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MAJOR ARTICLE

Poststudy Point-of-Care Oral Fluid Testing in Human Immunodeficiency Virus-1 Vaccinees

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Background. Experimental human immunodeficiency virus (HIV)-1 vaccines frequently elicit antibodies against HIV-1 that may react with commonly used HIV diagnostic tests, a phenomenon known as vaccine-induced seropositivity/seroreactivity (VISP/VISR). We sought to determine, under clinic conditions, whether a patient-controlled HIV test, OraQuick ADVANCE Rapid HIV-1/2 Antibody Test, detected HIV-1 vaccine-induced antibodies.

Methods. Plasma assessment of HIV-1 cross-reactivity was examined in end-of-study samples from 57 healthy, HIV-uninfected participants who received a candidate vaccine that has entered Phase 2B and 3 testing. We also screened 120 healthy, HIV-uninfected, unblinded HIV-1 vaccine participants with VISP/VISR for an assessment using saliva. These participants came from 21 different parent vaccine protocols representing 17 different vaccine regimens, all of which contained an HIV-1 envelope immunogen. OraQuick ADVANCE was compared with results from concurrent blood samples using a series of commercial HIV screening immunoassays.

Results. Fifty-seven unique participant plasma samples were assayed in vitro, and only 1 (1.8%) was reactive by OraQuick ADVANCE. None of the 120 clinic participants (0%; 95% confidence interval, 0% to 3.7%) tested positive by OraQuick ADVANCE, and all were confirmed to be uninfected by HIV-1 viral ribonucleic acid testing. One hundred eighteen of the 120 (98.3%) participants had a reactive HIV test for VISP/VISR: 77 (64%) had at least 1 reactive fourth-generation HIV-1 diagnostic test ($P < .0001$ vs no reactive OraQuick ADVANCE results), and 41 (34%) only had a reactive test by the less specific third-generation Abbott Prism assay.

Conclusions. These data suggest that this widely available patient-controlled test has limited reactivity to HIV-1 antibodies elicited by these candidate HIV-1 vaccines.

Keywords. HIV diagnostics; HIV vaccine; immunogenicity; vaccine safety.

Control of the human immunodeficiency virus (HIV)-1 pandemic will almost certainly require a safe and effective vaccine [1–3]. To successfully identify an effective HIV-1 vaccine, numerous additional vaccine concepts are currently being tested in an iterative fashion [2, 4, 5]. These experimental vaccines are designed to elicit anti-HIV-1 immune responses, some of which induce anti-HIV-1 antibodies that can be detected by commonly used diagnostic tests used for screening for HIV infection. Vaccine-induced seropositivity (VISP) or vaccine-induced seroreactivity (VISR) is therefore an anticipated likely occurrence with participation in HIV vaccine trials [6] and has been identified as a common reason why potential participants decline participation [7, 8]. Furthermore, VISP/VISR can result in social harms such as misdiagnosis of HIV infection status [9, 10]. During the active phase of an HIV-1 vaccine clinical trial, knowledge of VISP/VISR could result in unblinding of the participant or study staff, and therefore blinding measures need to be undertaken for any on-study HIV tests that are performed. Because memory B cell responses can be long-lived, VISP/VISR may persist well after study participation ends [11], and clinical research sites and sponsors need to mitigate potential harms from the misinterpretation of VISP/VISR results [12]. The HIV Vaccine Trials Network (HVTN) has established a comprehensive program (https://www.hvtn.org/en/participants/visp-hiv-testing.html) to mitigate these risks for participants in their studies. This commitment provides HIV testing to vaccine recipients for as long as necessary to distinguish between vaccine

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responses and HIV infection, including for vaccinees who have relocated from any clinical trial sites.

