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Substance use patterns of HVTN phase I clinical trial participants: Enrollment, Risk Reduction Counseling and Retention

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Abstract

Background—The primary objectives of HIV Vaccine Trials Network (HVTN) phase 1 preventive HIV vaccine clinical trials are to assess safety and immune response to study products. Participant alcohol and drug use may affect adherence, retention, and risk of HIV infection. Data on the effects of substance use are limited to medical care compliance and treatment adherence in HIV infected participants. To our knowledge, there are no data assessing substance use and retention in these vaccine trials.

Methods—We performed a meta-analysis on substance use and its impact on retention in HVTN phase I trials that recruited participants demonstrating lower risk profiles for HIV infection. Our analysis included data from 10 HVTN phase 1 clinical trials conducted between February 2009

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Ethics

The study is covered by an approval from the Fred Hutchinson Cancer Research Center Institutional Review Board (IR 8023).

Conflict of Interest

All authors have reviewed the manuscript and approved submission for publication. The authors have declared no potential conflict of interest in the material included in this manuscript.

and September 2014 in the Americas and Switzerland that utilized the identical interviewer-administered behavioral risk assessment questionnaire to capture participant self-report of substance use in the previous six months. Chi Square tests were used to assess statistical differences between variables.

Results—Among the 964 participants, 170 (18%) missed a clinic visit and 78 (8%) terminated early from clinic follow-up; 75/774 (10%) on studies with multiple vaccination timepoints did not complete their vaccinations. Neither frequency of alcohol use, binge drinking, marijuana, nor other drug use reported at screening visits were associated with the three adherence/retention measures. Binge drinking was associated with higher rates of unprotected sex while drunk ($p<0.001$).

Conclusions—Light to moderate alcohol use does not negatively impact adherence or retention in phase I clinical trials. Based on these screening data and the low infection rate of participants during the trial period, the screening process for participation in HVTN phase 1 trials has largely been successful in enrolling and retaining individuals with lower risk profiles. Focusing on binge drinking and increased HIV/STI risk during risk reduction counseling may be warranted.

Keywords

HIV; Biomedical interventions; substance use; vaccine clinical trials

1. Introduction

The primary objectives of phase 1 preventive HIV vaccine clinical trials are to assess safety and immune response to study products. To successfully complete these objectives, it is essential that participants be healthy, remain HIV seronegative, adhere to the intervention schedule and complete study follow-up visits to assess study endpoints. Participant alcohol and drug use are factors that may potentially affect participant adherence, retention and risk of HIV infection. There is a great deal of evidence linking substance use to higher risk sexual behavior (e.g., condomless sex, exchange sex, sex while high or intoxicated) [1–4]. However, excluding potential participants reporting limited substance use from phase 1 trials may be too restrictive, given the prevalence of substance use in the United States (US). Data from the 2015 National Survey on Drug Use and Health indicated that 10% of people aged 12 and older used illicit drugs in the past month [5].

There is a lack of research exploring the effects of substance use on compliance with a vaccine regimen in preventive HIV vaccine clinical trials. Most of the existing research in the HIV literature focuses on the effects of substance use on medical care compliance and treatment adherence in HIV seropositive individuals or participants with mental health disorders. [5, 6]. In studies that assess behavioral risk patterns of HIV infected populations, alcohol and illicit drug use are common and may be associated with less engagement with medical care, decreased interaction with healthcare providers and poorer adherence to HIV antiretroviral therapy (ART) [7, 8]. Pecoraro et al (2013) found that among patients receiving HIV treatment in a US inner city HIV primary care clinic dropping out of care was associated with drug and alcohol use. Returning to care was associated with substance abuse treatment and recovery [6].

There is some evidence that conducting randomized controlled clinical trials in alcohol and drug-using populations poses additional challenges including decreased retention and difficulty maintaining contact with trial participants [7]. However, limited information is available on the relationship of substance use to retention in preventive HIV vaccine clinical trials. The STEP trial, evaluating the MRKAd4 HIV-1 vaccine in participants at high risk of HIV-1 infection, found that the use of speed, poppers, and any recreational drugs were associated with higher loss to follow-up among male participants [10]. Among North American women, use of recreational drugs was prevalent (95%) and associated with better retention, which may be the result of the financial compensation provided for adherence to study visits in that trial [8].

