Individuals with acute HIV infection (AHI) pose a greater transmission risk than most chronically HIV-infected patients and prevention efforts targeting these individuals are important for reducing the spread of HIV infection. Rapid and accurate diagnosis of AHI is crucial. Since symptoms of AHI are nonspecific, its diagnosis requires a high index of suspicion and appropriate HIV laboratory tests. However, even 30 years after the start of the HIV epidemic, laboratory tools remain imperfect and only a few individuals with AHI are identified. We review the clinical presentation of the acute retroviral syndrome, the laboratory markers and their detection methods, and propose an algorithm for the laboratory diagnosis of AHI.

**Keywords**: acute HIV infection • diagnosis • primary infection • retroviral syndrome

Diagnosis of acute and early HIV infection has become essential because of its importance for HIV transmission, which is critical to the epidemic spread of HIV. The probability of transmitting HIV is closely related to the viral load [1]. Since patients with acute HIV infection (AHI) have an extremely high HIV viral load in both blood [2] and genital secretions [3,4], the risk of transmission is very high. Phylogenetic studies have shown that secondary HIV transmission from recently HIV-infected individuals are likely responsible for up to 50% of all new infections [5–8]. The role of AHI or early infection in the spread of HIV has been estimated using various mathematical models [9,10]. Transmission studies with serodiscordant couples estimated that during AHI the rate of HIV transmission was up to 26-times higher than the rate during established HIV infection [11,12]. In a recent study conducted in Malawi, 38% of new HIV cases were related to sexual exposure to patients in the first 5 months of their HIV infection [13]. However, these estimations vary greatly among studies. They depend on the epidemic phase with a higher proportion related to AHI in recent, as opposed to established, epidemics, but also on sexual behavior where data are often scarce or unreliable. In the context of the implementation of early antiretroviral treatment as a strategy to prevent new infections, the detection of AHI and early infection is essential [14].

There is no widely accepted definition of AHI, which is best understood as a clinical syndrome plus a combination of virologic and immunologic features as reflected in the results of laboratory investigations. One of the most widely used definitions of AHI is the detection of HIV RNA or HIV p24 antigen before the detection of specific HIV antibodies. This definition is influenced by the sensitivities of the assays, which have considerably improved in recent years.

Most of our knowledge of the first stages of HIV infection has been obtained from studies with SIV [14–16]. Following HIV infection, there is local replication in the mucosa. The preponderance of evidence implicates CD4+ T cells and Langerhans cells as the first targets of HIV. The virus is then transported to draining lymph nodes where further replication occurs. This is the end of the eclipse phase with the first detection of HIV RNA in blood and the spread of the virus to other lymphoid tissues, particularly gut-associated lymphoid tissue (GALT), resulting in the depletion of approximately 80% of CD4+ T cells in GALT [17–19]. While viral replication occurs in GALT and other lymphoid tissues, plasma HIV RNA increases exponentially [19–21].

**Signs & symptoms: the acute retroviral syndrome**

AHI is often asymptomatic, but sometimes it presents with serious manifestations requiring hospital admission. There is a wide spectrum between complete absence of symptoms during the time of seroconversion and severe disease (Tables 1 & 2). Therefore, it is not surprising
Yerly & Hirschel

Table 1. Signs and symptoms of acute HIV infection (reported by >5% of symptomatic patients).