For non-HVTN protocols, to meet the ethical obligations of assisting vaccinees poststudy, clinical trial sites may continue to perform all HIV tests [12]. However, poststudy testing for participants who relocate poses considerable logistical challenges including potentially establishing a contract with a phlebotomy service to obtain and ship the sample as well as with a central laboratory that can perform HIV testing to distinguish between VISP/VISR and HIV infection. Alternative methods of rapidly and accurately distinguishing VISP/VISR from actual HIV infection are needed, and the development of such tests is currently being supported [12, 13].

Human immunodeficiency virus testing kits using oral fluid are available and marketed both for rapid testing in emergency rooms, clinicians' offices, as well as for home self-testing [14–16]. We hypothesized that the antibodies elicited by candidate HIV vaccines would not be detected by one of these patient-controlled testing kits (OraQuick ADVANCE), in contrast to a series of commercial HIV screening immunoassays performed on concurrent blood samples.

METHODS

Participants and Study Design

A subset of plasma samples from participants who enrolled in the Phase 1/2a HVTN 117/HPX2004 vaccine study [17] were assayed using the OraQuick ADVANCE Rapid HIV-1/2 Antibody Test (OraSure Technologies, Inc., Bethlehem, PA) as per manufacturer's instructions for blood testing [18]. The OraQuick immunoassay platform uses gp41- and gp36-derived antigens for detection [19]. Participants had been randomized to 2 doses of either adenovirus serotype 26 (Ad26) delivering trivalent or tetravalent mosaic HIV immunogens followed by 2 doses of the same Ad26 in combination with clade C Env gp140 or placebo [17]. These plasma samples had been designated for evaluation of HIV seroreactivity (EOS) and were drawn at a participant's end-of-study (final) visit, 24 weeks after their final vaccination. These plasma samples comprised all the available EOS samples from US participants in the HVTN 117/HPX2004 study as of May 2018; this subset represents approximately half of US enrollees. Because the parent study was still blinded at the time, samples were recoded with a sequential number so that the HIV results did not inadvertently unblind staff as to which participants received product versus placebo.

The point-of-care OraQuick ADVANCE saliva assessment focused on participants enrolled at the Brigham and Women's Hospital (BWH) Clinical Research Site who had previously received a candidate HIV-1 vaccine and are followed in 1 of 2 long-term follow-up protocols that assess the persistence of VISP/VISR. The first protocol (HVTN 910) follows participants from HVTN-coordinated preventive HIV vaccine trials [20], whereas the second is a site-specific protocol that provides follow-up testing for participants from HIV-1 vaccine studies conducted at BWH in Boston, Massachusetts. We screened 120 healthy, HIV-uninfected, prior candidate HIV-1 vaccine recipients who were followed at BWH (Table 1).

Oral fluid testing was performed in the clinic using the OraQuick ADVANCE by the participant by swabbing the outer gums per manufacturer's instructions [18]. A blood sample was taken concurrently. Immediately after the oral sample collection, the test device was inserted into the vial of developer solution outside of the participant's view. After 20–40 minutes of incubation, the device was read and the result of the test was recorded. Standard pretest and posttest HIV counseling was provided to the participants along with the results of their blood tests as per the Centers for Disease Control and Prevention (CDC) guidelines [21].

For the concurrent blood testing as well as for EOS evaluation in HVTN 117/HPX2004 participants, 3 different fourth-generation antibody/antigen-based HIV-1 diagnostic tests were used: Bio-Rad GS HIV Combo Ag/Ab EIA, Abbott Architect HIV Ag/Ab Combo, and Alere Determine HIV-1/2 Ag/Ab Combo. The Bio-Rad GS and Abbott Architect platforms provide a quantitative sample to cutoff (S/CO) ratio for each assay [22]; S:CO ratios between 0.7 and 0.99 were reported as "equivocal." Several groups have reported that S:CO ratios on the Abbott Architect platform typically exceed 100 in individuals chronically infected with HIV [22, 23]. If reactivity was noted on any of the fourth-generation tests, quantitative HIV-1 viral load testing was done using the Abbott m2000 RealTime PCR HIV-1 platform. If no reactivity was noted on any of the fourth-generation tests, then samples were further assayed with the less specific third-generation Abbott Prism O Plus Anti-HIV-1/2 test.

