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Performance of rapid tests compared to conventional tests used for HIV diagnosis

Desempenho dos testes rápidos em relação aos testes convencionais utilizados no diagnóstico de HIV

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ABSTRACT

Introduction: Early diagnosis is an important tool for strategies to fight human immunodeficiency virus (HIV) infection. **Objective:** The main objective of this study is to evaluate the comparability of the results of rapid tests (RT) used for the HIV diagnosis in relation to conventional molecular and serological tests in blood samples from a population of men who have sex with men (MSM), from 12 Brazilian capitals. **Material and methods:** 591 HIV-1 reactive test samples from 4176 MSM participants were submitted to Instituto Adolfo Lutz (IAL) for evaluation by conventional laboratory tests. From these samples with at least one RT reagent, 522 samples were analyzed, and in 493 (94.4%) the HIV positivity was confirmed, with 33% HIV-1 viral load above 5,000 copies/mL and 67% by the serological tests. A total of 336 (10%) samples with a non-reactive RT result were evaluated by standard serology, four (1.2%) tested positive for HIV. **Results and conclusion:** The results showed a high percentage of samples with confirmed HIV positivity in the conventional laboratory tests, as well as some non-reactive results that were confirmed positive, indicating some limitations of the RT single-step method. Therefore, the serological tests had a fundamental role in clarifying the diagnosis.

Key words: anti-HIV antibodies; immunoassay; viral load; serology; male homosexuality; Brazil.

INTRODUCTION

The human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (Aids) epidemic continues to be a major public health problem, despite recent advances in different countries, especially in relation to prevention and treatment strategies. In Brazil, the prevalence of HIV infection is estimated between 0.4% and 0.5% in the adult population; the epidemic is predominantly sexually transmitted and is concentrated in vulnerable populations at high risk of exposure to HIV (key populations), including injecting drug users (IDU), sex workers, and especially men who have sex with men (MSM)[1].

Since the description of the first Aids cases in the early 1980s, HIV has disproportionately affected the MSM population. The risk of infection remains high; a proportionately higher increase in HIV infection among MSM has been observed in the last decade, particularly in industrialized countries[2, 3]. The high prevalence of HIV in MSM has also been reported in the Caribbean, Africa, Asia and Latin America[2, 4, 5].

Brazil, as other countries, has been facing increasing HIV incidence in the MSM population in recent years, with worrying rates of late diagnosis[6, 7]. This population presents one of the highest HIV prevalence rates – 18.4%, with estimates varying from 5.8% to 24.8% in different regions of Brazil[8] – with a rate 18 times higher than that of heterosexuals and 22 times higher than that observed in the general population[9]. According to data from the Brazilian Ministry of Health (MoH), there is an increasing trend in the proportion of Aids cases in MSM, which increased from 35.3% in 2006 to 45.4% in 2015[6].

Regardless the different approaches currently being carried out in relation to the cascade of HIV/Aids care, there is a consensus that diagnostic testing is the first step, and registration

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allows assessments of patient adherence and retention to health services and missed opportunities in treatment and prevention strategies[10-12].

The importance of periodic testing for HIV, as a prevention strategy in the programmatic response to the HIV/Aids epidemic has been highlighted globally, especially in disproportionately affected segments in concentrated epidemics situations, particularly in MSM[7]. In addition, screening for HIV in primary health care has shown to be cost-effective, with undoubted benefits for both clinical and public health[13,14]. Specifically for the MSM population, literature data suggest that early diagnosis is the main tool for the appropriate cascade of care to infected individuals, and the prevention of new transmission correlated over time and space[15].

According to the study by Delaney *et al*. (2011)[16], the results of six different rapid tests (RT) when compared to conventional assays, exhibit high sensitivity and specificity. For some samples of patients receiving antiretroviral therapy (ART), some RT presented lower sensitivity, but the difference was not statistically significant. Similarly, the study by Manak *et al*. (2015)[17] demonstrated high agreement of the results of the rapid test for HIV with those established in laboratories; and stressed that the knowledge on the principle and the antigens/antibodies used in a test is extremely important for the development of highly sensitive, specific and effective test strategies. It is known that the quality of the results can be influenced by different factors, such as systematic and random errors intrinsic to the assays, or biological factors of the host and the agent, such as viral diversity and ART[18-20].

