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Acute and Early HIV Infection: A Missed Opportunity for Behavioral and Biomedical Combination Strategies for HIV Prevention in Sub-Saharan Africa

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Abstract

Acute HIV Infection impacts on both patient management and public health interventions targeting HIV/AIDS epidemic. The ongoing unchanged HIV incidence in the era of treatment as a prevention intervention may be attributable in part, to current programs failing to diagnose and treat AHI. This review maps the current knowledge of AHI in SSA where 5% to 38% of new HIV infections originate from individuals being in the acute stage of the infection. The amount of infection attributable to AHI depends on the individual risk-level behavior. The unavailability of POC appropriate diagnostic tool in SSA results in many cases of AHI being missed by HIV prevention, care and treatment programs. Clinicians should be aware of common signs and symptoms and how to screen for AHI especially in high-risk group population. Patients screening positive for AHI should have their risk-level behavior assessed followed by risk behavior reduction interventions with appropriate follow-ups in order to diagnose HIV at the earlier stage, and ensure linkage into care, which results in immune preservation, prevention of morbidity and mortality in addition to the prevention of further transmission of HIV infection to other sexual partners.

Keywords: Acute HIV infection; Enzyme immunoassay; HIV testing and counseling; Acquired immunodeficiency syndrome; Sub-Saharan Africa

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Acronyms: AHI: Acute HIV Infection; AIDS: Acquired Immunodeficiency Syndrome; EIA: Enzyme Immunoassay; HIV: Human Immunodeficiency Virus; HTC: HIV Testing and Counseling; NAT: Nucleic Acid Testing; POC: Point-of-Care; STI: Sexually Transmitted Infection; SSA: Sub-Saharan Africa

Introduction

Human immunodeficiency virus (HIV) infection progresses through different stages namely: early including acute, chronic, and late stage [1]. Acute HIV Infection (AHI) spans from the acquisition of the virus to the presence of HIV-specific antibodies after a rapid rise and peak of plasmatic viral load, whereas early HIV infection which include acute stage is the period running from HIV acquisition to the viral set point [1].

AHI has impact on both patient management and public health interventions targeting HIV/AIDS epidemic [2]. Much attention has been recently directed towards AHI because of its possible contribution to the growth of the epidemic [3]. The ongoing unchanged HIV incidence in the era of treatment as a prevention intervention may be attributable in part, to current programs failing to diagnose and treat AHI [4]. With

regard to the patient management; diagnosing and treating AHI results on the control of viral load at the earlier stage, lower viral set point, reduction of the number of infected cells, limitation of the latent pool of HIV-1 infected CD4+ T cells, and the preservation of the immune function [5]. Researches on AHI in low and middle-income countries are emerging [6]. However, the state of current evidence on AHI has not been yet systematically investigated in Sub-Saharan Africa (SSA).

The objectives of this review is to answer the following questions regarding AHI in SSA: (a) what is the contribution of the acute stage to the spread of HIV infection; (b) what are the clinical manifestations and risk-score algorithm for AHI in place, and (c) what strategies are required for the diagnosis and treatment of AHI at large scale? For the purpose of this review the term acute HIV, early HIV, primary HIV infections are used interchangeably.

Contribution of the acute stage to HIV transmission

High level of plasmatic viral load which is proportional to HIV genital shedding is observed during early HIV infection resulting in individual being highly infectious during this stage compared to the chronic stage of the infection [7]. The peak of plasmatic viral load seems to occur around 17 days after infection [7] and the mean duration of high viral load before the set point is estimated around 76 days [8]. The viral load during AHI peaks at about 6.5 $\log_{10}$ copies per mm [7,9] and the set point is approximately around 4 $\log_{10}$ [8-10]. There is a direct correlation observed between HIV-1 cervical and plasmatic viral load levels during early infection and the mean cervical set point is at around 1.64 $\log_{10}$ copies per swab, occurring at around 174 days after infection [10].

To assess the proportion of HIV infections attributable to the early stage on the assumption of high risk transmission due to high viral load observed during this stage; we identified studies based on the mathematical modelling approach conducted in the SSA region, and analysed their findings. It results in general that early stage of HIV is responsible for a substantial number of HIV transmission in the region. For instance, HIV transmission attributable to primary stage was found to be 26 times higher compared to the chronic stage [11]. Powers and colleagues [12] found that 38.4% of HIV infections were attributable to an index case being in the early stage of the infection, and Pinkerton [13] reported that as high as 89.1% of all HIV transmission events that occurred in a cohort followed up during 20 mon, happened while the index case was in the early stage with the average per act transmission probability calculated at 0.03604 in the acute stage compared to 0.00084 in the chronic stage [13]. These evidences were challenged by another study suggesting that the proportion of HIV infections attributable to early stage was overestimated in previous studies and stating that only 5.3% of HIV infections were attributable to the early stage of the infection [14]. However, the same study acknowledged that the proportion of HIV infections attributable to the early stage was dependent on the individual risk-level behavior and HIV prevention interventions [14].

