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The HIV treatment cascade in acutely infected people: Informing global guidelines

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Abstract

Purpose of Review—Acute and early HIV (AHI) is a pivotal time during HIV infection, yet there remain major shortfalls in diagnosis, linkage to care, and antiretroviral therapy (ART) initiation during AHI. We introduce an AHI-specific cascade, review recent evidence pertaining to the unique challenges of AHI, and discuss strategies for improving individual and public health outcomes.

Recent Findings—Presentation during AHI is common. Expanding use of 4th generation testing and pooled nucleic acid amplification testing (NAT) has led to improved AHI detection in resource-wealthy settings. Technologies capable of AHI diagnosis are rare in resource-limited settings; further development of point-of-care devices and utilization of targeted screening is needed. Rapid ART initiation during AHI limits reservoir seeding, preserves immunity, and prevents transmission. Reporting of AHI cascade outcomes is limited, but new evidence suggests that impressive rates of diagnosis, linkage to care, rapid ART initiation, and viral suppression can be achieved.

Summary—With advancements in AHI diagnostics and strong evidence for the therapeutic and prevention benefits of ART initiated during AHI, improving AHI cascade outcomes is both crucial

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Conflicts of interest

None

and feasible. HIV guidelines should recommend diagnostic algorithms capable of detecting AHI and prescribe rapid, universal ART initiation during AHI.

Keywords

Acute HIV infection; HIV cascade; HIV diagnostics; linkage to care; guidelines

Introduction

Acute HIV is a very brief but critical phase of HIV infection. Historically, acute HIV infection has been defined as lasting only until the emergence of HIV-specific antibodies (1), since lack of antibodies in the presence of viral RNA was used as an operational definition of the stage of disease. However, as antibody tests have become ever more sensitive and many patients have been followed from infection onward (2), it is wiser to consider acute and early HIV infection as a package (sometimes referred to as “primary infection”), since clearly the important events that transpire after infection extend for a longer time than required for antibodies to form (3). The exact time at which acute and early infection should be considered as “established” infection has not been resolved. However, the transmission risk associated with acute and early infection lasts at least 4 months (4).

Acute HIV infection and early HIV infection (heretofore referred to as AHI) are associated with extremely high viral loads, seeding of viral reservoirs and a disproportionate contribution to onward HIV transmission. Failure to diagnose and treat persons with AHI has significant individual and public health implications. Responding to these consequences, revised US HIV management guidelines now include HIV screening algorithms to detect AHI, and recommend antiretroviral therapy (ART) regardless of CD4+ T cell counts in persons with AHI (5). The updated International AIDS Society guidelines also recommend universal ART, and the most recent European AIDS Clinical Society Guidelines advocate consideration and discussion of ART initiation with the patient with AHI (6, 7). However, prominent international guidelines, such as those from the World Health Organization (WHO), have not yet defined a diagnostic strategy nor made any specific recommendation regarding ART initiation for persons with AHI (8).

In this paper, we propose an AHI-specific cascade (**Figure 1**) and explore the critical concerns that could be targeted in guidelines. AHI has unique challenges. These include limited detection of AHI through HIV testing algorithms, delays in ART initiation that compromise the individual and public health benefits of ART, and limited knowledge regarding success rates of linkage to and retention in HIV care.

Diagnosis of acute HIV infection

Perhaps no topic related to AHI attracts more attention and frustration than identification of this stage of infection. Identifying persons with AHI is complicated by the brevity of the phase, the non-specific symptoms associated with the HIV infection, and (at first) the absence of anti-HIV antibodies. Traditional point-of-care (POC) antibody tests cannot directly address this earliest phase of infection, so the diagnosis of AHI relies on the direct

detection of virus or viral antigen. (Parenthetically, discordance in particular POC rapid tests strongly suggests AHI, as discussed below).

Revised CDC guidelines outline diagnostic algorithms that detect AHI using a combination of 4th generation enzyme immunoassays (EIA) and nucleic acid testing (NAT) (9). Although WHO guidelines characterize 4th generation assays as "A1 assays" to be used where feasible for the detection of AHI, they provide no guidance for AHI screening or diagnosis (10). Expanded utilization of 4th generation assay can clearly help to diagnose persons earlier in the course of infection.

