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Clinical signs and symptoms associated with acute HIV infection from an intensely monitored cohort on 2 continents

Andrew G. Letizia, MD[a],*, Leigh Anne Eller, PhD[b,c], Christopher Bryant, PhD[d], Peter Dawson, PhD[d], Sorachai Nitayaphan, MD[e], Josphat Kosgei, MBChB[f], Hannah Kibuuka, MBChB[g], Lucas Maganga, MBChB[h], Eugène Kroon, MD[i], Somchai Sriplienchan, MD[e], Nelson L. Michael, MD, PhD[b], Robert J. O'Connell, MD[j], Jerome H. Kim, MD[b,k], Merlin L. Robb, MD[b,c],*, RV 217 Study Team

Abstract

Define the clinical presentation of acute human immunodeficiency virus infection (AHI) among men and women from 2 continents to create a clinical scoring algorithm.

Comparison of incident sign and symptom between those with and without AHI.

At-risk human immunodeficiency virus (HIV) negative men and women in Thailand, Kenya, Tanzania, and Uganda underwent twice-weekly testing for HIV. Newly diagnosed participants were evaluated twice weekly for 21 days after infection.

Of the 3345 participants enrolled, 56 African females and 36 biological males from Thailand were diagnosed with AHI. Four hundred fifty-two of their encounters were compared to 18,281 HIV negative encounters. Due to a high degree of heterogeneity among incident symptoms, 2 unique subgroups based upon geography and sex were created. Among Thai males, the signs and symptoms with the greatest odds ratio (OR) between AHI and uninfected participants were nausea (OR 16.0, 95% confidence interval [CI] 3.9–60.2, $P < .001$) and lymphatic abnormalities (OR 11.8, 95% CI 4.2–49.0, $P < .001$); and among African females were pain behind the eyes (OR 44.4, 95% CI 12.0–158.0, $P < .0001$) and fatigue (OR 22.7, 95% CI 11.3–44.3, $P < .001$). The Thai male scoring algorithm had a 66% sensitivity and 84% specificity while the African female algorithm had a sensitivity of 27% and specificity of 98%.

The different incident symptoms during AHI necessitated creating 2 different scoring algorithms that can guide diagnostic testing among a particular sex in the appropriate geographic setting. Further research on risk exposure, sex, and demographic specific models is warranted.

Abbreviations: AHI = acute human immunodeficiency virus infection, AUC = area under the curve, CI = confidence interval, HIV = human immunodeficiency virus, OR = odds ratio, RNA = ribonucleic acid.

Keywords: acute HIV, acute HIV presentation, clinical scoring algorithm

1. Introduction

Attempts at curbing the human immunodeficiency virus (HIV) emphasize detection of acute human immunodeficiency virus infection (AHI).[1,2] This critical window defined as the 2 to 4 weeks prior to the development of measurable antibodies,[3] is when recently infected individuals are highly contagious and potentially asymptomatic, creating an ominous combination for transmission and spread of HIV.[4–6] Early therapy initiated during or shortly after AHI lowers morbidity, preserves immune function and, by decreasing viral load, lowers transmission.[2,7,8] In settings where routine laboratory screening is limited due to financial constraints, an understanding of the clinical presentation of AHI can guide the use of rapid and sensitive point-of-care testing and enhance detection of AHI.[9]

Some authors emphasize targeted testing for groups at high-risk such as men who have sex with men or young febrile adults in Africa.[10,11] Identifying patient populations and geographical areas where HIV-infections are most prevalent could be a cost effective strategy to identifying AHIs.[12] Although nucleic acid amplification testing is a fundamental diagnostic tool for AHI, the technique remains expensive and the optimal use of these tests in an appropriate diagnostic strategy has yet to be defined.[3,13] The cost of individual testing of all at-risk individuals, especially with newer fourth generation tests, is prohibitively expensive in resource-limited settings.[14] The diagnosis of AHI is even delayed in settings that are not as constrained by finances, including high-risk patient populations.[15] Consequently, a better understanding of the clinical presentation of AHI and subsequent development of a scoring algorithm, particularly in high-risk groups in resource limited areas could assist in improving utilization of testing and earlier identification of cases.[5,16]

In sub-Saharan Africa, where resources are limited and the symptoms of AHI can mimic more prevalent diseases including malaria, diagnosis is difficult.[17] Previous studies have attempted to define the signs and symptoms of AHI to create a scoring algorithm in both resource-rich[18] and resource-limited settings.[19–23] Subsequently, 4 of these studies were pooled to create a screening algorithm for AHI in sub-Saharan Africa.[11] In all these studies, the clinical predictors for AHI may be limited by recall and detection bias since they utilized monthly or quarterly follow-up.[24] Ideally, the signs and symptoms as well as demographic risk factors of AHI would be defined through a closely monitored longitudinal cohort regularly assessed for acute infection[24,25] by highly sensitive diagnostics with an interval of a few days between encounters. The aim of this study was to utilize the RV-217 study, a prospective high-risk cohort with twice-weekly laboratory and clinical follow-ups which has been previously described,[26] to identify signs and symptoms associated with AHI among females and biological males from multiple resource-limited countries using a standardized methodology. These data and subsequent clinical scoring algorithms could then be used to help guide the use of point-of-care acute HIV-1 testing.

