.

where they tested HIV positive, this was not statistically different than comparison periods since fevers were frequently reported during HIV-uninfected periods (40.0% vs. 18.8%, P=0.105). During EHI-identified periods, 50% of women met the risk score cutoff of ≥2, indicating benefit from early diagnostic testing for HIV[10], compared to 23% during seronegative periods (P=0.042) and 24% during chronic HIV infection (P=0.071). None of the 13 women with EHI reported STI symptoms in the previous month. In contrast, 69% (9/13) self-reported having malaria during the previous 4 months compared to 25% of women during HIV-uninfected periods (P<0.001) and 29% during periods of chronic HIV infection (P=0.002).

Young Malawian women in our cohort frequently attended health centers (Table 2). The most common reasons for visiting health facilities during the study period were malaria treatment, family planning, and care of children under 5. During periods of EHI, women were no more likely to attend a health clinic for any reason than were women who remained HIV-uninfected or had chronic HIV infections. Health-seeking behavior for family planning, under 5 clinics, antenatal care (ANC) and treatment of STIs was similar during periods of EHI compared to the other two periods; however, differences were noted in health-seeking behavior for symptoms of malaria. During EHI, 46% of women (6/13) sought malaria treatment at a health clinic, compared to 17% and 16% of women during HIV-uninfected periods and periods of chronic HIV infection, respectively (P=0.005 for both). None of the women who tested HIV positive through the study received an HIV test at their malaria-related clinic visit. In contrast, all 3 of the pregnant women we retrospectively identified as having EHI through TLT testing reported recently having been tested for HIV at ANC. We cannot clearly tell from our data whether these women tested HIV-positive at ANC, as their ANC test may have occurred before seroconversion.

Discussion

The failure to identify and diagnose acute and early HIV infections is a serious barrier to curtailing the sub-Saharan pandemic. Our study contributes to understanding EHI in the region using a population-based cohort from southern Malawi. In doing so, we identify a more representative sample of new infections in Malawi's generalized epidemic than typically used in studies of EHI.

We find that over periods of EHI, women were more likely to have multiple sexual partners, miss days of school/work, have body aches, and self-report malaria compared to HIV-uninfected periods. Our data are consistent with a recent publication from Zambia that found malaria symptoms were more common and more severe during EHI[13]. The fact that multiple partnerships are prevalent during the EHI period further underscores the importance of diagnosing individuals at the earliest stages of infection. Having multiple sexual partners not only increases the likelihood that partners will become infected but also that they will transmit their undiagnosed infection to others.

That overall healthcare use was not distinct during periods of EHI in our sample of young Malawian women indicates a pressing need for targeted programs to detect EHI. Our findings support a growing evidence base[7–9] that people with EHI in malaria-endemic

Africa frequently present at primary health clinics with malaria-like symptoms. Indeed, almost half of the young women with new infections in our sample sought care for malaria in the 4-month period before their seroconversion was documented, three times the level of malaria-related healthcare visits at other times.

As has been found in high-resource settings[14], women in Malawi with new HIV infections frequently sought care for symptoms, yet were not tested. The only women with EHI who received an HIV test outside of our study were the three who seroconverted during pregnancy. This speaks to the largely successful integration of HIV and maternal services in Malawi. Because of the implications of undetected high viral loads for maternal to child transmission[15], antenatal clinics have been prioritized as a critical venue for the early detection of HIV. Since 2011, Malawian women who test positive at antenatal care are supposed to be initiated on lifelong ART under Option B+[16]. In combination with newer HIV tests that detect infection earlier, the prevention benefits could be even greater.

Despite interest in STI clinics as sites for AHI screening[10,17], none of the women with EHI in our sample reported seeking care for STI symptoms. There are a number of plausible explanations. First, earlier studies focused on AHI among men attending STI clinics, and men's and women's health-seeking behavior related to STIs may differ. Second, reporting bias may lead women to underreport their STIs and related health-seeking behaviors; the low level of self-reported STI visits among our sample supports this possibility. Third, the discrepancy may reflect a broader methodological problem, wherein distinct conclusions emerge when comparing population-based samples to those drawn from clinics—particularly STI clinics. Our study is the first population-based perspective on clinic usage during the EHI period. By using a representative sample to distinguish between typical patterns of accessing malaria versus antenatal versus STI clinics during the EHI period, these findings offer insight into the relative promise of these sites as venues for targeted early detection of HIV. Given the shortage of HTC counselors in Malawi, understanding the relative yield of testing at different clinical sites should inform policy decisions around use of limited resources.