Patient Consent Statement

This protocol was approved by the BWH institutional review board and written informed consent was obtained from each participant.

Vaccines

The parent protocols (n = 21) in which the oral fluid testing participants had been vaccinated are summarized in Table 2.

Table 1. Oral Fluid Participant Demographics

Demographic	Number (%)
Sex	
Female	69 (58%)
Ethnicity	
Hispanic	10 (8%)
Race	
Black or African American	11 (9%)
Asian	8 (7%)
White or Caucasian	92 (77%)
Mixed or Other	9 (8%)

Table 2. Vaccine Regimens Previously Administered to Clinic Participants Who Underwent Oral Fluid Testing

Parent Protocol	Number	Prime-Boost Strategy	Participants and Regimens	Env Immunogen	Reference
HVTN 057	1	DNA + viral vector	DNA + Ad5	gp140	NCT00091416
HVTN 065	3	DNA + viral vector	DNA + MVA	gp160	[24]
HVTN 069	1	DNA + viral vector	DNA + Ad5	gp140	[25]
HVTN 077	1	DNA + viral vector	DNA + Ad35	gp140	[26]
	1	Viral vector	Ad35 + Ad5		
HVTN 082	2	DNA + viral vector	DNA + Ad5	gp140	NCT01054872
HVTN 083	1	Viral vector	Ad5	gp140	[27]
	1	Viral vector	Ad35 + Ad5		
HVTN 085	2	Viral vector	Ad5	gp140	NCT01479296
HVTN 094	5	DNA + viral vector	DNA + MVA	gp160	[28]
HVTN 106	4	DNA + viral vector	DNA + MVA	gp160 + gp150	NCT02296541
HVTN 114	1	DNA + viral vector + protein	DNA + MVA + gp120	gp160 + gp120	NCT02852005
HVTN 117/	28	Viral vector + protein	Ad26 + gp140	gp140	[17]
HPX2004	1	Viral vector	Ad5 + Ad26[a]		
HVTN 118/ HPX2003	10	Viral vector + protein	Ad26 + gp140	gp140	NCT02935686
	1	Viral vector	Ad26[b]		
HVTN 204	3	DNA + viral vector	DNA + Ad5	gp140	[29]
HVTN 205	1	DNA + viral vector	DNA + MVA	gp160	[30]
HVTN 505	8	DNA + viral vector	DNA + Ad5	gp140	[31]
	1	DNA	DNA[c]		
IPCAVD 001	1	Viral vector	1×10^9 Ad26	gp140	[32]
	2	Viral vector	1×10^{10} Ad26		
IPCAVD 002	1	Viral vector	1×10^9 Ad5HVR48	gp140	[33]
	2		1×10^{10} Ad5HVR48		
	3		1×10^{11} Ad5HVR48		
IPCAVD 003	1	Viral vector	5×10^{10} rAd26	gp140	[34]
IPCAVD 004/	3	Viral vector	Ad26 + Ad35	gp140	[35]
IAVI B003/ HVTN 091	2	Viral vector	Ad35 + Ad26		
IPCAVD 006	2	Viral vector	MVA	gp140	[36]
	3	Viral vector	1×10^{10} rAd26 + MVA		
	1	Viral vector	1×10^{11} rAd26 + MVA		
IPCAVD 009/ HIV-V-A004	9	Viral vector + protein	Ad26 + MVA + gp140[d]	gp140	[5]
	7		Ad26 + MVA		
	3		Ad26		
	4		Ad26 + gp140		

Abbreviations: Ad, adenovirus; DNA, deoxyribonucleic acid; Env, envelope; HVTN, HIV Vaccine Trial Network; IAVI, International AIDS Vaccine Initiative; IPCAVD, Integrated Preclinical/Clinical AIDS Vaccine Development; MVA, modified vaccinia Ankara.