2. Methods

At-risk HIV negative men and women from key populations in Kericho, Kenya; Mbeya, Tanzania; Kampala, Uganda; and Pattaya, Thailand were enrolled in a prospective observation cohort study with twice-weekly ribonucleic acid (RNA) testing to detect AHI.[26] Individuals were all informed of their diagnosis of AHI, educated on contemporary local treatment guidelines, and those that chose not to initiate antiretroviral therapy at the time of diagnosis from July 2009 to February 2016 were analyzed. Demographics, risk factors, signs, and symptoms prior to and during AHI were collected. These data were then used to identify clinical signs and symptoms that were associated with AHI and subsequently develop a clinical scoring algorithm. Ethics approval for the study was obtained through the Walter Reed Army Institute of Research and all other local applicable ethics committees.

HIV uninfected participants with repeatedly reactive Aptima HIV-1 RNA Qualitative Assay (Gen-Probe Inc., San Diego, CA) were defined as having AHI. These individuals received a standardized history and physical examination and intensive counseling for transmission prevention every 3 to 4 days for the first 28 days and then weekly for 42 weeks. The individual encounters within the first 21 days after the initial blood test reactive for HIV RNA defined the AHI window. The remainder of participants who completed follow-up and continually tested negative for HIV were defined as exposed, uninfected controls, and served as a comparison group to the AHI population. The demographic, risk factor, signs, and symptoms from an individual encounter were recorded within a single category ensuring no overlap or double counting.

2.1. Statistical methods

All analyses were conducted separately for Thai biological males and African females. Demographics were summarized by infection status and compared between participants with AHI and uninfected participants via Fisher exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables.

The primary analyses assess frequencies and incidences of clinical signs and symptoms in AHI compared to uninfected participants. The frequencies of reported signs and symptoms were computed as the percent of all AHI visits and uninfected visits with available symptom data in which each sign or symptom was reported. Prevalence was compared between visit types using Wald tests from logistic regression models with random intercepts to account for correlation between each participant's symptoms across visits. Incidence was computed across all AHI visits and all uninfected visits for each participant,

Table 1

Baseline characteristics of acute human immunodeficiency virus infection cases and HIV-negative participants.

	African female participants				Thai biological male participants			
	# AHI cases (%)	# HIV uninfected (%)	# Total (%)	P value*	# AHI cases (%)	# HIV uninfected (%)	# Total (%)	P value*
Gender				NA				NA
Female	56 (100)	2452 (100)	2508 (100)		0 (0)	0 (0)	0 (0)	
Male	0 (0)	0 (0)	0 (0)		21 (58.3)	424 (52.9)	445 (53.2)	
Transgender	0 (0)	0 (0)	0 (0)		15 (41.7)	377 (47.1)	392 (46.8)	
Total	56 (100)	2452 (100)	2508 (100)		36 (100)	801 (100)	837 (100)	
Median age in years (range)	24 (18–34)	24 (18–49)	24 (18–49)	.16	22 (18–35)	24 (18–49)	24 (18–49)	.003
Number of male partners in past 3 mos								
None	1 (1.8)	105 (4.3)	106 (4.2)	.91	0 (0)	31 (3.9)	31 (3.7)	.58
1–2 partners	24 (42.9)	1142 (46.6)	1166 (46.5)		22 (61.1)	375 (46.8)	397 (47.4)	
3–10 partners	18 (32.1)	663 (27)	681 (27.2)		10 (27.8)	233 (29.1)	243 (29)	
More than 10 partners	11 (19.6)	427 (17.4)	438 (17.5)		3 (8.3)	104 (13)	107 (12.8)	
Refuse to answer	1 (1.8)	57 (2.3)	58 (2.3)		1 (2.8)	23 (2.9)	24 (2.9)	
Do not know	1 (1.8)	46 (1.9)	47 (1.9)		0 (0)	32 (4)	32 (3.8)	
Missing	0 (0)	12 (0.5)	12 (0.5)		0 (0)	3 (0.4)	3 (0.4)	
Number of female partners in past 3 mos								
None	54 (96.4)	2278 (92.9)	2332 (93)	.73	30 (83.3)	526 (65.7)	556 (66.4)	.5
1–2 partners	0 (0)	69 (2.8)	69 (2.8)		5 (13.9)	121 (15.1)	126 (15.1)	
3–10 partners	1 (1.8)	32 (1.3)	33 (1.3)		1 (2.8)	70 (8.7)	71 (8.5)	
More than 10 partners	0 (0)	26 (1.1)	26 (1)		0 (0)	23 (2.9)	23 (2.7)	
Refuse to answer	0 (0)	7 (0.3)	7 (0.3)		0 (0)	30 (3.7)	30 (3.6)	
Do not know	0 (0)	13 (0.5)	13 (0.5)		0 (0)	23 (2.9)	23 (2.7)	
Missing	1 (1.8)	27 (1.1)	28 (1.1)		0 (0)	8 (1)	8 (1)	
Number of transgender partners in past 3 mos								
None	49 (87.5)	2246 (91.6)	2295 (91.5)	0.21	33 (91.7)	577 (72)	610 (72.9)	0.3
1–2 partners	2 (3.6)	72 (2.9)	74 (3)		2 (5.6)	117 (14.6)	119 (14.2)	
3–10 partners	1 (1.8)	59 (2.4)	60 (2.4)		0 (0)	38 (4.7)	38 (4.5)	
More than 10 partners	3 (5.4)	29 (1.2)	32 (1.3)		0 (0)	16 (2)	16 (1.9)	
Refuse to answer	0 (0)	7 (0.3)	7 (0.3)		0 (0)	24 (3)	24 (2.9)	
Do not know	0 (0)	14 (0.6)	14 (0.6)		1 (2.8)	22 (2.7)	23 (2.7)	
Missing	1 (1.8)	25 (1)	26 (1)		0 (0)	7 (0.9)	7 (0.8)	

