A simple algorithm for selecting cases to investigate acute and early HIV infections in low- and middle-income countries

ELAINE MONTEIRO MATSUDA (✉ elainemmatsuda@gmail.com)

Santo André <https://orcid.org/0000-0002-0254-4154>

Cintia Mayumi Ahagon

Adolfo Lutz Institute: Instituto Adolfo Lutz

Luana Portes Ozório Coelho

Adolfo Lutz Institute: Instituto Adolfo Lutz

Ivana Barros Campos

Adolfo Lutz Institute: Instituto Adolfo Lutz

Daniela Rodrigues Colpas

Adolfo Lutz Institute: Instituto Adolfo Lutz

Norberto Camilo Campos

Adolfo Lutz Institute: Instituto Adolfo Lutz

Giselle Ibetê Silva López-Lopes

Adolfo Lutz Institute: Instituto Adolfo Lutz

Valeria Oliveira Silva

Adolfo Lutz Institute: Instituto Adolfo Lutz

Isabela Penteriche de Oliveira

UNESP: Universidade Estadual Paulista Julio de Mesquita Filho

Luis Fernando de Macedo Brígido

Instituto Adolfo Lutz

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Abstract

We documented the outcome of an over 10-year effort to diagnose acute and early HIV infections (AEHI) in an Infectious Diseases Outpatient Clinic with limited resources. Of a total of 132 cases, 119 HIV-RNA tests were performed from 2017–2020, 12 cases were identified, using a simple algorithm: risk exposure of six weeks or less before the visit and/or symptoms compatible with acute retroviral syndrome 7–30 days after exposure and/or undetermined 3rd generation rapid diagnostic test or serology. AEHI diagnoses varied from 2.4% among asymptomatic to 25% for undetermined serology cases using a simple screening applicable to different settings.

Brief Reports

The concept that individuals with viremia lower than 200 copies/mL do not transmit has led to support the strategy of universal treatment of the human immunodeficiency virus (HIV) for prevention of transmission (*TasP*– treatment as prevention) [1,2,3]. Increasing the diagnosis of infected individuals is the initial step to epidemic control, the first 90 of the bold UNAIDS goal “90-90-90.” This strategy, based on modeled scenarios, predicts that by diagnosing 90%, treating 90%, and suppressing 90% of persons living with HIV, a reduction in the annual number of new HIV infections by more than 75% could be achieved. This would decrease new infections to 500,000 in 2020 and 200,000 in 2030, eventually ending the epidemic [4]. We reached 2021 with many improvements, but far from this goal, with an estimated 1.7 million new infections occurring annually [5]. The implementation of strategies to diagnose acute and early HIV infections (AEHI) may significantly reduce the time between the diagnosis of HIV and viral suppression [6]. Targeting this population might be especially relevant as different studies suggest that 10% to 50% of HIV transmission events occur during AEHI [7,8-10]. This is a period in which antibodies are undetectable (acute infection) or inconclusive (early infection) [11], representing cases that may be missed by current serology tools. The detection of viremia after the first week, and of the p24 antigen after the second week, may improve diagnosis in this phase of greater transmissibility [12]. Ideally, all people at risk of HIV acquisition should be tested for AEHI with a molecular test, as viral load [13], but this is not feasible in resource-limited settings due to logistical issues and the high costs of molecular testing [11]. Tests to diagnose AEHI are not routine in Brazil and elsewhere, and the use of the 3rd generation rapid test (RDT3) in the routine of Brazilian public services makes diagnosis even more difficult.

Our study was conducted in an Infectious Diseases Outpatient Clinic in Santo André, in the greater São Paulo, Brazil that offers HIV tests and treatment. Individuals’ non-reactive or undetermined/inconclusive serology/RDT3 with a risk exposure of six or fewer weeks before the visit and/or that reported symptoms compatible with the acute retroviral syndrome from 7 to 30 days after exposure were selected for quantitative HIV-RNA test (Real-Time HIV, Abbott, USA). One individual (case 6) performed a qualitative HIV-RNA test. When available, the 4th generation rapid diagnostic test (RDT4) (Alere HIV Combo, Abbott) was performed concurrently with the HIV-RNA test for comparison. A few asymptomatic individuals considered at higher risk were also tested. Children under 18 months of age tested for HIV-RNA for diagnosis of vertical infection were not included.