<table>
<thead>
<tr>
<th>Symptom/sign</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reported by &gt;50%</strong></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>77</td>
</tr>
<tr>
<td>Lethargy/fatigue</td>
<td>66</td>
</tr>
<tr>
<td>Rash</td>
<td>56</td>
</tr>
<tr>
<td>Myalgia</td>
<td>55</td>
</tr>
<tr>
<td>Headache</td>
<td>51</td>
</tr>
<tr>
<td><strong>Reported by 20–50%</strong></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>44</td>
</tr>
<tr>
<td>Cervical adenopathy</td>
<td>39</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>31</td>
</tr>
<tr>
<td>Oral ulcer</td>
<td>29</td>
</tr>
<tr>
<td>Pain on swallowing</td>
<td>28</td>
</tr>
<tr>
<td>Axillary adenopathy</td>
<td>24</td>
</tr>
<tr>
<td>Weight loss</td>
<td>24</td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23</td>
</tr>
<tr>
<td>Night sweats</td>
<td>22</td>
</tr>
<tr>
<td>Cough</td>
<td>22</td>
</tr>
<tr>
<td>Anorexia</td>
<td>22</td>
</tr>
<tr>
<td><strong>Reported by 5–20%</strong></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>17</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
</tr>
<tr>
<td>Photophobia</td>
<td>12</td>
</tr>
<tr>
<td>Meningitis</td>
<td>12</td>
</tr>
<tr>
<td>Genital ulcer</td>
<td>7</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>7</td>
</tr>
<tr>
<td>Depression</td>
<td>7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
</tr>
</tbody>
</table>

Data taken from [22,24–30].

that opinions vary about the percentage of patients who have symptomatic AHI (often referred to as ‘acute retroviral syndrome’). A physician’s previous experience with AHI and a high index of suspicion greatly increase the number of diagnoses. Retrospective analysis from the US armed forces showed that 33% of patients suffered from an identifiable disease between their last seronegative and first seropositive serum samples. At the other extreme, in Australia, 93% of seroconverting persons reported having been ill compared with 40% of controls; 12% of seroconverting patients were hospitalized [22].

It is not known what factors determine the severity of the acute retroviral syndrome. In theory, the size of the inoculum, the virulence of the infecting HIV strain (including factors such as cellular tropism and cytopathogenicity) and the patient’s immune status could be involved, but evidence as to whether these factors are important is lacking. One case series of transfusion-associated cases found that symptomatic AHI was more frequent among those infected by individuals with late-stage disease [23]. There is little evidence that the frequency or severity of AHI differs between transmission categories or between men and women. Symptomatic AHI can occur with HIV-2 infection and in children, although almost all cases have been reported in adults infected with HIV-1. There are theoretical reasons to believe that coinfection with other viruses, particularly from the herpes group, might enhance the proliferation of HIV, and patients who are simultaneously coinfected with CMV have presented with particularly severe symptoms.

Symptoms typically start 2–4 weeks after infection; in exceptional cases, as early as 5 days, or as late as several months after infection. The median duration of symptoms is difficult to quantify and ranges between 12 and 28 days. Moderate and subjective symptoms, such as fatigue, may persist for months, although almost all patients eventually enter an asymptomatic phase lasting years [22,24–30]. None of the features of the acute retroviral syndrome is specific for HIV infection and symptom-based algorithms are generally not helpful in detecting AHI. However, epidemiological risk factors are important [31,32] and assessment should include all activities that potentially involve HIV exposure. Both clinical and epidemiological information are key components of effective suspicion of AHI and this information will be crucial for the laboratory in order to perform the appropriate HIV screening assays.

**Fiebig stages: laboratory events during AHI**

Using stored plasma samples from seroconverting donors with clade B infections, Fiebig et al. described six stages of acute viremia and early HIV seroconversion (Figure 1) [21]. The time between infection and the first detection of HIV RNA in the plasma is referred to as the eclipse phase. Because HIV RNA is the earliest virological marker of AHI, the sensitivity of nucleic acid amplification tests (NATs) is critical and the limit of detection of these assays has decreased recently to 20–40 HIV RNA copies/ml. Plasma virus levels increase exponentially and peak approximately 3–4 weeks after infection. Immune complexes of antibodies with HIV proteins, such as envelope glycoprotein (gp41), precede the appearance of free antibodies to gp41 [33] and, subsequently, plasma HIV RNA plasma levels decrease. Conversion to a clearly positive Western blot or immunoblot occurs approximately 1 month after infection. Fiebig categorized patients with AHI into stages according to the sequential gain in positive HIV diagnostic assays: HIV RNA measured by NAT; p24 viral antigen measured by enzyme immunoassay (EIA); HIV-specific antibody detected by EIA; and Western blot or immunoblot.