AHI = acute human immunodeficiency virus infection, HIV = human immunodeficiency virus, NA = not applicable.

* Fisher exact tests were used for categorical variables and Wilcoxon rank-sum tests were used for continuous variables, comparing acutely infected participants to uninfected within each gender subgroup. Nineteen participants recorded as acutely infected who only had symptom data available for pre-infection and/or postacute visits were considered as uninfected here.

and the number of visits of each type and the length of time over which incidence was calculated were determined in order to account for the varying follow-up schedules. We used logistic regression models to assess symptoms associated with AHI incidence. The covariates in these models included infection status, the number of visits, and the amount of time over which incidence was calculated for each participant. Signs and symptoms that occurred in fewer than 10 total participants were dropped from the analysis, since the study is not powered to detect group differences in incidence probabilities for extremely uncommon symptoms. The incidence prior to AHI was excluded from the analysis for cases, to avoid the analytical complexities relating to the correlation between incidence reported before and after AHI onset in the same participant. P values were not adjusted for multiple comparisons but thresholds of 0.001, 0.01, and 0.05 were considered strong, moderate, and weak evidence of association, respectively.

As an exploratory analysis, a clinical scoring algorithm was developed to predict infection status for a participant presenting with a given set of signs and symptoms at an individual clinic visit, via logistic regression in independent development and testing subsets of the data. Random intercepts were utilized to help account for the varying number of encounters, and model selection was based on the $\alpha = 0.1$ threshold. Within each subgroup, two-thirds of participants with AHI and two-thirds of uninfected participants were randomly selected as a development dataset and the remaining one-third were used to evaluate the algorithm's predictive accuracy, similar to an AHI symptom score study performed in the United States.[18] After a univariable screening step to select signs, symptoms, and demographic variables positively associated with AHI encounters, backward selection was performed to select the final models. The coefficients from these models were used to predict infection status at each encounter in the testing datasets and evaluated for specificity and sensitivity using the pROC R package (Vienna, Austria)[27] utilizing the optimal cut-point determined in the development datasets based on Youden J statistic.[28] The performance of these subgroup-specific scoring algorithms in the testing datasets were then compared to that of the Sanders et al[11] method, which was the only published HIV scoring algorithm from the resource-limited world that was based on symptoms and risk factors that were also collected in the RV 217 study.