HIV-RNA tests were performed in 132 cases for possible AEHI between September 2011 and March 2021, more systematically during 2017-2020 (119 cases). Most cases were males (73.5% 97/132), 64% (62/97) men who have sex with men (MSM). As for gender, 90.3% 112/124 cisgender and 9.7% 12/124 transwomen; 9% of cases with a known HIV seropositive partner. Table 1 shows HIV-RNA, RDT4 and AEHI diagnosed each year. A total of 4/16 cases (25%) of individuals with indeterminate/discordant serology/RDT3 had confirmed AEHI, 3/4 symptomatic and 1/4 asymptomatic. Table 2 considers different denominators to calculate detection rates to diagnose acute and early HIV infections. The yield varied from 2.4% among all asymptomatic individuals to 25% for cases with inconclusive serology or RDT3. HIV-RNA test diagnosed 11/12 cases of AEHI. There were suspicious symptoms of acute retroviral syndrome (ARS) in 91 cases, 11 of them diagnosed as AEHI. Among 41 asymptomatic cases, 3 had indeterminate serology and 5 discordant RDT3.

With increasing access to knowledge about infection and recommendations for immediate treatment, the closer health systems are to these goals, the more acute/early undiagnosed individuals will proportionally contribute to a larger share of newer infections. Several studies assessed the ability of algorithms to screen which subpopulations should be subjected to molecular testing for AEHI, especially among men who have sex with men [14,15]. In a systematic review and meta-analysis, the overall pooled AEHI yield was 6.3% (95% CI, 2.1 to 12.4; five studies); but varying among the different targeting strategies used, from 11.1% (95% CI, 5.9 to 17.6; three studies) to 1.6% (95% CI, 0.8 to 2.4; two studies) in universal testing strategies [11]. In the first years of our study, the use of HIV-RNA tests for diagnostic purposes was rare and not systematically recorded. From 2017 to 2020, in which the search for suspected cases of AEHI was incorporated more consistently the yield was 6.2% among those screened by the algorithm. To account for this, we calculated the rate considering different denominators. Using different scenarios, it appears that the algorithm proposed was useful for case selection, as all but one, were diagnosed by HIV-RNA tests in the AEHI had suspected symptoms of the acute retroviral syndrome in the last 30 days of collection. This one exception (case 12) was screened due to a discordant RDT3. This young woman was the only AEHI identified among 41 asymptomatic individuals, an elite controller (undetected viral load, that could have been dispensed as not infected with HIV RDT4 had not been performed). After one month her plasma was reactive to 4th generation serology (Chemiluminescence, architect®, Abbott) and Western blot indeterminate.

Important to note that a way to improve the sensitivity of these RDT is the potential benefit of performing the test in plasma. Although blood collection and processing may not be feasible in some places, testing plasma may improve detection. One example of this was a negative RDT3 and RDT4 at fingerstick, that was however RDT4 positive in plasma sample collected for HIV-RNA, that showed a viral load of 3,430,777 copies/mL (case 10). This case illustrates what has been suggested in antibody detection to various agents [16], that plasma or serum from processed blood may be more sensitive than whole-blood from fingerstick testing. If we take this into account, RDT4 diagnosed all four cases of AEHI that RDT4 was applied, including the asymptomatic elite controller case.

Another interesting finding was that all the reactive cases in RDT4 showed the line of reactive antibodies and only one with antigen and antibodies line (case 8). Therefore, it was expected that they would be diagnosed with RDT3 if the differential of RDT4 was only the addition of antigen line, implying that the sensitivity for detecting RDT4 antibodies is higher than that of RDT3. Despite the limited number of cases, our study suggests that the plasma RDT4 technology could be a reasonable alternative to HIV-RNA test, at a much lower cost, point of care (POC), with easy execution and immediate diagnosis, allowing linking to a specific treatment on the same day, as an important strategy to reduce the high viremias of highly infectious variants of acute/early infection. The better sensitivity of RDT4 could be even more important alternative to RDT3, in candidates for HIV pre-exposure prophylaxis (PrEP), as many, by definition, could be at a RDT3 immunological window from a recent risk event. Improving AEHI identification with simple screening based on symptom/timing of risk assessment and the use of at least an RDT4 test seems a reasonable task for HIV testing sites, but still many cases would not be reached. The increasing use of POC viral load tests may further favor the ability of HIV testing centers to improve AEIH diagnosis, but cost is still a limiting factor.