Limitations of the Fiebig staging system are related to the variability of early replication kinetics and the host immune response among individuals. However, despite different routes of HIV acquisition and different virus–host interactions [34], the sequence of appearance of viral markers is uniform [35], and the timing of the Fiebig stages is similar from patient to patient. Variability is observed in the interval between infection and the first appearance of HIV RNA (start of Fiebig stage 1); well-documented cases from the 1990s show that this interval can exceed 100 days in exceptional cases [36].
Laboratory tools for diagnosis of AHI

First-, second- & third-generation EIA

The first-generation EIA, developed in 1985 for the diagnosis of HIV infections, relied on the detection of antibodies to HIV viral proteins obtained from lysates of viral cultures. The second-generation assays used HIV recombinant antigens instead of viral lysate and also incorporated a recombinant antigen for HIV-2. As recently as 2006, most of the US public health laboratories used first- or second-generation assays to detect only IgG to HIV. The average window period (time between acquisition of infection and detectability in blood) was 30–60 days after infection [21,37]. The introduction of the third-generation EIA, which allowed the detection of both IgG and IgM antibodies, reduced the average window period to 20 to 25 days after infection [38,39].

Fourth-generation EIA

Combination p24 antigen–antibody HIV tests, called fourth-generation EIA, have been widely used as screening tests in Europe and Australia since 1997, but were only approved in 2010 by the US FDA. Because the p24 antigen, a major core HIV protein, can be detected earlier than HIV antibody, fourth-generation assays can identify infection sooner than third-generation EIA and reduce the window period for the detection of AHI by 4 days on average (range: 2 days to 2 weeks) [40–43].

Nonetheless, fourth-generation assays miss some AHI cases revealed by NATs. According to the clinical setting, 62–94% of the NAT-positive, third-generation EIA-negative AHI cases were detected by the fourth-generation EIA [44–46]. Most of the missed samples show low HIV RNA levels (<15–30,000 copies/ml) [45–49]. Thus, sensitivity of the p24 antigen detection is critical in these fourth-generation assays. Sensitivity varied from 20 to 160 pg/ml [43]. A recent prospective study compared fourth-generation EIA to third-generation EIA in combination with pooled NAT and reported that fourth-generation EIA detected all HIV infection (sensitivity 100%) with a specificity of 99.9% [50]. Notably, the median turnaround time from sample collection to fourth-generation EIA result was 26 h, compared with a median time of 12 days for pooled NAT results [46,51].

NATs

Since HIV screening assays including p24 antigen detection were not available until very recently in the USA, strategies including NAT were applied in several institutions to reduce the diagnostic window period. All HIV antibody-negative specimens were tested for HIV RNA using pooled NAT (NAT performed on a pool of 10–500 individual samples) and resolution algorithms.

These approaches have shown an increase of 0.1–23% of AHI detected depending on the population tested and the generation of the screening tests [46,52–61]. Figure 2 summarizes results of these studies by reporting the minimal and maximal increase in yield of newly diagnosed HIV using NAT. As expected, the added benefit of AHI detection using NAT strategies was lower when fourth-generation EIA was used. NATs face the constraints of technical complexity, and the cost and delay from blood sampling to results. In this context, a large study conducted by the CDC based on data from sexually transmitted disease (STD) clinics reports that only 23% of those identified with AHI received their NAT results within 7 days, with one-third having to wait more than 2 weeks [46]. In a recent study including participants at high risk, individual NATs increased the overall yield of newly diagnosed HIV cases by 23% compared with a third-generation rapid antibody test. Interestingly, among the 15 patients with AHI, five patients had low HIV RNA levels (<1300 copies/ml) that might not have been detected by pooled NAT [59].

Rapid screening tests

In 2002, the FDA approved rapid HIV antibody tests with sensitivities and specificities similar to those of conventional first- or second-generation EIAs [62]. Rapid HIV testing can increase the effectiveness of testing and prevention programs because they can be performed outside of centralized laboratories in less than 30 min. Reduced delays are essential for emergency interventions, such as postexposure prophylaxis or prevention of mother-to-child HIV transmission. Last but not least, rapid HIV tests ensure that all infected individuals receive their results; using conventional tests, only 62% of those who tested HIV-positive received their results [63,101].

