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BRIEF REPORT

False-negative Results of Human Immunodeficiency Virus (HIV) Rapid Testing in HIV Controllers

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Serological assays were performed on 85 human immunodeficiency virus-controller samples . 6% presented a negative rapid screening test 7% presented an indeterminate Western blot. The enzyme immunoassay ratio decreased in controllers who had continual negative ultrasensitive HIV RNA results since inclusion.

Keywords. HIV controllers; HIV diagnosis; ELISA; HIV-1 Western blot; HIV rapid screening test.

Human immunodeficiency virus type 1 (HIV-1) controllers (HICs) are a rare group of individuals living with HIV who maintain HIV viremia at extremely low or even undetectable levels in the absence of antiretroviral treatment (ART) [1]. In this context, some cases of downregulation of the antibody response to HIV infection have been described [2–5].

It is well described that false-negative and weakly reactive HIV fourth-generation assay and rapid screening test (RST) results can occur in another context of viremia control, in long-term virally suppressed individuals receiving ART [6, 7]. RSTs are increasingly being used, including by patients themselves in settings "outside of the laboratory."

Taking such issues into account, this study was designed to evaluate the risk of false-negative results contributing to HIV misdiagnoses in the HIC group. We investigated anti-HIV humoral antibody detection and its evolution in a group of HICs who had a particularly efficient control of the infection for a long period of time (all HIV RNA plasma loads <100 copies/mL except at time of diagnosis).

METHODS

The French multicenter Agence Nationale de Recherches sur le SIDA et les hépatites virales CO21 Cohorte des Extrêmes (ANRS CO21 CODEX) cohort included 220 HICs based on the following characteristics: an individual living with HIV who never received ART, with a follow-up time longer than 5 years, and with the last 5 HIV RNA plasma measurements <400 copies/mL. All HICs from this cohort who presented HIV RNA plasma loads <100 copies/mL at each point of their monitoring (except at the time of diagnosis) were selected for the study. All participants gave written informed consent. The Regional Investigational Review Board (Comité de Protection des Personnes Ile-de-France VII, Paris, France) approved the study protocol, which was performed in compliance with the tenets of the Declaration of Helsinki.

A highly sensitive and specific HIV RST (INSTI bioLytical/Nephrotek, Boulogne-Billancourt, France) [8], 2 fourth-generation HIV enzyme immunoassays (EIAs; VIDAS HIV DUO ULTRA, bioMérieux, Marcy l'Etoile, France, and ARCHITECT HIV Ag/Ab Combo, Abbott, Abbott Park, IL), and an HIV-1 Western blot (WB) confirmation assay (BioRad, Marnes la Coquette, France) were performed on the first frozen plasma sample available since inclusion in the cohort and, if sufficient plasma was available, on the last sample collected in the cohort with an undetectable viral load. The HIV antibody specificity against 10 HIV-1 antigens (gp160, gp110/120, p68/66, p55, p52/51, gp41, p40, p34, p24, and p18/17) was scored by WB analysis. WBs were considered positive when at least 2 positive antibody reactions to *env* proteins and 1 to *gag* or *pol* proteins occurred. Otherwise, the profile was considered indeterminate (presence of some antibodies without meeting the criteria for positivity) or negative.

HIV RNA was quantified in a large volume of frozen plasma every 12 months by ultrasensitive quantitative reverse-transcription polymerase chain reaction (qRT-PCR) as previously described [5, 9]. The threshold ranged from 1 to 40 copies/mL, depending on the available plasma volume (0.5 to 15 mL); more than 90% of quantifications were performed with a threshold of <5 copies/mL. HIV DNA was quantified in frozen peripheral blood mononuclear cells (PBMCs) by ultrasensitive PCR (Biocentric, France) [9, 10]. More than 90% of quantifications were performed with a threshold of <20 copies/million PBMCs.

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The results are reported as median levels with interquartile ranges (IQRs). GraphPad Prism software (San Diego, CA) was used for the statistical analyses (Wilcoxon test).

RESULTS

Eighty-five HICs (39%) with all HIV RNA <100 copies/mL except during the diagnosis were selected from the ongoing ANRS CODEX cohort enrolled from 2009 to 2017. The characteristics of the study population are provided in Table 1. The median and range of the number of ultrasensitive HIV RNA tests performed during the observation period were 5 (range, 1–9; IQR, 4–7). Only 1 HIC had HIV RNA consistently <100 copies/mL but never undetectable, with the highest HIV RNA at 33 copies/mL. Globally, during follow-up with the ultrasensitive assay, 9 HICs among the 85 had had at least 1 positive HIV RNA load. These viral loads were then positive in 1/9 to 3/5 samples.

The RST was negative in 3/85 cases (4%; Supplementary Table 1), while samples from 21 cases (25%) were weakly reactive with a very faint band. HIV-1 EIA tests were positive in the first serum sample of all tested participants with results that were sometimes near the positivity cutoff threshold (85/85 for the bioMérieux assay with values ranging from 6.89 to 24.74 arbitrary units (positive when >0.25), 82/82 for the Abbott assay with signal-to-cutoff (S/CO) ratios between 4.72 and 1044.08 (positive when S/CO ratios were >1). WBs presented 3 HIV-1 bands (anti-gp160, anti-p55, and anti-p24 antibodies) in 3/85 cases (3.5%), 6 bands in 4/85 (4.7%), 7 bands in 3/85 (3.5%), 8 bands in 3/85 (3.5%), 9 bands in 4/85 (4.7%), and 10 bands in 68/85 (80.1%). Overall, WBs were positive in 80/85 (94%) cases and indeterminate in 5/85 (6%) cases (Supplementary Table 1). For these 5 cases, the RST was negative for 3 and weakly positive for 1. Interestingly, HICs with indeterminate WBs and/or false-negative RSTs in the cohort had at least 1 positive HIV DNA test during the follow-up in the cohort, most often <10 copies/million PBMCs, which could help to confirm the HIV diagnosis.