[a]Ad5-vectored vaccine received via prior enrollment in HVTN 084 [NCT01159990], not known by site staff until after first vaccination with Ad26-vectored vaccine.

[b]Participant missed Ad26 + trimeric Env gp140 boosters.

[c]Participant missed Ad5 booster.

[d]One participant missed final MVA + gp140 booster.

Most participants had received vaccines delivering gp140 envelope (Env) constructs; gp160 constructs were used in HVTN 065, HVTN 094, HVTN 106 (MVA boost delivered gp150), HVTN 114, and HVTN 205. The Env protein boosts were given in HVTN 117, HVTN 118, and IPCAVD 009 (trimeric gp140) as well as HVTN 114 (monomeric gp120). Participants had been vaccinated between 8 months and 13 years, 11 months (median 34.5 months) before the oral fluid HIV testing.

Statistical Methods

All analyses of the oral fluid data in this post hoc, cross-sectional, cross-protocol study are based on the per-protocol (PP) principle because participants were recruited based on known EOS VISP positivity; analyses of the plasma EOS samples were blinded as to product allocation before study unblinding. Results of the oral fluid and plasma assays are reported as proportions. Differences in proportions were tested with 2-sided McNemar's test. Two-sided 95% confidence intervals (CIs) for binomial proportions were calculated using the score test method [37]. Tests with a 2-sided $P < .05$ were considered significant. No adjustment for multiple comparisons was made.

RESULTS

Assessment of OraQuick ADVANCE Reactivity Using Plasma

Using routine fourth-generation antigen/antibody (Ag/Ab) tests, blinded HVTN 117/HPX2004 participant EOS plasma samples had a high rate of reactivity. Most (66 of 71 [93%]) samples were concordant across the 3 platforms. Two samples were equivocal by the Bio-Rad GS but nonreactive by the Abbott Architect and Alere Determine. One sample was nonreactive by the Bio-Rad GS but reactive by the Abbott Architect and Alere Determine. Two samples were nonreactive by the Alere Determine but reactive by the Bio-Rad GS and Abbott Architect. Samples that tested nonreactive on all 3 fourth-generation assays were further tested by the Abbott Prism assay.

After unblinding of the primary study, we found that the 14 samples that tested nonreactive by all 4 platforms were from placebo recipients. When the 57 plasma samples from active vaccinees were assayed using OraQuick ADVANCE (Table 3), only 1 of 57 (1.8%; 95% CI, 0% to 10.2%) was reactive. The single sample that cross-reacted with OraQuick ADVANCE had a high S/CO ratio on both the Bio-Rad GS and Abbott Architect platforms (Figure 1). All samples that tested positive by any of the immunoassays were found to be negative by HIV-1 ribonucleic acid (RNA) testing.

Assessment of OraQuick ADVANCE Reactivity Using Oral Fluid

The 120 subjects that participated in the saliva study were derived from 21 different candidate HIV-1 vaccine protocols. Of the 120 participants, 76 received an Ad26-vectored HIV-1 vaccine (Table 2), which included the following: 8 received Ad26 alone, 11 received Ad26 prime with a modified vaccinia Ankara (MVA) boost, 42 received Ad26 with a protein boost, 9 received Ad26 with both MVA and protein boost, and 5 received Ad26 and Ad35 in a heterologous prime/boost study; 1 participant received Ad5 before Ad26 because of inadvertent prior enrollment. In addition, 27 received other adenovirus vectors: 3 received Ad5, 15 received deoxyribonucleic acid (DNA) priming with an Ad5 boost, 2 received Ad35 and Ad5 heterologous prime-boosting, 1 received a DNA prime and an Ad35 boost, and 6 received an Ad5HVR48 chimeric vector. The remaining 17 received a DNA prime with an MVA boost: 14 received DNA and MVA, 2 received MVA alone, and 1 received