3. Results

Of the 4042 enrolled participants, 183 had prevalent HIV infection and they were not considered in the analyses, and 3345
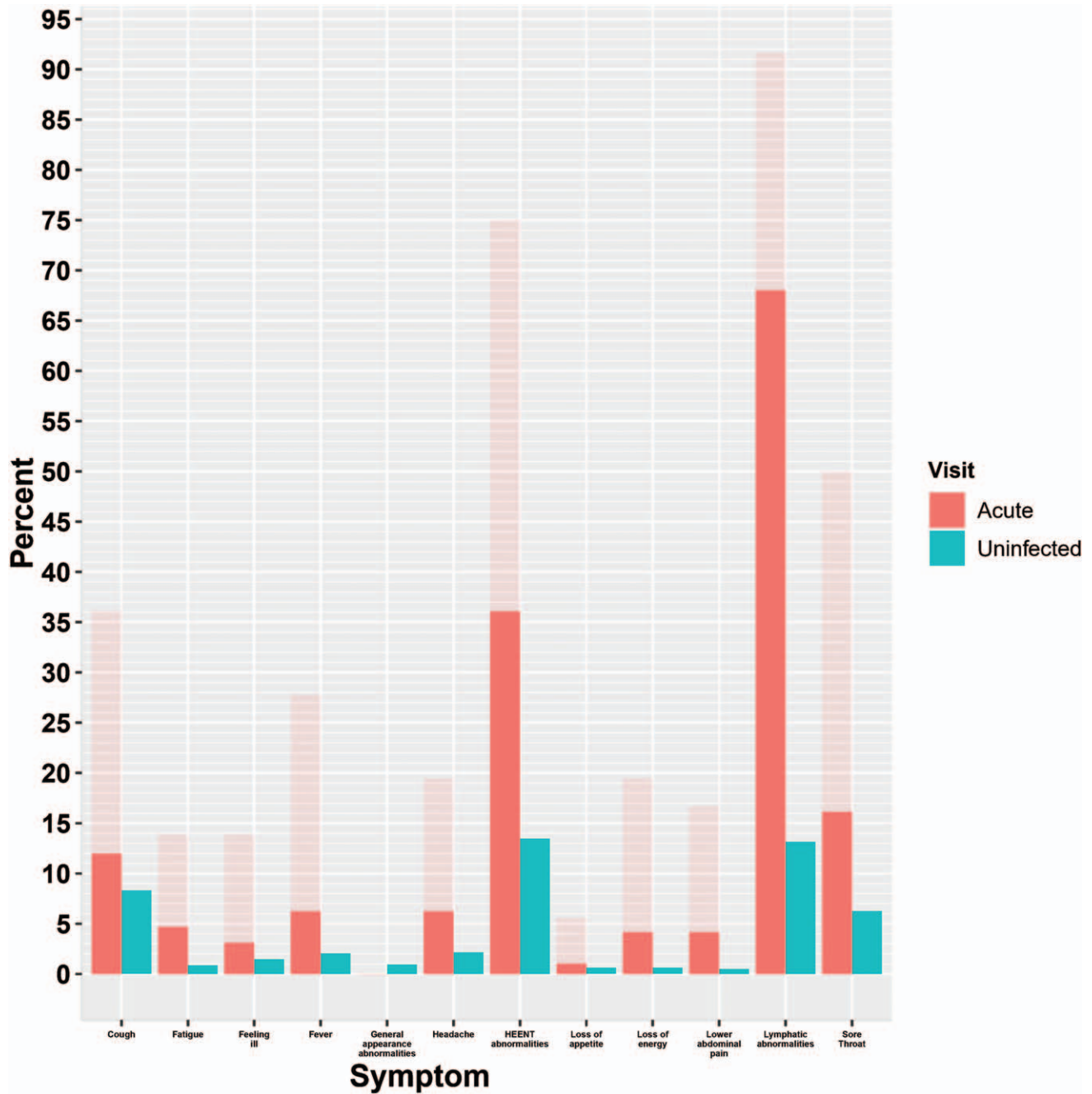
Figure 1. Frequency of Selected Symptoms in Acute Human Immunodeficiency Virus (HIV). Infection and HIV-Negative Study Visits for Thai Biological Male Participants. HEENT, head, eyes, ears, nose and throat. *The lighter red shading represents the percent of Thai male and transgender AHI participants reporting a given symptom sign at any encounter during the 21-day acute HIV infection window, e.g. 26% of AHI encounters reported cough. The darker red and blue shading represent the percent of individual AHI and uninfected encounters, respectively, at which Thai male and transgender participants reported a given symptom. AHI = acute HIV infection.

participants had at least 1 encounter with non-missing signs and/ or symptoms. A total of 120 participants with AHI were identified, and 92 of these had at least 1 encounter with recorded signs and symptoms during the acute phase. Fifty-six of these AHI participants were African women, 36 were Thai biological males (including 21 cis-gendered males and 15 transgender females) and 2 were Thai females who were not included in this analysis. A total of 18,281 HIV-negative encounters were compared to 452 individual AHI encounters, with a median time between acute

encounters of 4 days. The participants with AHI had a median of 5.5 encounters (range 1–8) during the AHI window with the first postinfection visit occurring a median 2 days and mean 3.8 days after the initial positive test. The median age (24 years) and baseline characteristics were similar for African females between participants with AHI and uninfected participants, but among Thai male participants, participants with AHI tended to be younger (median 22 years compared to 24, $P < .003$; Table 1).
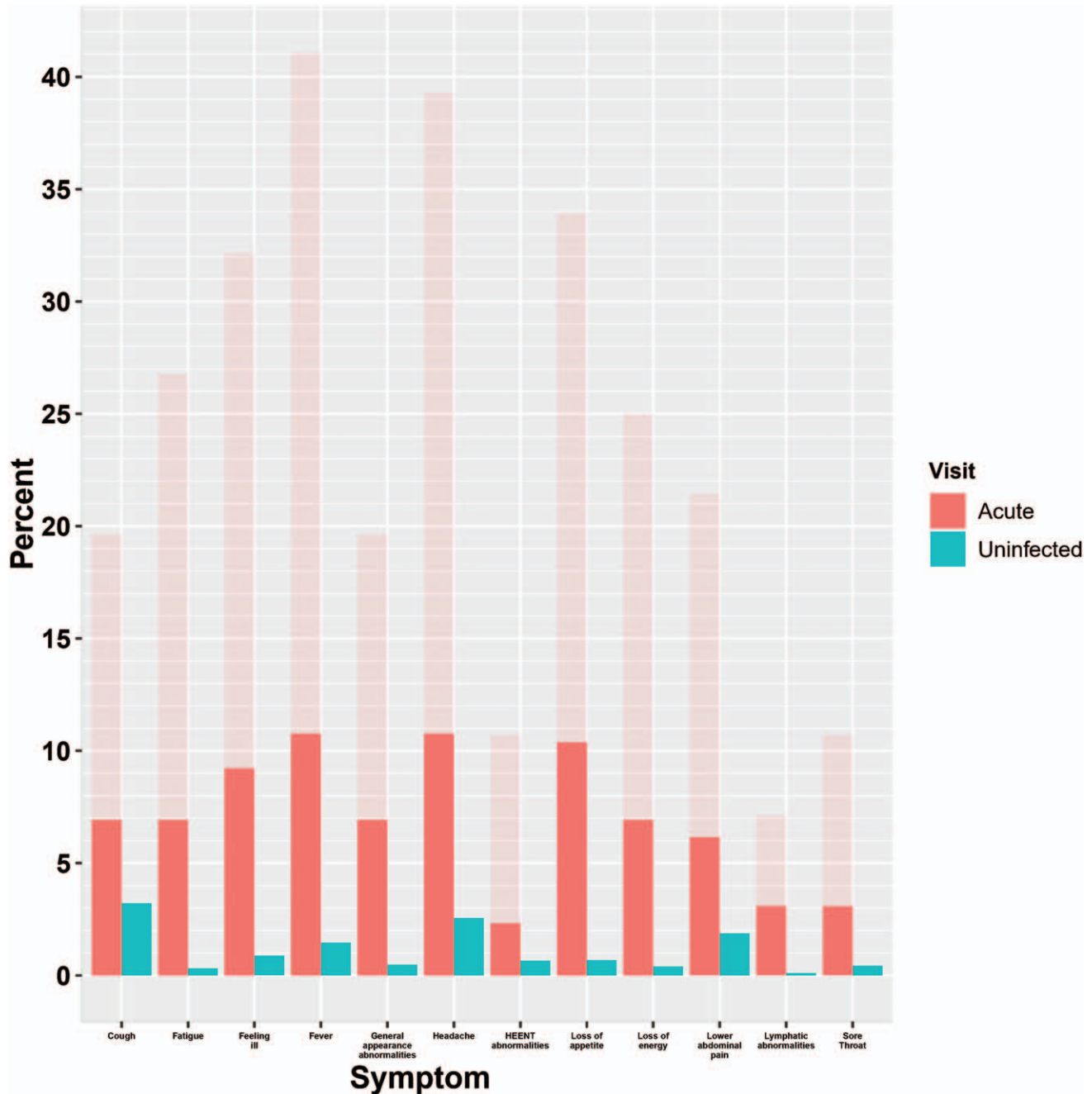
Figure 2. Frequency of selected symptoms in acute human immunodeficiency virus (HIV) infection and HIV-negative study visits for African female participants. HEENT, head, ears, eyes, nose, and throat. *The lighter red shading represents the percent of female AHI participants reporting a given symptom sign at any encounter during the 21-day acute HIV infection window, while the darker red and blue shading represent the percent of individual AHI and uninfected encounters, respectively, at which African female participants reported a given symptom. AHI = acute HIV infection.