In this context, HIV testing algorithms, based on the detection of specific antibodies or the detection of virological markers, should be constantly evaluated for their performance. Therefore, this study aims to evaluate the comparability of the point of care test used in the diagnosis of HIV infection in relation to conventional molecular and serological tests in samples of a biological and behavioral survey among MSM in 12 Brazilian cities.

MATERIAL AND METHODS

The serum samples analyzed were from the "Nationwide study of behaviors, attitudes, practices and prevalence of HIV, syphilis and hepatitis B and C among men who have sex with men"[8]. The population was composed of men who reported having had at least one sexual relationship (anal or oral) with another man in the last 12 months and were 18 years or older. They did not identify themselves as transgender or transsxual, accepted to participate by signing the Free and Informed Consent Form (IC). They live, work or studied in the following survey participating cities: Manaus and Belém (Northern region); Fortaleza, Recife and Salvador (Northeast region); Brasília and Campo Grande (Central-West region); Belo Horizonte, Rio de Janeiro, Campo Grande and São Paulo (Southeast region); Curitiba and Porto Alegre (South region). Participants were recruited using the Respondent Driven Sampling (RDS).

RDS is a recruitment process based on chain-referral sampling method, known as snowball sampling[21-25]. RDS was chosen as the most appropriate method among the available alternatives of sampling of hard-to-reach people, as long as it could include the large hidden social networks of MSM and to allow comparability with the previous survey[26, 27]. A formative survey was conducted in almost 200 MSM, between December 2015 and March 2016, aiming at exploring sex and gender identities, changes in HIV-related behaviors in the community, the organization of these communities, logistical and ethical issues, as well as location of the study office, level of encouragement, willingness of the community to participate and performing the available laboratory tests, possible bottlenecks and other operational issues. The study began with five to six seeds chosen by the researchers in each capital. Each seed received three coupons to recruit other participants for the study. These participants, in turn, received three more coupons with the same purpose, repeating the process until the desired sample size was reached. Each participant received a primary incentive of BRL 25 (~ US$ 7) and a secondary incentive of BRL 25 for each recruited participant who completed the research. The coupons and identification numbers in the study were monitored with an online coupon generator that was part of software specially developed for data entry. The social network of each participant was the result of a cascading question summarized as follows: "How many men do you know, who also know you, who have had sexual intercourse with men (oral ou anal) in the last 12 months, who live, study or work in (study city), how many would you invite to participate in this study? From these (repeat number provided by participant) how many would you invite to participate in this study?" The study used the Audio Computer Assisted Self-Interview (ACASI) system on a tablet. All data were encrypted and sent to a password protected project database.

From the 4,176 volunteers in the study, 3,958 (94.8%) authorized blood collection for RT for HIV diagnosis.

Blood samples were obtained by venous puncture of individuals who, after the interview and by signing the IC, accepted to perform blood tests for HIV diagnosis. The procedures were carried out in accordance with the law in force in Brazil[28].

Serological screening for HIV was performed using an initial immunochromatographic assay – RT1, of high sensitivity and

specificity for the detection of anti-HIV 1+2 antibodies [HIV Test Bioeasy (Standard Diagnostic, Inc, Yongin-Si, Korea)]; the samples with reagent results were subjected to a second immunochromatographic assay other than the first one – RT2 [ABON (Abon Biopharm, Hangzhou, China)]. The RT used was acquired by the Ministry of Health (Brazil) and carried out at the sites of this study. All the applicators were trained to perform the tests, which were performed in conditions considered satisfactory and according to the standardized protocol of the test sites established in the research.