Due in part to their non-specific nature, clinical manifestations of acute infection are frequently misclassified (11, 12). In the United States, 55% of persons eventually diagnosed with AHI were missed on their first visit to the healthcare system (13). Patients in resource-limited settings also commonly seek medical care for symptoms related to acute infection, but are instead often presumptively treated for malaria (11, 14). In one survey of Kenyan adults presenting to outpatient health centers with fever, the prevalence of AHI and malaria was identical at 1.7% (95% confidence interval (CI) 0.5%−4.2%) (15). Among febrile seronegative persons presenting to outpatient clinics Uganda, 2.8 % had AHI ; in Mozambique, AHI prevalence was 3.3% (95% CI 1.3%−6.7%) (16, 17). Risk score algorithms demonstrate the utility of AHI screening among seronegative patients presenting with certain symptoms and risk behavior histories (18, 19). Among higher risk patients, such an algorithm can lead to correct and efficient diagnosis of AHI, detecting 81.0% of patients with AHI by screening only 20.1% of the targeted patient population. These AHI detection algorithms deserve more attention.

Increased targeted screening for AHI may unearth substantial missed diagnoses. In resource-limited settings, symptom-derived AHI risk scores help focus testing resources (12, 15, 18, 20). Nonetheless, AHI is rarely considered among febrile adults in sub-Saharan Africa (21). WHO guidelines recommend HIV testing in the setting of >30 days of unexplained fever with a negative malaria test, but AHI is not mentioned as a potential cause of fever of shorter duration nor is AHI screening recommended for this patient population (22). Numerous technologies are available to narrow the window of diagnosis for persons with AHI; some have been incorporated into testing algorithms in resource-wealthy settings but none are routinely applied in resource-limited settings.

Fourth generation EIAs detect p24 antigen and antibody isotypes that emerge soon after infection. These assays serve as the backbone for HIV testing algorithms in the US (9). Identifying persons earlier in the course of infection compared to previous generations, 4th generation tests substantially improve AHI detection (23-26). In a Texas emergency department, 18/78 (23%) with confirmed positive results were acutely infected and would not have been diagnosed without 4th generation assays (27). However, these assays still miss high-risk populations presenting to care in the critical gap before emergence of p24 antigen (28). Additionally, the ARCHITECT HIV Ag/Ab (Abbott Diagnostics, Chicago IL), a widely used 4th generation assay, does not discriminate between the antigen and antibody targets of the assay and thus does not distinguish between acute and established HIV. The use of a modified signal-to-cutoff ratio in 4th generation EIAs may improve detection of

early HIV infection and improve discrimination between AHI and established infection (29). Ultimately though, nucleic acid amplification (NAT) testing is required to identify persons in this earlier window via detection of HIV RNA.

Use of pooled NAT (30) instead of or in conjunction with 4th generation assays identifies persons with AHI earlier than 4th generation alone (i.e. in the first two weeks of infection), and pooled specimen throughput and costs may be more suitable for AHI screening in resource-limited settings. In high- and low-prevalence settings, pooled NAT substantially increases the number of persons identified with AHI compared to standalone 4th generation testing (31, 32). Although pooling for AHI may be cost-effective (33), financial feasibility will depend on the underlying prevalence of AHI and specific pooling strategy. Ideal pooling strategies maximize batch size according to population risk profiles and HIV prevalence, with a tradeoff of increased complexity with larger pools. In a high-prevalence Thai cohort, addition of pooled NAT after 4th generation testing increased acute diagnosis by nearly 40% but also increased screening costs by 22% (31). Besides costs, laboratory-based assays introduce logistical barriers to AHI screening, requiring venipuncture and patient follow-up

Effective POC tests for AHI would allow better widespread diagnostic capacity. The Alere Determine HIV-1/2 Ag/Ab lateral flow test was designed with this goal in mind. However, extensive field-based testing demonstrated that the product lacks the ability to reliably detect p24 antigen in blood, and is also compromised by false positive results (34-36).

Three recently introduced first-generation rapid NAT devices may be more promising: The Alere Q demonstrated excellent performance for early infant diagnosis in Mozambique (37); the SAMBA semiquantitaive assay, with a 1,000 copy/ml threshold, has demonstrated adequate performance on plasma (38); and the Liat HIV Quant cartridge-based viral load assay has shown promising results for POC viral load quantification (39). The ability of these POC technologies to detect HIV RNA suggests potential for an AHI screening assay. However, none of these tests have been field tested for detection of AHI, a critical requirement.

Antiretroviral therapy for acute and early HIV infection

During AHI, the virus integrates into host cell DNA, allowing the formation of a “latent reservoir”. ART initiated in AHI is to date the most effective strategy to limit HIV reservoir seeding (40-44) and reduce the number of infected cells (2, 45-48). Timing of ART initiation is critical as reservoir size is significantly smaller and decline in the number of infected cells is much faster in those who initiated ART within the first 2 weeks (prior to HIV IgM formation) vs. later (2). Cell-associated HIV DNA levels as low as those observed in elite controllers and post-treatment controllers can be achieved through very early treatment (42, 45, 49-51). In contrast, once individuals enter the chronic HIV infection phase, despite fully suppressive ART, they maintain a large reservoir size in blood and tissue that decays little over time (52, 53), leading to a rapid recrudescence of plasma viremia when ART is interrupted (54).