Table 3. Analysis of OraQuick ADVANCE Cross-Reactivity With Plasma Samples From HVTN 117/HPX2004

HIV-1 Diagnostic Test	Participants Testing Reactive n (%)	*P* Value vs OraQuick ADVANCE
OraQuick ADVANCE	1 of 57 (1.8%)	–
Bio-Rad GS	53 of 57 (93%)	<.0001
Abbott Architect	54 of 57 (95%)	<.0001
Alere Determine	52 of 57 (91%)	<.0001
Abbott Prism[a]	1 of 1 (100%)	–

Abbreviations: HIV, human immunodeficiency virus; HVTN, HIV Vaccine Trial Network.

[a]Abbott Prism was only used if samples tested negative on all 3 of the fourth-generation antigen/antibody tests (n = 15).

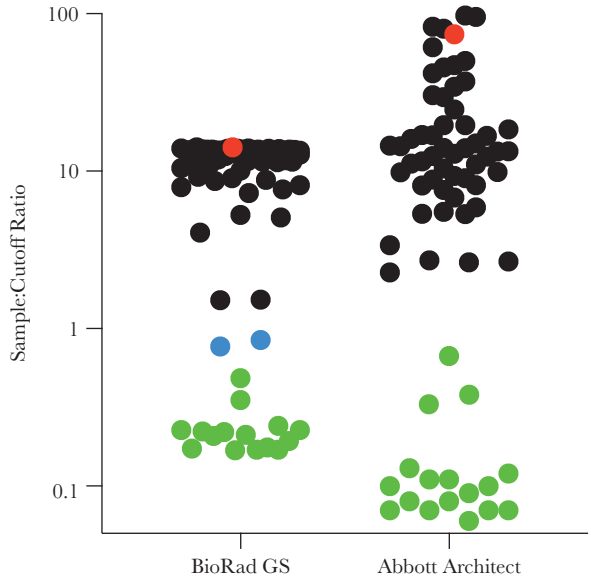

Figure 1. Assessment of fourth-generation human immunodeficiency virus (HIV) tests compared with OraQuick ADVANCE. End-of-study plasma samples from participants in the HIV Vaccine Trial Network (HVTN) 117/HPX2004 study were assayed for vaccine-induced seropositivity using 2 routine fourth-generation HIV tests. Sample/cutoff ratios are given: nonreactive samples are green, samples reported as equivocal are blue, reactive samples are black except for the lone sample that was reactive by OraQuick ADVANCE, which is red.

DNA alone. All participants had received vaccines that included an Env immunogen.

None of the 120 participants tested reactive (0%; 95% CI, 0% to 3.7%) by OraQuick ADVANCE, and all were negative by HIV-1 RNA testing. When comparing the participants' plasma test results (Table 4), 77 (64%) tested reactive by 1 or more of the fourth-generation antibody/antigen-based HIV-1 diagnostic assays; 65 (54%) were reactive by Bio-Rad GS HIV Combo Ag/Ab EIA, 76 (63%) were reactive by Abbott Architect HIV Ag/Ab Combo, and 58 (48%) were reactive by Alere Determine HIV-1/2 Ag/Ab Combo. Fifty-four participants were reactive by all 3 standard assays; 14 participants were reactive by 2 of the assays (either Bio-Rad GS and Abbott Architect or Alere Determine and Abbott Architect); and 9 participants were reactive by 1 of the assays (8 on the Abbott Architect and 1 who was only reactive by Bio-Rad GS). The remaining 41 (34%) participants were only reactive by the Abbott Prism assay. Two participants did not test reactive by any blood diagnostic test.

Of note, after unblinding, the lone plasma sample that tested positive by OraQuick ADVANCE was found to have come from a participant at the BWH site who had received the tetravalent Ad26 and clade C gp140 Env regimen. This participant's oral fluid tested negative by OraQuick ADVANCE, although the 2 assays were performed 14 months apart.