The casuistry of this study was composed of two subsets of the samples; 591 blood samples with at least one reagent result in RT for HIV [RT1 positive (+) and RT2 negative (-) or RT1 and RT2 (+)],who were referred to the Instituto Adolfo Lutz (IAL) for performing additional conventional tests to diagnose this infection. In addition, with the purpose of performing analytical verification tests, 10% (336/3.367) of the samples with non-reactive HIV result sent to the IAL were evaluated for the purpose of storage and performing other laboratory tests. These were randomly selected in a ratio similar in the 12 test sites, prioritizing the syphilis reagent samples, when available and with adequate volume for the trials.

Conventional tests for HIV diagnosis were performed with reagents available from the IAL at the time of this study, as follows.

Viral load (VL) and HIV serology

From the 591 samples with reagent results in RT1, 569 samples were reactive in both tests [RT1 (+) and RT2 (+)] and 22 presented discordant results [RT1 (+) and RT2 (-)].These were initially processed for molecular testing (Abbott HIV RT-PCR). The ribonucleic acid (RNA) of the samples was extracted in the Abbott Real time M2000sp automated device and analyzed using the real-time polymerase chain (RT-PCR) (Abbott Real Time M2000rt), following the manufacturer's recommendations, the result was expressed in copies/ml.

Samples with detectable VL, below 5,000 copies/ml and above 40 copies/ml, and undetectable RNA were subsequently analyzed by conventional serology using as initial screening test the chemiluminescent immunoassay (CLIA) [Advia Centaur HIV Ag/Ab Combo (CHIV); Siemens Healthcare Diagnostics, Inc, NY, USA] and the confirmatory rapid immunoblot assay (IBR) [Imunoblot Rápido (IBR) DPP HIV1/2 (IBR DPP HIV); Bio-Manguinhos-Fiocruz, Rio de Janeiro, Brazil]. Samples with indeterminate IBR results were evaluated by Western blot assay (WB) HIV New Lav Blot I (Bio-Rad Laboratories, Marnes-la-Coquette, France).

Evaluation of laboratory results

All samples that showed VL ≥ 5,000 copies/ml or, simultaneously, CLIA and confirmatory (IBR or WB) reagent tests were considered "HIV positive".

The interpretation of the levels of agreement between the results of the RT1 and CLIA tests and Flowchart 1 (two RT)/ Flowchart 6 (CLIA and confirmatory) was performed using the Kappa index (*K*), as proposed by Altman (1999)[29, 30] and adapted from Landis and Koch (1977), according to which, the $K < 0.20$ value represents poor agreement; from 0.21 to 0.40, regular; 0.41 to 0.60, moderate; 0.61 to 0.8, good; and 0.81 to 1, very good. For *K* analysis, besides the samples with reagent results in RT, the non-reagent samples used to verify the analytical performance were considered.

Verification of analytical performance

Non-reactive samples were randomly selected in the RT to be analyzed in the conventional tests in order to verify the agreement with the results observed.

We analyzed 336 HIV RT samples, – non-reagent using the Advia Centaur HIV Ag/Ab Combo kit (CHIV) and, when reagents, submitted to the IBR DPP HIV confirmatory test.

ETHICAL CONSIDERATIONS

The research project was approved by the Research Ethics Committee of the Universidade Federal do Ceará, accredited by the Brazilian National Commission of Ethics in Research [no. 1.024.053 (23 June, 2015)] and CTC-IAL 26-I/2016.

RESULTS

Among the 591 samples sent to the molecular test, 36 (6%) presented insufficient volume, and therefore, 555 (94%) samples were analyzed in HIV-1 VL.

In 569/591 (96.3%) cases with RT1 and RT2 reagents, 252 (44.3%) volunteers reported using ART, seven (1.2%) reported have used in the past, and 310 (54.5%) did not report treatment. It was not possible to determine whether ART was referring to prior use of post-exposure prophylaxis (PEP) or to conventional treatment.