Cell-associated HIV DNA levels may also predict subsequent ability to control viremia following treatment interruption (55, 56). AHI individuals who were randomized to immediate vs. deferred ART displayed significantly longer time to viral rebound and lower viral set point when ART was discontinued (49, 57-60). In addition, the actual decrease in time of exposure to ART by deferring treatment of patients with AHI is small, since most patients followed prospectively required treatment by traditional guidelines within a few years (57, 58).

CD4+ T cells depletion, immune exhaustion and immune activation occur early in HIV infection, and chances for a full recovery are reduced when ART is delayed (46, 50, 61-63). Viral escape from host immunologic response increases when HIV is left untreated leading to an alteration in the “viro-immunological” landscape that could impact natural control of the virus and efficacy of future immunotherapeutic interventions (64-66).

A related issue is the attempt to modify the course of infection with alternative, more aggressive treatment regimens. Several randomized studies comparing standard ART vs. regimens intensified with integrase and entry inhibitors showed plasma HIV RNA to decline more rapidly in the intensified arm; but all regimens were similarly effective in lowering cell-associated DNA and RNA and markers of immune activation as well as raising CD4+ T cell counts (49-51). Other non-randomized studies showed minimal to no benefit in intensifying standard ART regimens (67, 68). However, the more rapid viral load decline in blood and genital secretions with integrase inhibitor-based regimens may prove beneficial in reducing transmission risk during AHI (69).

Leveraging the acute HIV cascade for prevention

The potential to stop transmission from people with AHI is of great public health importance. Several lines of evidence suggest that HIV transmission is greatly amplified during AHI infection (4). The HIV founder virus(es) causing infection are particularly contagious (70) and the viral loads in AHI are exceptionally high (71). A series of modeling exercises suggest that patients with AHI fuel the epidemic (72) and phylogenetic analysis from Montreal (73), Switzerland (74), Amsterdam(75, 76) and San Francisco (77),all demonstrate exceptional contribution of AHI to spread of HIV in MSM. Studies from San Diego (78) and Malawi (3, 4) suggest that intervention in the first 4 months can reduce HIV spread.

A key barrier to intervention in AHI is the belief that action geared toward public health is infeasible. However, North Carolina’s Screening and Tracing Active Transmission Program has since 2002 successfully carried out statewide AHI screening and linkage to care, with 30 day linkage and ART initiation rates of 80% and 61% (79, 80). An AHI study in New York City reports similar rates between patients newly diagnosed with AHI and established HIV of linkage within 3 months (92% vs 91%) retention at 12 months (86% vs 83%, p= 0.78) and suppression (65% vs 60%) (81). Additionally, a recent study reports 111/112 participants diagnosed with AHI at a Thai clinic were initiated on ART at their first care visit, a median of 19 days from the estimated date of their exposure to HIV, with excellent subsequent retention and viral suppression outcomes (31). Other studies involving rapid linkage and

ART initiation are currently in process (MP3, SEARCH, rapIT, Brigham/GHESKIO, Engage4Health, all clinicaltrials.gov).

The prevention benefits of diagnosis and care linkage during AHI extend beyond the opportunity to initiate early ART. Diagnosis during AHI coupled with risk reduction education or counseling has been associated with rapid reduction in self-reported transmission risk behaviors (82), and mathematical modeling suggests diagnosis during AHI and associated behavior change could have a significant impact on the UK MSM epidemic even in the absence of ART initiation (83).

The acute HIV cascade in practice

The concept of the HIV cascade has helped synchronize terminology and spur publication of large amounts of data on population-level HIV outcomes. However, information regarding AHI care outcomes outside of a research context remains scarce: public health surveillance data has traditionally not distinguished between AHI and established HIV diagnoses. However, when surveillance includes attempts to find infected people who are antibody negative, screening yield increases between 2-10% (30, 84-91). Yield varies according to diagnostic assays, risk profile of population (i.e. public health vs STI clinic), and underlying HIV prevalence. AHI screening yield is especially high among urban MSM in the US (84, 88, 89).

In 2008 New York City implemented citywide AHI surveillance and procedures for streamlined entry to HIV care for AHI patients. Thus far, published cascade data outcomes are limited but demonstrate 77% of the 62 city residents diagnosed with AHI were linked to care within 3 months (92). Another series of one-year cascade outcomes in a U.S. community health clinic cohort of 93 patients diagnosed with AHI reports 87% retained in care, 62% initiated on ART, and 46% virally suppressed (93). The proportions were all slightly higher for AHI patients compared to the clinics' patients newly diagnosed with established HIV.