To investigate a possible decline in HIV antibodies associated with HIV control, we examined the variation over time for 65 HICs who had available plasma at a second collection time point with a median follow-up of 3.2 years since inclusion in the cohort (IQR, 2.0;4.7). The evolution of the RST results, EIA ratio, and anti-HIV band numbers was analyzed. RST results were stably positive for 61/64 HICs tested; 2 HICs with all ultrasensitive viral loads that were undetectable from inclusion presented with RST seroreversion (6 and 1 years between the 2 samples); and 1 patient presented with RST seroconversion (2 years between the 2 samples; Supplementary Table 1). The EIAs remained positive for all HICs (n = 65). Interestingly, HICs with HIV RNA undetectable by the ultrasensitive assay since inclusion in the cohort had a significant decrease in the EIA ratio (median, −0.1) over time (P = .01), indicating a decrease in HIV antibody titer, whereas those who had at least 1 positive result (HIV RNA range, 21–557 copies/mL) had no change in the ratio (P = .78).

While 92% of HICs (60/65) had no change in the WB pattern, 3 participants lost HIV-1 antibodies: 1 participant lost 4 antibodies, and the WB became indeterminate; 1 participant lost 2 antibodies; and 1 participant lost 1 antibody without a change in the interpretation of the assay. Two participants had 1 additional detectable antibody.

Combining the results of 2 points of analysis, 5/85 (6%) HICs had a negative RST and 6/85 (7%) had an indeterminate WB in at least 1 of the analyzed samples (Supplementary Table 1). Among these HICs with "indeterminate WB" samples, all had a negative HIV viral load during the follow-up since their inclusion in the cohort, and 4 also had a negative RST.

DISCUSSION

Our objective was to determine whether some HICs with robust viral control of HIV could present false-negative HIV diagnosis assay results due to a low antibody response during

Table 1. Main Characteristics of the 85 Human Immunodeficiency Virus Controllers

Characteristic	Value
Men, n (%)	31 (36)
Age at inclusion in the cohort, median (IQR), y	52 (46–57)
Transmission	
Blood, n (%)	1 (1)
Sex, n (%)	57 (67)
Intravenous drug use, n (%)	18 (21)
Other, n (%)	9 (11)
HLA B27/57 alleles, n (%)	33 (39)
HIV RNA VL at inclusion, median (IQR), log copies/mL	Und. (und.–und.)
Percentage of detectable ultrasensitive HIV RNA VL since enrollment	0 (0–100)
(IQR)	(0–0)
HIV DNA at inclusion, median (IQR), log copies/million PBMCs	1.30 (1.0–1.64)
HIV DNA at last point, median (IQR), log copies/million PBMCs	1.07 (0.6–1.38)
$CD4^+$ T-cell count at inclusion, median (IQR), cells/mm^3	775 (619–989)
$CD4^+/CD8^+$ ratio at inclusion, median (IQR)	1.35 (0.94–1.86)
EIA bioMérieux antibodies, median (range), arbitrary units[a]	
First measurement available (n = 85)	22.05 (6.89–24.74)
Second measurement available (n = 65)	21.95 (8.96–24.74)
EIA Abbott antibodies ratio,[b] median (range)	
First measurement available (n = 82)	443.8 (4.72–1044.08)
Second measurement available (n = 60)	487.5 (5.95–1106.64)
WB number of HIV-specific antibodies	
First WB, median (range) (n = 85)	10 (3–10)
Second WB, median (range) (n = 65)	10 (3–10)

Abbreviations: EIA, enzyme immunoassay; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; IQR, interquartile range; PBMCs, peripheral blood mononuclear cells; und., undetectable; VL, viral load; WB, Western blot.

[a]Positive when >0.25.

[b]Positive when the signal-to-cutoff ratio is >1.

infection. The negativity of RSTs and indeterminate or negative profiles of WB have even been described in isolated cases of elite controllers in cohorts of people living with HIV among whom the majority were progressors [11–13]. For the first time, this large study dedicated to HICs included a large number of well-characterized participants and showed that most HICs maintained an HIV-specific antibody response sufficient for HIV diagnosis. Nevertheless, in the context of the increasing use of rapid tests in settings outside of the laboratory, HIV diagnosis may be missed in 6% of HICs, and the low antibody response makes results difficult to interpret in 25% of cases (low reactivity that could easily be missed in a nonlaboratory testing environment). WB analysis could not confirm HIV seropositivity in 7% of cases. HICs with very tightly controlled HIV replication had a decrease in these HIV-specific antibody responses over time. This decrease observed for the first time in some HICs is consistent with recent studies showing HIV antibody reactivity loss in adults living with HIV [6], children and adolescents on long-term suppressive ART [14], and in the Berlin Patient [15], whose common characteristic is the absence of HIV antigenic stimulation. We recently described that some HICs have a decrease of HIV DNA over time, reflecting a particularly high control of viral replication [9]. The decrease of HIV-specific immune responses observed in this study is in accordance with this strong HIV control.

In conclusion, our results show that the RST may not be reliable in the context of natural control and very low immune stimulation over a period of several years. HIV diagnosis in HICs can be difficult, and quantification of HIV DNA with ultrasensitive assays is sometimes needed to definitively confirm infection.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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APPENDIX

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