From the 569 reagent samples in the two rapid tests, VL was successfully performed in 537 (94.4%) cases. From these, 212

(39.5%) did not produce the RNA presence signal (undetected RNA), 37 (6.9%) presented signal below the analytical limit of 40 copies/ml, and the others (288) presented quantified viremia, with a median of 7,194 copies/ml (IQR 898-25521), ranging from 42 copies to 1.9 million copies/ml. In 162 (56.3%) samples, the VL was above 5,000 copies/ml, which allowed to define the diagnosis of the infection, according to the current MoH criterion[28].

Regarding the 22 samples with discordant results in the RT, RT1 (+) and RT2 (-), one (4.5%) presented viremia above 5,000 copies/ml; one (4.5%) sample with a signal > 40 copies/ml (215 copies/ml); 16 (72.7%) with no RNA signal detected; and four (18.2%) samples could not be tested because they did not present sufficient material. Resolution of the reactivity of these samples, with no RNA signal detected or below 5,000 copies/ml, was only possible after the subsequent step of conventional serology. Among these, 12 were non-reactive (70.6%), one indeterminate (5.9%) and four HIV reagents (23.5%).

Table 1 shows the VL results obtained from the 555 samples (537 with two reagent RT and 18 with discordant RT) and the responses of the 537 volunteers with the rates of viral RNA detection facing the response obtained from the participant through the applied questionnaire containing a question about the use of ART.

The data summarized in **Table 2** suggest an inversely significant ($p < 0.001$ Yates correct, two tailed) relationship between VL detection and ART.

The 392/555 (70.6%) samples that showed VL quantification results < 5,000 copies/ml, including those with undetected RNA, were analyzed by standard serology assays. **Table 3** shows the results profile of the conventional serology for HIV of the 392 reactive samples in RT1. From these, 33/392 (8.4%) samples did not present sufficient material for the performance of the anti-HIV laboratory tests.

According to the data in Table 3, 375 (95.7%) samples showed reactive results in the two HIV RTs (RT1 and RT2). From the nine cases undetermined by the IBR, when analyzed by WB, six (66.7%) were positive, one negative (11.1%) and two (22.2%) remained indeterminate. Regarding the CLIA result close to the cut-off (3.21/1) and non-reactive IBR, the sample was considered indeterminate.

According to the criteria established for the interpretation of the *K* index, the degree of agreement for RT1/CLIA was considered very good ($K = 0.91$), in which the agreement rate of approximately 96% was observed. Likewise, the degree of agreement for the diagnosis of HIV by Flowchart 1 (two RT)/Flowchart 6 (CLIA and confirmatory) was also considered very good ($K = 0.90$) and with a concordance correlation of approximately 95%.

TABLE 1 – HIV RT results and its relationship to HIV-1 VL detection

VL	UD	< 40 copies/ml	42-1.9 million	copies/ml	Total
TR1 (+)/TR2 (+)	212	37	> 5,000 162	< 5,000 126	537
TR1 (+)/TR2 (-)	16	0	1	1	18

HIV: human immunodeficiency virus; RT: rapid test; VL: viral load; (+): reagent; (-): non-reactive; UD: undetectable.

TABLE 2 – Relationship between ART use and viral RNA detection rate

	Treatment and VL (RT1 and RT2 reagents)		
ART	Viremia not detected	Viremia detected	Total
Yes	159	78	237
No	51	243	294
In the past	2	4	6

ART: antiretroviral therapy; RNA: ribonucleic acid; VL: viral load; RT: rapid test.