While rapid HIV tests have considerably expanded access to testing, there is a need to consider performance and quality assurance. Decentralized testing requires adapted procedures for
quality assurance and the documentation of results. Adequate training of assay operators is essential for the reliable performance of rapid HIV tests. Since these rapid tests are immunoassays that are read subjectively, they are open to variability in interpretation both by the individual reader and between readers. Interpretation of rapid HIV tests is improved using photographed results.

Recent research revealed some rapid HIV tests to be considerably less sensitive in identifying early infection detectable with EIA or NAT. In the setting of STD clinics, a rapid HIV test on oral fluid and finger-stick whole blood was shown to be positive in only 91% of HIV-infected individuals who were detected by EIA and/or NAT. A South African field study also noted the lack of sensitivity of a rapid HIV test compared with EIA and pooled NAT, with 5% of pregnant women showing false-negative results.

In addition, a low specificity of some rapid HIV tests was reported. One study in the Democratic Republic of Congo yielded 10% of false-positive results using a rapid two-test diagnostic algorithm. In the setting of circumcision trials for HIV prevention (Rakai district, Uganda), the rate of false-positive results was approximately 44% using a rapid three-test algorithm. In the context of antiretroviral treatment, scaling-up with such false-positive HIV results might lead to the initiation of treatment in a substantial number of noninfected persons. Novel rapid fourth-generation assays are being developed to capture more window phase infections. However, there are few published studies on the sensitivity of these assays and performance characterizations in different clinical settings are still in progress.

**Confirmatory tests**

All reactive HIV rapid tests should be confirmed by EIA and/or HIV RNA assays, and Western blot or immunoblot. An additional, separate, second blood sample should be tested for confirmation of HIV infection to exclude misidentification or contamination. In the case of AHI, immunoblot should be performed within 4–6 weeks to document seroconversion. Specific Western blot or immunoblot should be used to distinguish HIV-1 from HIV-2 infections. It should be noted that commercially available HIV RNA assays did not detect HIV-2 RNA and that underquantification of some HIV-1 strains has been described.

Several additional laboratory tests should be performed once AHI is diagnosed, including CD4⁺ T lymphocyte counts, HIV RNA level, screening for other STDs, and hepatitis B and C. Given the reported prevalence of transmitted drug resistance, HIV resistance testing should be strongly considered.

**Laboratory algorithms for diagnosing AHI**

Figure 3 describes a suggested laboratory algorithm for diagnosing AHI. This algorithm focuses on diagnosing AHI in persons with clinical and/or epidemiological risk factors for HIV infection. Indeed NAT or HIV-1 RNA assays are not available everywhere and regulatory barriers impact their use as diagnostic tools in...
some countries. In the USA, HIV viral load assays are not FDA-approved for diagnosis; however, two NAT assays could be used as confirmatory tests. More importantly, technical and cost issues should be addressed. Many laboratory HIV diagnostic algorithms have been proposed, depending on the setting and the availability of HIV diagnostic assays \cite{105,106}. However, most of them are not designed for the detection of AHI. Moreover, cost–effectiveness studies are lacking in particular in the setting of AHI.

The choice of the first screening assay (i.e., fourth-generation) and the implementation of confirmatory HIV tests are important points to consider when designing AHI diagnostic algorithms. Discordant results between screening assays and confirmatory tests should alert any diagnostic laboratories. In particular, in case of discordant results between screening assay and Western blot or immunoblot assay (longer window period than screening assays), individuals need to be further evaluated for AHI. A negative result with third-generation screening assay and positive result with fourth-generation (p24 antigen) assays should also be considered as suspicious of AHI. Clinical and/or epidemiological information is crucial in this context. Modifying procedures in order to extend the so-called ‘gray zone’ of the serological screening assay, beyond the manufacturer’s recommendation, might also increase the rate of AHI detection. Although we recognize that modifying the manufacturer’s recommendations should not be the rule and should be done within specific conditions, it is the duty of any laboratory to implement appropriate procedures for specific clinical situations when this can improve the performance. In any case, follow-up samples within 3–5 days usually provide an unambiguous answer.