Among the Thai males, the signs and symptoms most frequently reported during the 21-day AHI window were lymphatic abnormalities (defined as palpable lymph nodes, often less than 0.5 cm in size) (68% compared to 13.2% in HIV-uninfected encounters), HEENT (head, ears, eyes, nose or throat) abnormalities that did not constitute any other specified symptom or examination findings pertaining to these body systems (36.1% compared to 13.5%), and sore throat (16.1% compared to 6.3%) (Fig. 1 and Table S1, Supplemental Digital Content, http://links.lww.com/MD/G603). After adjusting for the number of visits, the signs and symptoms with the greatest differences in incidence between participants with AHI and uninfected participants were nausea (odds ratio [OR] = 15.4, 95% confidence interval [CI] 3.8–58, $P < .001$); lymphatic abnormalities (OR 12.5, 95% CI 4.4–52.1, $P < .001$); diarrhea (OR 8.2, 95% CI 3–20.2, $P > .0001$); abdominal pain (OR 7.5, 95% CI 2.6–19.1, $P < .001$); and feeling of loss or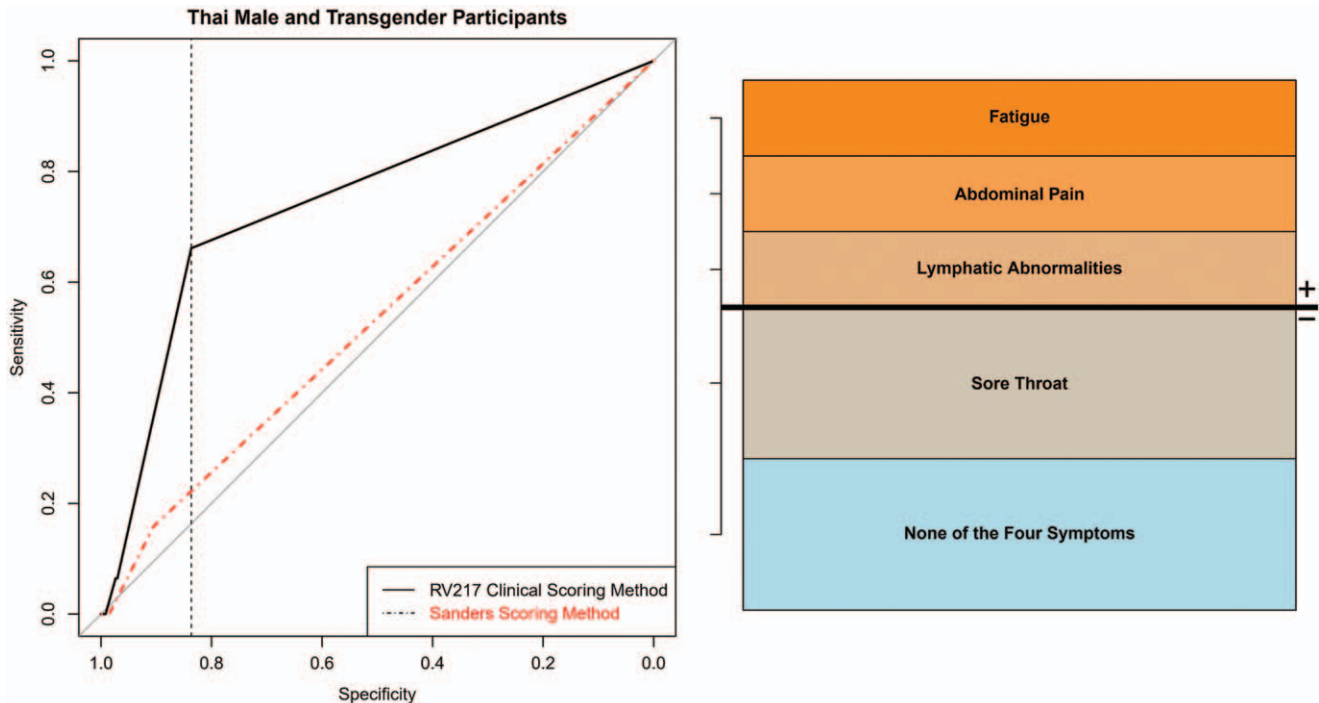 absence of energy (OR 7.5, 95% CI 2.8–18, $P < .001$) (Table S2, Supplemental Digital Content, http://links.lww.com/MD/G603).