TABLE 3 – Profile of the results of the 392 reagent samples in RT1 evaluated in conventional serology

no. of samples ($n = 392$)		RT1	RT2	CLIA	IBR	WB
321	81.8%	(+)	(+)	(+)	(+)	NC
13	3.3%	(+)	(+)	(-)	(-)	NC
11	2.8%	(+)	(-)	(-)	(-)	NC
1	0.3%	(+)	(-)	(-)	NC	NC
3	0.7%	(+)	(-)	(+)	(+)	NC
5	1.3%	(+)	(+)	(+)	I	(+)
2	0.5%	(+)	(+)	(+)	I	I
1	0.3%	(+)	(+)	(-)	I	(-)
1	0.3%	(+)	(-)	(+)*	(-)	NC
1	0.3%	(+)	(-)	(+)	I	(+)
33	8.4%	(+)	(+)	IM	IM	IM
Total (+)		392	375	333	324	6

*RT: rapid test; CLIA: chemiluminescence immunoassay; IBR: rapid immunoblot assay; WB: Western blot assay; (+): reagent; (-): non-reactive; NC: not conducted; I: indeterminate; *value close to the cut-off; IM: insufficient material.*

Table 4 shows the laboratory results profile for HIV of the 522 samples by VL and serological tests.

From the 522 samples with sufficient volume for analysis, 94.4% (493) samples confirmed positive in the laboratory tests for VL HIV-1 or by serology (CLIA + IBR/WB), 5% (26) and 0.6% (three) presented, respectively, non-reactive and indeterminate results in the HIV serology test flowchart.

For the quality control samples, the 336 non-reactive samples for HIV in RT (RT1) obtained the following results in conventional serology (Flowchart 6): 332 (98.8%) non-reagents in the CLIA and four (1.2%) reagents. All (4/4) samples confirmed IBR positivity (confirmatory).

From the 591 samples referred to the IAL, the laboratory tests (VL and serology) were not performed in 11.7% (69) because of

the insufficient blood volume, which prevent the conclusion of the laboratory diagnosis of HIV and to compare the results in relation to the RT results.

TABLE 4 – Profile of HIV laboratory results performed at the IAL by HIV-1 viral load tests and serological tests

Location	Examinations performed at IAL				
	VL > 5,000 copies/ml	HIV serological results			HIV-positive
		Positive	Undetermined	Negative	
Manaus	22	34	0	1	56
Belém	28	24	0	0	52
Fortaleza	12	20	0	3	32
Recife	13	44	0	1	57
Salvador	14	19	0	4	33
Campo Grande	10	10	0	1	20
Brasília	6	20	1	3	26
Belo Horizonte	17	32	1	1	49
São Paulo	8	62	1	1	70
Rio de Janeiro	11	17	0	0	28
Curitiba	8	35	0	10	43
Porto Alegre	14	13	0	1	27
Total	163	330	3	26	493

HIV: human immunodeficiency virus; IAL: Instituto Adolfo Lutz; VL: viral load.

DISCUSSION

Since 1988, in Brazil, the MoH has standardized HIV testing algorithms, which are revised as the available technologies evolve. Currently, different flow diagrams are standardized for diagnosis in different situations and local conditions of laboratorial infrastructure[28]. Thus, according to need, they can be used from rapid tests to molecular tests to ensure that the diagnosis of HIV is safe and completed quickly. In this study, the laboratory evaluation of the samples with reactive field results in HIV RT was initiated by the molecular tests for quantification of RNA.

According to the results found, serological tests play a fundamental role in the resolubility of inconclusive cases, because in 68.2% (356/522) of the samples evaluated in IAL, serology enabled to elucidate the diagnosis of HIV/Aids (330 reagent and 26 non-reactive samples for HIV). It is possible that the high number of non-detectable VL samples was due to problems during the pre-analytical phase (transport and packaging of blood). As well as any laboratory assay, the molecular test result is subject to failures, especially those that may occur in the pre-analytical phase. The conditioning, transportation and storaging of the biological sample until the actual exam is performed are fundamental procedures to guarantee the quality of the sample and, consequently, of the result. It is estimated that 46% and 68% of laboratory errors are due to problems occurring during this phase, such as: incorrect collected sample or insufficient volume, incorrect identification and inadequate transport or storage conditions[31]. A fact observed in this study, in which the volume of blood was insufficient to carry out the tests prevented the laboratory diagnosis in 11.7% of the samples.