Since false-positive HIV-1 RNA has been reported \cite{84–86}, HIV-1 RNA below 1000–5000 copies/ml should be rechecked rapidly on a new sample as it is often attributed to cross-contamination problems. Clinical cases from our routine practice are described in Boxes 1–3.

**Prevalence of AHI: targeted HIV testing**

Prevalence of AHI is difficult to evaluate and few field studies have been published. A US study based on a national probability sample of adult (aged 15–49 years) patients presenting to a physician, emergency department and hospital outpatient clinic, estimated...

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**Box 1. Case 1.**

The laboratory receives a sample from a 31-year-old man who had sex with another man and complains of fever and pharyngitis. Both third- and fourth-generation EIAs are performed. The fourth-generation screening test is negative (index 0.4; index >1.0 defined as positive) and the third-generation screening test is indeterminate (index 0.6; index 0.6–1.0 defined as indeterminate). Since clinical information was suggestive of AHI, HIV RNA assay was performed and returns positive at 32,000 HIV RNA copies/ml. Four days later, both third-generation (index 6.1) and fourth-generation (index 1.4) EIAs are positive, but with a weak value for the latter assay. Interestingly, HIV RNA remains low (46,000 copies/ml) and p24 antigen is undetectable by EIA on both samples. The virus has multiple mutations associated with drug resistance, including some known to impact on the replicative capacity.

**Take-home message**

- EIA fourth-generation can be negative in the presence of low HIV RNA levels (sensitivity of p24 antigen detection).
- Definition of the gray zone for EIA assays beyond the manufacturer’s recommendation is useful.
- Follow-up testing is required in individuals with a high suspicion of AHI.
- Clinical information is essential for the laboratory in order to perform the correct diagnostic assays.

AHI: Acute HIV infection; EIA: Enzyme immunoassay.
rates of AHI to be 0.13% in patients presenting with pharyngitis and 0.66% among patients with rash [87]. Other studies indicate that approximately 1% of clinic patients with nonspecific viral syndromes or for whom mononucleosis testing were ordered had AHI [88,89]. In a cross-sectional study conducted in Uganda, AHI was found to be highly prevalent with 1% of symptomatic patients initially suspected of malaria found to have HIV RNA and a serology consistent with AHI [90]. AHI screening programs with pooled NAT found that AHI generally represents only a small proportion (0.02–0.3%) of those with negative antibody tests.

**Box 2. Case 2.**

A physician presents to an ER and requests an HIV test because she thinks that she might have AHI following sexual contact with a man from sub-Saharan Africa 2 weeks earlier. A rapid third-generation test is performed at the ER and is negative. The laboratory receives the sample to perform EIA tests; the third-generation test returns negative (index 0.3), whereas the fourth-generation test is positive (index 5.4). To confirm AHI, HIV RNA assay is performed and a very high viral load is measured (1,300,000 HIV RNA copies/ml). At this time, the laboratory contacts the clinician in charge of the patient to report presumption of AHI and asks for a confirmatory sample. On the confirmatory sample, received 3 days later, EIA third-generation is still negative (index 0.4), fourth-generation has increased slightly (index 7.3), whereas HIV RNA peaks at 6,800,000 copies/ml. In retrospective analyses, these two samples were negative using a rapid fourth-generation test.

**Take-home message**

- EIA fourth-generation is more sensitive than third-generation for AHI detection.
- EIA format is more sensitive than rapid-format for AHI detection.
- In case of doubt about the diagnosis, HIV RNA measurement usually provides an unambiguous answer.
Recent advances. Highly sensitive fourth-generation assays are cheaper and easier to implement. Since the decrease in sampling to results would be required to achieve a reasonable positive predictive value. In most screening programs. HIV assays with very high specificity in high-risk populations, the prevalence of AHI is likely to be low but constitutes a substantial proportion of new HIV diagnoses, especially in high-risk individuals [46,52–61]. A study of pooled NAT following third-generation EIA testing established that this strategy will be cost effective only in the setting of high HIV incidence [91]. The cost–effectiveness of individual NATs was also recently suggested in high-risk individuals with influenza-like illness [92]. However, the cost–effectiveness of these strategies depends not only on the incidence of HIV infection, but also on the performances of both NAT and HIV screening tests. Using fourth-generation assays for the detection of AHI may further reduce the cost–effectiveness of NAT. Even with targeting of high-risk populations, the prevalence of AHI is likely to be low in most screening programs. HIV assays with very high specificity will be required to achieve a reasonable positive predictive value.