Regarding the role of individual risk-level behavior, evidences show that the number of transmission occurring during the primary infection is proportional to the amount of concurrence. According to the calculations of Eaton and colleagues [15], the proportion of HIV infections attributable to the early stage was estimated between 16% and 28% depending on the amount of concurrency. They demonstrated that primary HIV in term of disease transmission can be understood only in combination with concurrent sexual partnerships and their combination may be the factor that has enabled HIV epidemic to grow in the general population [15]. One study found no dominancy across the different stages of HIV in term of contribution to the disease transmission [16]. The estimated contribution to HIV transmission in this study was 17%, 51% and 32% for acute, chronic and late stage respectively. Chronic stage contributed with more than half of all HIV transmissions because of its long duration. However, acute stage was estimated to be more contributive to HIV transmission in the context of high risk sexual behavior despite its short duration [16]. The association of acute HIV stage and sexual risk behavior were explored in other studies, and it results from these studies that the epidemic cannot be sustained in the general population without the role played by AHI and high-risk sexual behavior [17]. The proportion of HIV transmission occurring while the index case is in the acute stage depends on the biological factors, behavioral patterns and the epidemic stage [18]. Regarding the epidemic stage, Powers and colleagues [12] demonstrated that AHI can still contribute to the spread of the disease in a matured epidemic as well as in early epidemic.

Targeting high-risk sexual behavior during acute HIV stage was also explored with promising results. In this regard, we identified three studies demonstrating that sustained behavior change after AHI diagnosis was achievable in majority of participants with either behavioral motivational counseling interventions, or brief education targeting risk reduction behavior [19-21]. In contrast, only one study found that the majority of participants surveyed failed to demonstrate good understanding of AHI including the notion of high infectivity thereof, in spite of information imparted to them several times in plain, no-scientific language supported by visual aid material [22].

Clinical manifestations and the risk-score algorithm for screening

Acute HIV infection is frequent in SSA. The lowest prevalence found were 0.1%, 95% CI (0.258%-0.002%) in a cohort from all hospital admissions in South Africa, and 0.21%, 95% CI (0.03%-0.40%) in a study involving pregnant women with a negative HIV antibody test in Malawi [23, 24]. The prevalence of approximately 1% was found in many other studies [25-29]. In malaria endemic area AHI is most often mistaken for malaria. According to Yeatman et al. [30], 46% of women with early HIV infection sought medical care for what they thought to be malaria.

Symptoms and signs accompanying AHI lack specificity and are present in a wide range of other morbidities [31]. Some studies have investigated clinical manifestations of AHI in SSA. More than half of women diagnosed with AHI in South Africa reported one or more signs or symptoms such as: rash, sore throat, weight loss, genital ulcer, and vaginal discharge [32]. Younger age of

less than 25 yrs was associated with AHI in the same study, and the specificity and likelihood ratio of AHI increased when more of these signs and/or symptoms coexisted in one patient [32]. In addition, unexplained fever, fatigue, swelling of inguinal lymph nodes was also found to be associated with early HIV infection in women from Zimbabwe [33]. Whereas in Uganda age less than 30 years, fever, STI, diarrhea, body aches and the history of multiple sexual partners were found to be predictive of AHI [29]. However, in another study conducted in South Africa; the number of lifetime sexual partners and frequency of sexual intercourses in the last 30 days before diagnosis were the most factors found to be associated with AHI [34].

Lack of specific signs and symptoms for AHI prompted the development of the risk-score algorithm for screening in 2007. According to this algorithm, one point is assigned in the presence of each of the following: fever, body ache, and more than one sexual partner in the previous two months. Two points are assigned in the presence of each of the following: diarrhea and genital ulcer disease. Four points are assigned in the case of a discordant rapid HIV antibody test. The cut-off score of two points is supposed to detect 95.2% of AHI cases [35].

The performance of the risk-score was assessed in three studies conducted in SSA. In Malawi; the risk-score algorithm was sensitive at 71% and specific at 73% in screening patients with AHI [36]. This specificity was lower (54%) among patients recruited at STI clinics with nearly half of the participants (46.4%) meeting the threshold of two points compared to patients recruited at HTC clinics in whom the score demonstrated better performance with the sensitivity of 73%, the specificity of 89% with only 11.7% of participants meeting the threshold score of two points [36]. The risk-score algorithm of at least two points had good performance in Kilifi (Kenya) and Lilongwe (Malawi), fair performance was observed in Mombasa (Kenya) whereas, and the risk-score algorithm had poor performance in Durban (South Africa) [37]. Finally, Wahome and colleagues [38] confirmed in their study the importance of fever, diarrhea and a serodiscordant rapid HIV test for the identification of early HIV infection in African population. The same study also demonstrated that targeted screening for early HIV infection in men who have sex with men could be performed with a limited set of characteristics including age younger than 30 yrs, fever, diarrhea, fatigue, any symptomatic STD, and discordant rapid serological HIV test [38].