Although our study was not designed as a formal external validation, we replicate data from Kenya suggesting the risk score approach is feasible for identifying AHI and EHI in African settings. Of note, multiple different risk scores have been employed with varying success[10,18,19]. We opted to use a scoring system that did not include discordant HIV test results or require clinical examination since we were focused on strategies that could be utilized to identify individuals for testing at the time of initial presentation to a health center. As others have reported[20], no single sign or symptom is a strong predictor of AHI or EHI, and developing and validating tools for identifying high-risk individuals for HIV testing in primary health settings in Malawi and similar countries is critically important.

Our study is limited by the small number of respondents with EHI and the exclusion of men. Men's health seeking behavior during EHI may differ and should be explored in future studies.

In conclusion, findings from the population-based TLT cohort support calls to combine a targeted risk score approach[21] with HTC at primary health care setting or at sites where people seek care for malaria-like symptoms. Such settings should be priorities for 4th generation HIV tests, which are currently being piloted in Malawi and can identify new HIV infections in as few as five days[22]. Limited lab capacity and resource constraints prohibit the use of quantitative viral load for AHI identification in Malawi. Until 4th generation tests are widely available, people presenting at clinics who meet AHI criteria but test negative with HIV rapid antibody tests should be counseled to return for another test in three to four weeks[23]. This strategy would benefit individuals by providing early diagnoses of HIV infection and possible early access to antiretroviral treatment; it would also convey public health benefits by identifying individuals at highest risk for transmitting HIV. Our findings also suggest a need for information campaigns around acute and early HIV infections. Both clinicians and the general public should be educated about the similarity in symptoms between AHI and malaria and the ease with which HIV spreads during this time. Given our findings, places where people often seek care for malaria may be ideal venues for such campaigns.

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Table 1

Risk criteria of young Malawian women during periods of early HIV infection, chronic HIV infection and seronegativity, TLT (2009–2011)

	Early HIV infection	Chronic HIV infection		HIV negative	
	Mean (SD) or %	Mean (SD) or %	p-value[a]	Mean (SD) or %	p-value[a]
Sociodemographic characteristics					
Age	21.3 (2.8)	23.5 (2.5)	**p<0.01**	20.9 (3.2)	p=0.622
Marital status: Married	46.2%	58.2%	p=0.392	54.5%	p=0.545
Never married	30.1%	14.8%	p=0.122	38.4%	p=0.572
Formerly married	23.1%	27.0%	p=0.755	7.1%	**p=0.025**
Risk criteria					
Multiple partners (last 4 mo)	7.7%	2.3%	p=0.226	0.4%	**p<0.001**
STI symptoms (last 4 mo)	0.0%	1.1%	p=0.699	1.4%	p=0.666
Fever (last mo)[b]	40.0%	21.3%	p=0.224	18.8%	p=0.105
Diarrhea (last mo)[b]	20.0%	5.6%	p=0.166	6.1%	p=0.087
Body aches (last mo)[b]	60.0%	27.4%	**p=0.027**	27.4%	**p=0.022**
Self-reported malaria (last 4 mo)	69.2%	28.9%	**p=0.002**	25.4%	**p<0.001**
Pregnant	23.1%	12.2%	p=0.249	11.2%	p=0.174
Days of work/school missed (last mo)[b]	2.7 (4.3)	1.1 (3.4)	p=0.106	1.0 (2.5)	**p=0.014**
Risk score ≥2[b]	50.0%	24.4%	p=0.071	22.9%	**p=0.042**
N (study visits)	13	263		2619	

[a] Compared to periods of early HIV infection

[b] Time points 16–32 months only, n=10 visits for early HIV infection, 197 for chronic HIV infection and 1805 for HIV negative Bold text indicates significant at p<0.05 level or higher

Table 2

Health-seeking behavior of young Malawian women in the 4 months prior to study visit by infection category, TLT (2009–2011)

	Early HIV infection	Chronic HIV infection		HIV negative	
	Mean (SD) or %	Mean (SD) or %	p-value[a]	Mean (SD) or %	p-value[a]
No. health center visits	1.6 (1.6)	1.4 (1.3)	p=0.590	1.2 (1.2)	p=0.154
Visited health center for any reason	76.9%	71.9%	p=0.691	64.0%	p=0.332
Visited health center for malaria	46.2%	16.0%	**p=0.005**	16.8%	**p=0.005**
Visited health center for family planning	15.4%	15.6%	p=0.984	19.6%	p=0.706
Visited health center for under 5 clinic	15.4%	16.4%	p=0.927	19.9%	p=0.682
Visited health center for antenatal care	23.1%	10.3%	p=0.147	9.9%	p=0.113
Visited health center for STI	0.0%	0.0%	n/a	0.4%	p=0.944
N (study visits)	13	263		2619	

[a]Compared to periods of early HIV infection

Bold text indicates significant at p<0.05 level or higher