Regarding the six samples with discordant results in the confirmatory tests, indeterminate IBR and positive WB, viremia was not detected in five samples and in the other the VL result was 91 copies/ml. According to the instruction manual of the IBR DPP HIV 1/2 kit, one of the limitations of the procedure concerns the possibility of a false negative result in samples from individuals known to be HIV positive, who are in ART. In these cases, all six volunteers used ART and, when the treatment is successful, it is believed that the low HIV replication level may prevent the induction of a high titer antibody response[32, 33]. Reduction of anti-HIV antibodies may have led IBR not to present the HIV positivity profile, unlike the result obtained in CLIA and confirmed by WB.

The verification of the analytical performance in non-reactive samples in RT was not limited to the concordance analysis of the test results used, but also to errors that may have occurred in the post-analytical phase, mainly due to the lack conferencing of data during its transcription and typing. Another fact is the false non-reactive results of HIV RT presented in some situations, for example, during the use of ART[27], therefore, the use of RT in these individuals is not indicated[28].

In this study, in the attempt to elucidate the case of the four samples that presented discordance between the rapid test (non-reagent result) and the conventional serology (reagent result), we chose to re-evaluate these sera in RT, all of them (4/4) with reagents results. This demonstrates, therefore, that the problem occurred during the interpretation or the typing/transcription of results, regardless of whether or not the individual uses ART.

In this same context, it can be verified that the 13 samples with reagent results by the two HIV RT (RT1 and RT2), non-detectable VL and non-reactive by conventional serology, when re-evaluated in RT (Bioeasy), 77% (10) were non-reactive and three (23%) samples kept reagent in RT. In these three cases, it may be considered the occurrence of false reagent results in the RT and, in the others, errors during the performance of the test or in the post-analytical phase.

CONCLUSION

The results obtained in this study, carried out in different regions of Brazil, showed that the point of care rapid tests have a

high confirmation rate when compared to the serological tests. On the other hand, we also observed a considerable rate of tests with incomplete results by insufficient sample. The data of this work corroborate the importance of verificating the performance of analytical methods used for the diagnosis of HIV/Aids infection, as well as the use of standardized procedures that aim at the quality of the pre-analytic, analytical and post-analytic phases to obtain reliable results.

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DATABASE

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CONFLICTS OF INTEREST

The authors reported no potential conflict of interest.

RESUMO

Introdução: *O diagnóstico precoce é um importante instrumento para estratégias de combate à infecção pelo vírus da imunodeficiência humana (HIV).* ***Objetivo:*** *O objetivo principal deste trabalho foi avaliar a comparabilidade do resultado de testes rápidos (TR) utilizados para o diagnóstico de HIV em relação a testes moleculares e sorológicos convencionais em amostras de sangue de população de homens que fazem sexo com homens (HSH) de 12 capitais brasileiras.* ***Material e métodos:*** *Foram encaminhadas ao Instituto Adolfo Lutz (IAL), 591 amostras com resultado reagente no TR HIV dos 4176 HSH participantes para serem avaliadas pelos testes laboratoriais convencionais. Dessas amostras com pelo menos um TR reagente, 522 amostras foram analisadas e em 493 (94,4%) confirmou-se a positividade para HIV, sendo 33% pela carga viral HIV-1 acima de 5.000 cópias/ml e 67% pelos testes sorológicos. Foram avaliadas pela sorologia convencional, 336 (10%) amostras com resultado de TR não reagente; quatro (1,2%) apresentaram-se reagentes para HIV.* ***Resultados e conclusão:*** *Os resultados mostraram elevado percentual de amostras com a positividade confirmada para HIV nos testes laboratoriais convencionais, bem como alguns resultados negativos que se confirmaram positivos, mostrando algumas limitações do método único do TR, destacando-se aos exames sorológicos papel fundamental à elucidação do diagnóstico.*

Unitermos: *anticorpos anti-HIV; imunoensaio; carga viral; sorologia; homossexualidade masculina; Brasil.*

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