Figure 3. Receiver operating characteristic curves for the RV217 Scoring Method (black) and the Sanders et al Scoring Method (red), applied to the Thai male and transgender test dataset and final Thai male and transgender scoring algorithm in graphical form. Panel A: RV217 algorithm: area under the curve (AUC) = 0.74, specificity = 84% and sensitivity = 66% at the optimal cut-point; Sanders et al: AUC = 0.53, specificity = 98.5% and sensitivity = 0% at the cut-point suggested by the authors. Panel B: The 4 significant symptoms are displayed in graphical form, with higher values indicating higher predicted probabilities and all encounters above the bolded threshold predictive of an acute infection at the optimal cut-point.

Among African female participants, headache (10.8% of AHI encounters compared to 2.6% of uninfected encounters), fever (10.8% compared to 1.5%), loss of appetite (10.4% compared to 0.7%), a feeling of being ill or sick (9.2% compared to 0.9%), were the symptoms with the greatest frequencies during AHI (Fig. 2 and Table S1, Supplemental Digital Content, http://links.lww.com/MD/G603). The symptoms with the greatest differences in incidence when comparing African female AHI participants with those that were uninfected were pain behind the eyes (OR 43.6, 95% CI 11.8–155.3, $P < .001$), fatigue (OR 25.4, 95% CI 12.4–50.2, $P < .001$); and unintentional weight loss (OR 22, 95% CI 6.7–63.7, $P < .001$) (Table S3, Supplemental Digital Content, http://links.lww.com/MD/G603).

Over the entire 21-day AHI window, 86% of participants with AHI reported at least 1 symptom, including 77% of African female and 100% of Thai male participants (Fisher exact test for difference between subgroups: $P = .001$). At least 1 symptom was reported at 56% of AHI encounters (40% for females and 77% for males), compared to 24% in HIV-negative encounters (21% for females and 31% for males). However, over 85% of all encounters reported 5 or fewer signs and symptoms (Figure S1, Supplemental Digital Content, http://links.lww.com/MD/G604).

After algorithm development as described above, the final scoring algorithm for Thai males of 6*fatigue + 5*abdominal pain + 4*lymphadenopathy + 2*sore throat yielded a sensitivity of 66%, specificity of 46%, positive predictive value of 14%, and negative predictive value of 98% at the optimal cut-point based on Youden statistic, with scores > 3 predicted to be an AHI encounter (Fig. 3 panel A and Table S4, Supplemental Digital Content, http://links.lww.com/MD/G603); the area under the curve (AUC) was 0.74. Among 33 AHI visits HIV-negative males made before additional testing confirmed they were not acutely infected, 27 (82%) were correctly classified as negative when the algorithm described here was applied. In contrast, using the Sanders et al algorithm with our data, the AUC was 0.53; at the cut-point of 2 suggested by the authors, the specificity was 98.5% and the sensitivity was 0%. Figure 3 panel B shows a practical clinical tool composed of the 4 significant symptoms in graphical form, with higher values indicating higher predicted probabilities and all encounters above the bolded threshold predictive of an acute infection at the optimal cut-point.

The final scoring algorithm for African females of 10*loss of appetite + 8*rash + 8*lymphatic abnormalities + 8*feeling sick + 7*general appearance abnormalities + 4*cough yielded an AUC of 0.62 and a sensitivity of 27%, specificity of 98%, positive predictive value of 17%, and negative predictive value of 99% at the optimal cut-point with scores > 6 predicted an AHI encounter (Fig. 4 panel A and Table S5, Supplemental Digital Content, http://links.lww.com/MD/G603). Among 375 AHI visits HIV-negative females made before additional testing confirmed they were not acutely infected, 369 (98%) were correctly classified as negative using this clinical scoring algorithm. The AUC for the Sanders et al algorithm was 0.56, and at the suggested cut-point, the sensitivity was 8% and specificity 99%. Figure 4 panel B shows the female clinical tool at the optimal cut-point.