Addressing the limited surveillance data collection on AHI outcomes, the CDC published new case definitions in 2014 creating an HIV stage 0, defined as a sequence of concurrent or sequential discordant test results indicative of AHI (94). This development promises to lead to a dramatically improved understanding of the state of the AHI cascade in the U.S.

Conclusion

The personal and public health benefits of treatment of AHI are now well established. Indeed, as the world moves toward a universal "test and treat" strategy it would seem very unwise to purposefully leave people with AHI untreated. A large series of randomized controlled trials (95-98) have all demonstrated an advantage to earlier ART. The Strategic Timing of AntiRetroviral Treatment (START) study was stopped by the NIH DSMB because of large differences in outcomes with early treatment started at CD4 counts >500 cells/mm^3. The cascade outlined in this report highlights the challenges unique to AHI: the differential diagnostic capacity according to resource setting, the highly time-sensitive nature of therapy initiation, and the opportunity to prevent transmission during a highly

infectious period. There are two critical levers through which modification of guidelines could improve AHI cascade outcomes: guidelines should incorporate diagnostic algorithms that include technologies capable of AHI detection, and, once diagnosed, guidelines must emphasize expedited linkage to care and ART initiation regardless of CD4+ T cell count. Maximal treatment benefits are gained through prompt ART initiation within days of diagnosis. This window is especially critical window for persons with AHI, and this opportunity will be missed if mechanisms to prioritize and urgently start ART in acutely-infected individuals are not in place. Same-day ART has been successfully implemented in low and middle income countries (31, 99). There are substantial financial, technical, and logistical barriers involved in AHI diagnosis, linkage, and treatment; but revision of international guidelines is essential in order to begin to address these obstacles (**Table 1**).

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Key points

- Diagnosis of AHI is frequently missed despite many patients presenting to care during this critical phase of infection.
- Use of 4th generation EIA with pooled NAT substantially improves AHI case finding, and although these laboratory-based diagnostic tools have been incorporated into testing algorithms in the USA and Europe, the technologies are rarely available in resource-limited settings
- Immediate initiation of ART during AHI is critical to limit reservoir seeding, preserve immunologic function, and reduce transmission events during this highly-infectious period.
- Revisions to prominent international guidelines should define a diagnostic strategy and make specific recommendations regarding ART initiation for persons with AHI

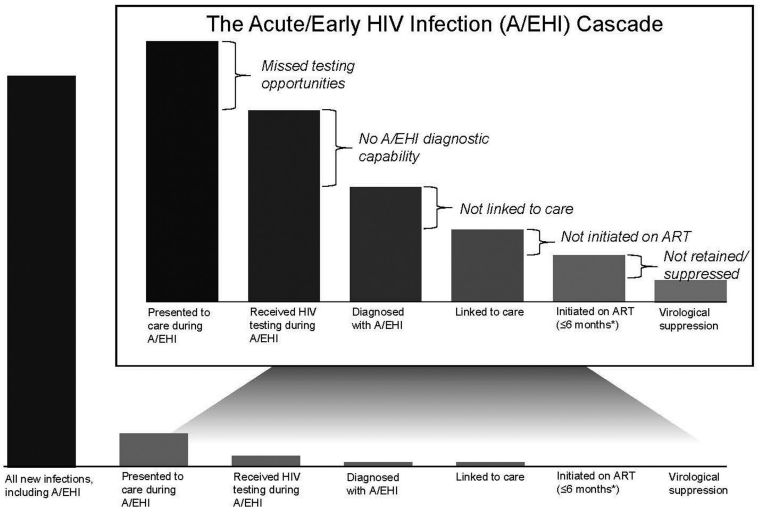

Figure 1. Acute HIV Infection Cascade

There remains little data to populate the acute HIV (AHI) cascade elements. Our proposed cascade highlights not only missed opportunities for diagnosis during this critical phase of infection, but also emphasizes opportunities to improve HIV outcomes through guideline modification that recognizes the importance of AHI diagnosis and immediate linkage to care with initiation of antiretroviral therapy.

Table 1

Proposed AHI Guideline Modifications

	Diagnosis	Treatment
Recommendation:	• Testing algorithms that effectively identify AHI should be used ○ Algorithms using 4th gen IA and pooled NAT should be used to diagnose AHI in EIA negative individuals • In resource-constrained settings, risk score algorithms should be used to target screening to persons at highest risk for AHI. • AHI screening should be included in clinical evaluations in settings whenever symptoms of acute retroviral syndrome are present, or when nonspecific symptoms such as fever are present in high HIV incidence groups.	• ART should be initiated regardless of CD4+ count and continued for life in persons diagnosed with AHI • Linkage to care and ART initiation should occur as rapidly as possible in AHI, with a maximum window of 3 months from diagnosis.