Point-of-Care diagnostic test for AHI

The above-given evidences have enlightened the need for diagnosing AHI at the POC in SSA. Hence some studies have attempted unsuccessfully to demonstrate in practice the theoretical possibility of the rapid fourth-generation test which can detect the HIV-specific antigen in addition to HIV-specific antibodies. For instance, the sensitivity and specificity of the p24 antigen component of the test were inadequate for widespread use to diagnose AHI in Malawi [39]. Similar results were found in Zambia whereby less than 2% of the cases antigen positive HIV infections were detected by the rapid fourth-generation test [40]. In addition, a national household survey conducted in Swaziland concluded that the rapid fourth-generation test failed to identify any true AHI, rather all the Ag+/Ab- identified by the test were falsely positive for AHI [41].

Discussion

Although one study challenged the high proportion of HIV infection attributable to AHI in SSA, most of the studies based on mathematical modelling approach examined in this review demonstrate that the early stage of the infection is associated with a substantial number of new HIV infections ranging between 16% and 38% of all HIV incidence cases. The number of new infections resulting from the index case being in the early stage is influenced by factors such as the stage of the epidemic in the society and the individual risk-level behavior. Combination of primary HIV infection and concurrent sexual partnerships, especially when new sexual partnerships are formed quickly may posit the high spread of HIV infection in region with generalised epidemic, but also in the context of concentrated epidemic [42-46]. We identified the opportunity for behavior change intervention coupled with routine screening for AHI provided by three studies with only one study rejecting this opportunity. Failure to screen and diagnose AHI in SSA constitutes a missed opportunity for behavioral and biomedical combination strategies for HIV prevention [47-49].

The clinical picture of AHI is vague and non-specific in SSA as it is elsewhere across the world [50-52]. This situation underpins the need for a risk-score algorithm for early HIV infection screening in the context of SSA. The need for a risk-score algorithm for AHI screening was also expressed in the USA in order to maximize the opportunity for targeting those most at risk [3]. Screening for AHI offers opportunity for early linkage to care and treatment with benefits ranging from immune system preservation to decrease onward transmission of HIV [53].

Both pooled NAT and fourth-generation HIV EIAs provide an increase yield for AHI diagnosis [54,55]. However, these assays are laboratory-based and not feasible at large scale in SSA [39]. Therefore, a rapid POC, cost-effective diagnostic test for AHI is highly desired in SSA [56]. In this regards, we identified studies that have investigated the practicability of the HIV rapid fourth generation EIA at POC in SSA which concluded in the non-suitability thereof. None study assessing the practicability of the POC NAT technology for AHI diagnosis in SSA was identified. Given the role played by AHI in the spread of the infection [57,58], continuous efforts are needed to close the gap of behavioral and biomedical combination strategies for HIV prevention in the early stage of the infection in SSA. In the meantime, clinicians should be aware of common signs and symptoms and how to screen for AHI especially in high-risk group population. Patients screening positive for AHI should have their risk-level behavior assessed followed by risk-behavior reduction interventions with appropriate follow-ups in order to diagnose HIV at the earlier stage, and ensure linkage into care which results in immune preservation, prevention of morbidity and mortality in addition to the prevention of further transmission of HIV infection to other sexual partners.

In summary, 5% (for some) and 38% (for others) of all new HIV infections occurring in SSA are attributable to the index cases being in the acute stage of the infection. Concurrent sexual partnerships associated with early stage of the infections are associated factors for high rate of HIV transmission. AHI is common in SSA and most patients seek healthcare for AHI syndrome which is mistaken for other conditions such as malaria. A risk-score algorithm has been developed for targeting and screening those most at risk of AHI. However, the unavailability of a POC diagnostic test for AHI limits its application in SSA. Continuous efforts are needed to develop a suitable POC diagnostic tool for AHI in the region. In the meantime, clinicians should initiate behavioral intervention and appropriate follow-ups for patients screening positive for AHI in order to minimize new HIV cases linked to the early stage of the infection.

Limitation

Only online published primary papers conducted in SSA between 2007 and 2017 were considered for this review. Relevant information regarding AHI in SSA contained elsewhere may be omitted.

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