Expert commentary & five-year view

As individuals with AHI pose a greater transmission risk than most chronically HIV-infected patients, prevention efforts targeting these individuals is an important strategy to reduce the spread of HIV infection. However, even 30 years after the start of the HIV epidemic, laboratory tools remain imperfect and only few persons with AHI are identified.

Integrating pooled NAT into HIV testing programs has proven to be feasible, but adds complexity and increases the delay from sampling to results [46,51,53]. Highly sensitive fourth-generation assays are cheaper and easier to implement. Since the decrease in the window period between NAT and EIAs is only approximately 3 days, these assays offer an alternative for the diagnosis of AHI. However, a comparative analysis of pooled and individual NATs, as well as fourth-generation HIV assays, in different clinical settings are needed to better evaluate the cost–effectiveness of each strategy.

To meet the diagnostic needs in resource-limited settings, new point-of-care NAT and antigen assays must be developed. Point-of-care assays would improve the efficiency and the cost in many parts of the world. Although no rapid, point-of-care tests to detect HIV RNA or viral antigens are available today, several new technologies are currently being explored [94–96]. Recent advances in nanotechnologies and microfluidics offer new strategies to develop low-cost, rapid, robust and simple assays that will greatly improve HIV diagnosis within the next 5 years [97].

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Acknowledgements

The authors thank Laurent Kaiser and Rosemary Sudan for their help in the preparation of the manuscript.

Key issues

- Both clinical and epidemiological information are key components feeding suspicion of acute HIV infection (AHI) and this information will be crucial for the laboratory in order to perform the appropriate HIV screening assays.
- Fourth-generation enzyme immunoassay should be selected for the diagnosis of AHI.
- In patients with signs and symptoms or recent risk exposure, individual HIV RNA assay should be performed.
- HIV infection should be confirmed with repeat EIA and specific Western blot or immunoblot tests to document seroconversion within 4–6 weeks.
- Following diagnosis of AHI, CD4 lymphocyte counts, HIV RNA and genotypic resistance should be checked.
- A comparative analysis of pooled and individual nucleic acid amplification tests, as well as fourth-generation HIV assays, in different clinical settings are needed to better evaluate the cost–effectiveness of each strategy.
- New point-of-care nucleic acid amplification tests and antigen assays must be developed to meet the diagnostic needs of resource-limited settings.
- Further research will investigate the use of nanotechnologies and microfluidics to develop low-cost, rapid, robust and simple assays to improve HIV diagnosis.

Box 3. Case 3.

During a neurosurgical procedure, an anesthesiologist sustained percutaneous exposure to blood (hollow-bore needle) of a 57-year-old man hospitalized for 6 months. A rapid fourth-generation test was performed on the patient and was positive. Postexposure prophylaxis was immediately started. The laboratory receives the sample the same day. EIA third-generation is negative (index 0.5) and fourth-generation is weakly positive (index 1.4). To exclude AHI (no risk factor for HIV infection), HIV RNA testing is performed and returns undetectable (<20 copies/ml). Immunoblot is reported as undetermined with only one reactive band for p24 antibody. Previous and follow-up samples of this patient show persistence of this nonspecific reaction on the EIA fourth-generation for 2 weeks. No known interference substances were found that could explain these results.

Take-home message

- Specificity of EIA and rapid-format fourth-generation tests could be an issue.
- Confirmation of HIV-positive results by immunoblot is needed.

EIA: Enzyme immunoassay.
This study involving 1763 serodiscordant couples of considerable interest


This study involving 1763 serodiscordant couples shows a relative reduction of 96% in the number of linked HIV transmissions resulting from the early initiation of antiretroviral therapy, as compared to delayed therapy.


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