4. Discussion

Our data demonstrate a considerable difference between regions and/or sexes in the occurrence of various signs and symptoms of
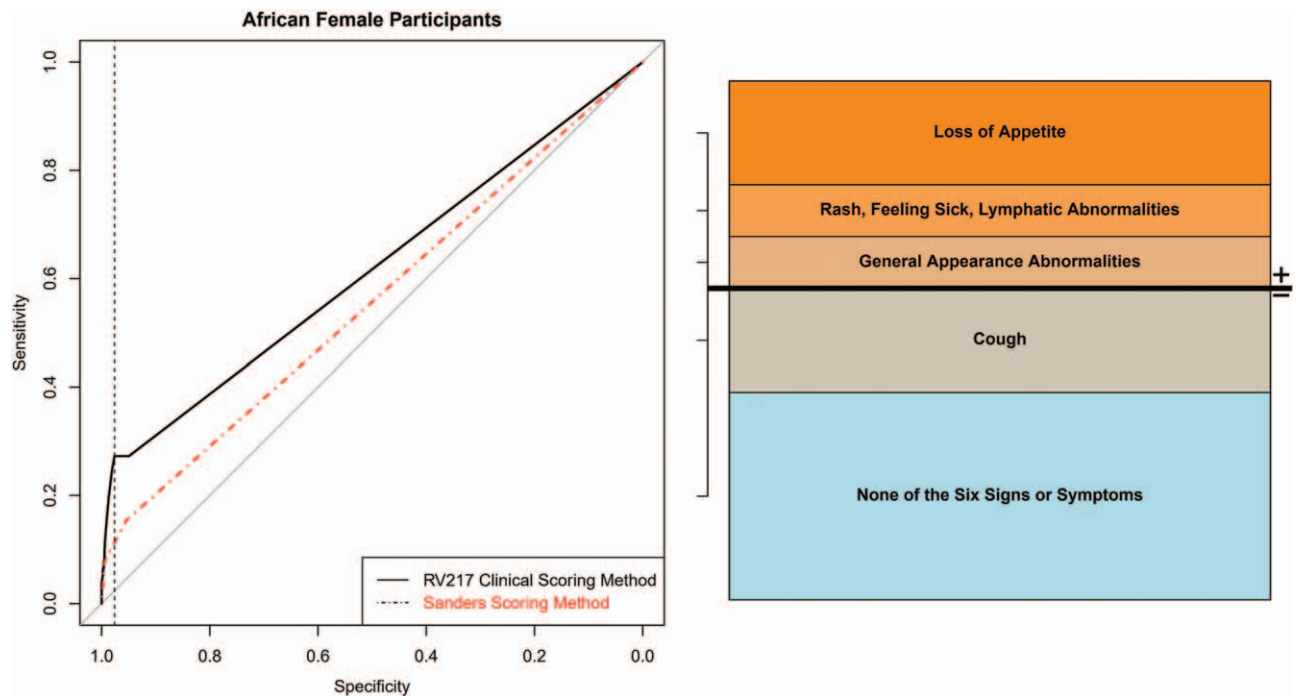
Figure 4. Receiver operating characteristic curves for the RV217 Scoring Method (black) and the Sanders et al Scoring Method (red), applied to the African female test dataset and final African female scoring algorithm in graphical form. Panel A: RV217 algorithm: area under the curve (AUC) = 0.62, specificity = 98% and sensitivity = 27% at the optimal cut-point; Sanders et al: AUC = 0.56, specificity = 99% and sensitivity = 8% at the cut-point suggested by the authors. Panel B: The 6 significant symptoms are displayed in graphical form, with higher values indicating higher predicted probabilities and all encounters above the bolded threshold predictive of an acute infection at the optimal cut-point.

AHI. The vast majority of African participants were female while most of the Thai participants were biological males. For the Thai males, incidence of nausea, lymphatic abnormalities, and diarrhea, had the strongest associations with AHI among the measured signs and symptoms, while for African females, fatigue, pain behind the eyes, and unintentional weight loss had the strongest associations. Using both sexes and participants from multiple African countries and Thailand allowed us to identify differences between these subgroups in which signs and symptoms are associated with AHI. This necessitated developing 2 subgroup-specific analyses and subsequently 2 different scoring algorithms to maximize predictive performance.

Among the Thai males in this study, diarrhea was found to be a predictor of AHI as was reported in other all-male[21] and predominantly male cohorts.[19] Similarly, adenopathy was previously reported among Kenyan women.[22] Among African females in this study, weight loss had been previously associated with AHI among African women [20] and American men [18] as well as fatigue among African men [21] and the related "too sick to work" among African women.[22] However, the increased incidences of pain behind the eyes for African females or nausea for Thai males had not been reported previously as an association with AHI.