To our knowledge, there are no data to inform our understanding of how substance use impacts retention in preventive HIV vaccine trials for participants with lower HIV risk profiles. To address this, we performed a meta-analysis to assess the patterns of substance use of enrolled participants and the impact substance use has on retention in phase I preventive HIV vaccine clinical trials conducted by the HIV Vaccine Trials Network (HVTN) that recruited participants who, through self-report, demonstrated lower risk profiles for HIV infection. A more accurate picture of substance use patterns may assist in the development of eligibility criteria, screening procedures and inform risk reduction counseling.

2. Methods

2.1 Study Design

Our analysis included data from 10 HVTN phase 1 preventive HIV vaccine clinical trials conducted between February 2009 and September 2014 in the Americas and Switzerland (Table 1). These phase 1 trials assessed safety, tolerability, and immunogenicity of preventive HIV vaccine products in healthy, HIV seronegative individuals at low risk for becoming HIV infected. All included trials had completed the clinic visit follow-up phase. To ensure comparable data, we included in the analysis only trials that utilized the identical interviewer-administered behavioral risk assessment (BRA) questionnaire to capture participant self-report of substance use. The study is covered by an approval from the Fred Hutchinson Cancer Research Center Institutional Review Board (IR 8023).

Among the 966 participants enrolled in these phase I trials, two participants were excluded from the analysis. One participant was an inappropriate enrollment and was taken off study after the first study visit (first vaccination). The second was discontinued from vaccinations after the first vaccination due to an unreliable medical history and continued in follow-up but on a reduced visit schedule.

2.2 Eligibility criteria

Participants had to be healthy, HIV seronegative adults aged 18–55 years at low risk for becoming HIV infected, who were able to comprehend the purpose of the study and provide written informed consent. Volunteers were recruited and screened; those determined to be eligible and provided informed consent were enrolled and followed in the clinic for a period

of 6–12 months depending on the protocol (Table 1). Several clinical parameters were used to screen potential participants and determine final eligibility determination based on the results of laboratory tests, medical and psychiatric history, and physical examinations. Any concurrent or prior participation in an HVTN HIV vaccine trial also prevented enrollment.

Protocols approved prior to May 2011 had specific guidelines for identifying low risk sexual and substance use behaviors. After that time, these guidelines were revised and site investigators were instructed to use their judgment to consider a broader view of the volunteer's behaviors and local epidemiologic information about HIV prevalence in making a final low risk determination. Sexual risk criteria excluded individuals with HIV-infected or illicit drug using partners. Eligible participants had 2 or fewer sexual partners, expanded in 2011 to 4 or fewer for opposite sex partners, with consistent condom use in non-monogamous relationships in the previous 12 months pre-2011 criteria or previous 6 months post-2011. A newly acquired sexually transmitted disease within the previous 12 months and beginning in 2011, exchange of sex for money, drugs, gifts or services were exclusionary.

Exclusionary substance use behaviors in protocols prior to May 2011 were excessive daily alcohol use (drinking 5 days or more each week on average, and on average > 12 drinks per week for women, > 18 for men) or frequent binge drinking (> 6 drinks on a single occasion on average > 2 times a month), chronic marijuana abuse, or any other illicit drug use within the last 12 months [9]. HVTN 090 (July, 2011) used the same criteria except the time period was the last 6 months. The definition of substance abuse provided in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders was adapted for use as guidance to define chronic marijuana abuse (i.e., repeated use under hazardous conditions; repeated problems in social/ occupational/ educational functioning related to use; or repeated legal problems related to use) [14, 15]. For other protocols approved after May 2011, exclusionary substance use behaviors within the last 12 months were injection drug use, repeated use of cocaine or methamphetamines, or repeated excessive alcohol use which in the investigator's judgment rendered the participant at greater than low risk for acquiring HIV infection.

2.3 Setting

The HIV Vaccine Trials Network (HVTN) is an international partnership that has conducted the majority of published, presented or ongoing clinical trials of preventive HIV vaccines worldwide. The Network includes over 30 Clinical Research Sites (CRSs) on five continents. This analysis includes 14 sites from 4 countries.