DISCUSSION

Persistence of HIV-1 vaccine-elicited antibodies can lead to diagnostic challenges as well as adverse social impacts in participants who received candidate HIV-1 vaccines [10, 12]. Our data suggest that the OraQuick ADVANCE oral point-of-care test infrequently detects HIV-1 antibodies elicited by the different candidate HIV-1 vaccines evaluated in these trials. Given the low rates of reactivity with plasma and oral fluid, it is possible that the HIV-1-derived antigens used in this point-of-care assay have limited epitope overlap with the immunogens in some of these candidate vaccines. Alternatively, there could be differences in epitope presentation or immunogenicity between vaccination and infection. However, because oral fluid levels of immunoglobulins are lower than in serum, our results may also reflect this assay's relative insensitivity for low antibody titers.

There are several limitations to our study. For in-home testing, the OraQuick In-Home HIV Test, available for over-the-counter purchase, would be used, and per the package insert, the test missed identifying 8 of 96 individuals with HIV infection (1 in 12), and it is to be used no less than 3 months after a potential exposure [38]. The test has insufficient sensitivity for detecting HIV infection during this time period [39]. There may also be delays in the appearance of HIV-1-specific antibodies associated with the use of antiretrovirals for pre-exposure prophylaxis [40]. Our study is further limited to the specific HIV-1 vaccine vectors and immunogens that were used in the parent vaccine studies. This is particularly true for the in vitro plasma testing, which assessed only a single vaccine regimen. Other candidate HIV-1 vaccines under development could be assessed for cross-reactivity by this (or other) detection systems to determine potential utility during the clinical trial to ensure minimization of the risk for possible unblinding. Furthermore, our data from plasma samples suggest that there may be a risk of reactivity with this point-of-care test at high antibody titers, as might occur at peak time points after vaccination. Because blood and tissue donation programs may use less specific tests such as the third-generation Abbott Prism [41], former vaccine recipients should be counseled that nonreactivity by this point-of-care testing may not exclude blood test reactivity by all testing platforms.

The rigorous HIV diagnostic algorithm established by the HVTN has dual purposes: (1) to identify HIV infection, and (2) to fully inform vaccinees of the likelihood that they may test HIV antibody positive in tests commonly used in circumstances such as blood donation, medical exams, during pregnancy and delivery, for life insurance applications, presurgical consultations, military service, international travel, and certain employment. Without the knowledge of their likelihood to test antibody positive in these circumstances, vaccinees may experience issues such as denial of life insurance, permanent deferral from blood or tissue donation, postponement of elective surgical procedures, and, in the case of perinatal care, the newborn may be unnecessarily placed on antiretroviral therapy [12].

Table 4. Analysis of OraQuick ADVANCE Saliva Cross-Reactivity With Blood Tests

HIV-1 Diagnostic Test	Participants Testing Reactive n (%)	*P* Value vs OraQuick ADVANCE
OraQuick ADVANCE	0 of 120 (0%)	–
Bio-Rad GS	65 of 120 (54%)	<.0001
Abbott Architect	76 of 120 (63%)	<.0001
Alere Determine	58 of 120 (48%)	<.0001
Abbott Prism[a]	41 of 43 (95%)	<.0001

Abbreviations: HIV, human immunodeficiency virus.

[a]Abbott Prism was only used if samples tested negative on all 3 of the fourth-generation antigen/antibody tests (n = 41).

CONCLUSIONS

Taken together, our data suggest that this point-of-care test may be an alternative, participant-controlled, HIV screening modality for individuals at low risk for HIV infection who previously participated in certain HIV-1 vaccine studies, developed VISP/VISR by routine blood tests, and have been counseled in the limitations of the test. This point-of-care test has the potential to provide an option to such vaccinees who have not had a potential exposure during the preceding 3 months, do not need to know their VISP status for circumstances for HIV testing in the community (eg, medical exam),

prefer the convenience of in-home testing, and have the resources to purchase the test (US ~$45).

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