Other environments that may receive individuals unaware of being at early HIV infection, as emergency units, or even settings outside regular health care system, should be stimulated to use strategies to reach out for AEHI patients, either referring to evaluation or conducting some level of laboratory testing. Return for reevaluation in some days of suspect cases might be warranted. In conclusion, our 10-year experience suggests the feasibility of strategies to target potential acute/early HIV infections. With the growing identification and incorporation of chronic infections with improvement in policies to treat all persons living with HIV, the acute/early cases will increasingly represent a larger pool that, if properly identified, treated, and suppressed, may favor the control of AIDS pandemic, not restricted to health care units.

Declarations

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study, commented on previous versions of the manuscript read, and approved the final manuscript. Conception and design, patient recruitment, data collection were performed and the manuscript was written by Elaine Monteiro Matsuda. 4th Generation rapid diagnostic

tests and laboratory data collection were performed by Cintia Mayumi Ahagon, Luana Portes Ozório Coelho, Valeria Oliveira Silva and Isabela Penteriche de Oliveira. HIV-RNA tests and laboratory data collection were performed by Ivana Barros de Campos, Daniela Rodrigues Colpas, Norberto Camilo Campos and Giselle Ibeta Silva López-Lopes. Conception and manuscript review were performed by Luís Fernando de Macedo Brígido.

CONSENT TO PARTICIPATE AND FOR PUBLICATION

All authors consent to participate and consent for publication.

ETHICAL COMMITTEE

The study was approved by the institutional ethical committee (CAAE: 69927317.8.0000.00590) and all participants provided informed consent for dual testing and use of anonymized data for research purposes.

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Tables

Table 1 – HIV-RNA and 4th generation rapid diagnostic tests and acute and early HIV infections diagnosed each year.

Quantity of tests performed				AEHI cases diagnosed			
Year of collection	HIV-RNA test	RD4 and RNA test	HIV-	Acute Infection	RD4	RD3	HIV-RNA test (copies/mL)
2011	1	0		Case 01	-	I	2,000,000
2012	1	0		Case 02	-	NR RD3	>Lim of detection ⁵
2013	3	0		Case 03	-	NR RD3	>Lim of detection ⁵
2014	1	0		Case 04	-	NR RD3	>Lim of detection ⁶
2015	11	0		Case 05	-	NR RD3	5,646,257
2016	1	0		Case 06	-	D RD3 ³	HIV detected by qualitative PCR
2017	22	0		Case 07	-	NR RD3	>Lim of detection ⁶
2018	29	0		-	-	-	-
2019	30	23		Case 08	R AG/AB ¹	NR RD3	2,209,736
				Case 09	R AB ¹	NR RD3	>Lim of

						detection ⁶
			Case 10	NR ¹	NR RDT3	3,430,777
2020	31	3	Case 11	-	D RDT3 ⁴	3,841,870
			Case 12	R AB ²	D RDT3 ⁴	Not detected ⁷
2021	2	2	-	-	-	-

AEHI, acute and early HIV infections; RDT4, 4th Generation rapid diagnostic test; RDT3, 3rd Generation rapid diagnostic test; AG, antigen; AB, antibody; Lim, Limit; NR, Non-reactive; R, Reactive; D, Discordant; I, Inconclusive serology

¹, fingerstick; ², plasma; ³, Abon® reactive and Bioeasy® non-reactive; ⁴, Abon® reactive and Biomanguinhos® non-reactive; ⁵, Lim of detection of 750,000 copies/mL; ⁶, Lim of detection of 10,000,000 copies/mL; ⁷, Lim of detection of 40 copies/mL

Table 2 - Detection rates of acute and early HIV infections (AEHI) with HIV-RNA tests performed considering different denominators

	2011-2021		2017-2021	
	AEHI / HIV-RNA tests	AEHI detection rate (%)	AEHI / HIV-RNA tests	AEHI detection rate (%)
With suspicious symptoms of ARS	11/91	12	5/81	6.2
Without suspicious symptoms of ARS	01/41	2.4	1/31	3.3
All collected	12/132	9.1	06/112	5.4

AEHI, acute and early HIV infections; ARS, acute retroviral syndrome.