The differences between studies among signs and symptoms observed during the time of AHI most likely represent the various methods of diagnosis of AHI, ascertainment of signs and symptoms, HIV strains, modes of transmission, and populations that were studied. Our novel methodology utilized frequent testing for AHI and repeated clinical examination immediately after diagnosis. Our cohort is one of the largest described for the

purpose of making an AHI scoring tool and is unique in that it involves 4 countries on 2 continents and both sexes. Additionally, our methodology limited recall bias. Patients often have poor recall of AHI signs and symptoms when they are evaluated weeks to months after infection.[29] In our cohort, the median duration between follow-up encounters during the AHI window was only 4 days. However, this could introduce recency bias into a patient's perception regarding the recall of symptoms what might not otherwise have been reported and attributing them to the recent diagnosis of HIV. The high accuracy of both algorithms (78% in males, 98% in females) in classifying false-positive AHI visits correctly as HIV-negative indicates that the performance of these algorithms was not driven by the differences in visit schedules between AHI and HIV-negative participants.

A total of 86% of participants with AHI reported at least 1 sign or symptom during the 21 day AHI window, which is higher but consistent with 57% to 81% previously reported.[19,20,22] The overall prevalence of symptoms might be lower than anticipated based upon the rigorous and abundant follow-up and supports the hypothesis that some patients do not manifest any signs or symptoms of AHI. In our cohort, 14% of newly HIV-infected individuals did not have any signs or symptoms and those that did often had few and were non-specific in nature, highlighting the extreme difficulty in diagnosing all AHI without active surveillance.

Among all participants with symptoms data, 97% of the female AHI participants were from Africa and all the biological males with AHI were from Thailand. Although scoring algorithms stratified by sex or region using this original data were similar to those presented (sensitivity analyses not shown),

our subgroup analysis was censored for African males and Thai females. This methodology allowed us to contrast the novelty of our Thai male data compared to other cohorts that identified signs and symptoms of AHI using African or American cohorts. It is difficult to determine if the differences in symptoms came from sex or other confounders related to geography, host genetics, co-morbid diseases, culture, different HIV subtypes,[29] variable routes of transmission, or a combination of factors. Our subgroup-based clinical scoring algorithms are particularly valid in the sexes and regions used to create them, males in Thailand and females in sub-Saharan Africa. These groupings highlight the probability of region- or sex-specific differences in the presentation of AHI and should be considered when applying a scoring algorithm to a population other than the one which was used to validate it. Future research on region, sex, gender, HIV-subtype, host factors, and demographic specific models are needed.

Both subgroup-specific scoring algorithms performed at least as well as the previously published algorithm by Sanders et al,[11] which used pooled data from 4 studies conducted in Africa with 90/122 (74%) being female. The Thai male algorithm had a substantially higher sensitivity and AUC than the Sanders et al model. The reduced prediction accuracy in the African female sub-group is likely related to the wider variability of signs and symptoms presented in that sub-group as compared to the Thai males, in which adenopathy in particular was frequently observed. Most previously published scoring algorithms assessed performance in the same data sets in which they were developed, therefore the independent development/testing approach used here is a relative strength with respect to validity.

5. Conclusion

Using an intensely monitored cohort, we observed substantial differences between the incidence rates of symptoms associated with AHI among sub-Saharan Africa female participants compared to biological male participants from Thailand, necessitating 2 subgroup-analyses. The variability among the odds of reporting certain symptoms for these 2 sub-groups, despite a standardized methodology, suggests the need for further research on risk exposure, sex, geographic, cultural, viral and other pathogen, host and environmental influences on the clinical presentation of AHI. Even utilizing our novel approach to identify AHI through twice weekly encounters during the study time period, and close follow-up during acute infection, one-seventh of participants never reported any symptoms and those that did often had less than 5 non-specific concerns demonstrating the difficulty in identifying all cases without active surveillance.

Author contributions

Contributions: Data analysis and writing of manuscript (AGL); study design and execution (LAE); data analysis and manuscript writing (CB); data analysis (PD); study execution and data acquisition (SN, JK, HK, LM, EK, SS); study design and oversight (NLM, RJOC); study design, oversight and principal editor of manuscript (MLR). All authors have reviewed, edited, and approved the text.

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Conceptualization: Andrew Letizia, Leigh Anne Eller, Hannah Kibuuka, Somchai Sriplienchan, Nelson Michael, Jerome Kim, Merlin Robb.

Data curation: Leigh Anne Eller, Christopher Bryant, Sorachai Nitayaphan, Josphat Kosgei.

Formal analysis: Andrew Letizia, Christopher Bryant, Peter Dawson.

Funding acquisition: Nelson Michael, Robert O'Connell.

Investigation: Sorachai Nitayaphan, Josphat Kosgei, Hannah Kibuuka, Lucas Maganga, Eugène Kroon, Somchai Sri-plienchan.

Methodology: Peter Dawson, Somchai Sriplienchan, Nelson Michael, Jerome Kim, Merlin Robb.

Project administration: Leigh Anne Eller, Lucas Maganga, Robert O'Connell.

Resources: Merlin Robb.

Supervision: Leigh Anne Eller, Nelson Michael, Merlin Robb.

Writing – original draft: Andrew Letizia.

Writing – review & editing: Andrew Letizia, Leigh Anne Eller, Christopher Bryant, Peter Dawson, Sorachai Nitayaphan, Josphat Kosgei, Nelson Michael, Robert O'Connell, Jerome Kim, Merlin Robb.

Correction

Nelson Michael's last name was spelled incorrectly as Micahel in the author contributions.

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