2.4 Intervention

In all of the included studies, trained study staff administered a BRA at the screening visit assessing substance use behaviors within the past six months. In all except two studies the same questionnaire was administered at a follow-up visit between 5 to 8 months from enrollment. The BRA assessed sexual practices (number of vaginal and anal sexual partners, condomless sex, exchange sex, STI diagnosis or treatment) and drug and alcohol use as well as partner behaviors (sexual practices, drug and alcohol use) with a six-month recall period.

Participants also receive ongoing HIV Risk Reduction Counseling (RRC) during screening and at follow-up clinic visits. HVTN RRC follows the Center for Disease Control and

Prevention (CDC) Revised Guidelines for HIV Counseling, Testing and Referral [10]. Individuals who present with substance use issues are referred for treatment or counseling.

2.5 Statistical Analysis

Substance use measures were: frequency and amount of alcohol consumed, frequency of binge drinking (≥ 6 alcoholic beverages on one occasion), marijuana use and other drug use. Other drug use included crack cocaine, powder cocaine, amphetamine/methamphetamine, heroin, prescription drugs used for recreational use, Ecstasy, Ketamine, GHB (Gamma Hydroxybutyrate), other hallucinogens, and poppers. These were combined into one variable due to infrequent use in this population. We assessed three measures of adherence/retention: missing at least one protocol-specified clinic visit, not completing the vaccination schedule and early termination from clinic follow-up for any reason including HIV infection. Participants from two trials with only one vaccination time point, synonymous with enrollment, are excluded from the assessment of completion of vaccination. Chi Square tests were used to assess statistical differences between substance use, demographics and retention/adherence measures. Multivariable logistic regression models were used to assess the association between binge drinking and unprotected sex while drunk when controlling for demographics, multiple partners and marijuana use. In addition, analyses were conducted comparing the data collected from the BRA at the screening visit with data from a follow up BRA (FUBRA) conducted at months 5–8 (varying per protocol). Studies that only conducted the BRA at the initial screening visit (HVTN 087 and 094) were excluded from comparison analyses. McNemar's statistical tests were used to compare individual participant behavioral risk assessment data at screening and follow-up. Statistical significance for all tests was defined as a p value <0.05.

3. Results

3.1. Demographics

Within the total sample size of 964 participants, 467 were male (48%) and 497 were female (52%), with a median age of 26 years (interquartile range 22,35). The majority of study participants (n= 667, 69%) were white/Caucasian (Table 2). Fifteen percent identified as black (n=145) and 13% identified as Hispanic (n=127). The majority of the study participants (n=870, 90%) resided in the US, and among US participants, 46% (n=402) resided in the Northeastern US (Table 2). Nineteen percent (n=185) reported unprotected sex while drunk on alcohol and 4% (n=40) while high on drugs (Table 3).

3.2. Substance use at baseline

With regards to substance use patterns reported at screening, 39% (n=182) of female and 49% (n=245) of male participants used alcohol more than once a week (p=0.01, Table 4). Among those reporting any alcohol use, 60% (n=506) had 1–2 drinks on average on days they drank. US participants reported a higher frequency of alcohol use than participants in South America (Brazil and Peru) or Switzerland (p<0.001). Eleven percent (n=109) of study participants reported binge drinking once a month or more frequently. Fifty-six percent (n=199) of those that reported any binge drinking had unprotected sex, compared with 46% (n=275) for participants who reported never engaging in binge drinking (p= 0.001). In

addition, 35% (n=124) of those who binge drank had unprotected sex while drunk compared to 10% (n=61) of non-binge drinkers ($p<0.001$). The association between binge drinking and unprotected sex while drunk was significant after controlling for other significant variables of age, enrolled in US and some marijuana use (adjusted odds ratio=4.6, 95% CI=[3.2,6.7]).

Marijuana use was reported by 22% (n=210) of participants, with statistically significant differences by sex, age and region (all p-values <0.001 , Table 4) but not by ethnicity or race (Table 5); 26% (n=130) of men, 30% (n=139) of those 25 or younger, and 42% (n=14) of participants in the Midwest US reported some marijuana use. Only 21 (2%) of participants reported any other recreational drug use, with most from the Northeast US (n=8) or West Coast (n=8). Other drug use included hallucinogens (n=10), poppers (n=4), heroin (n=2), amphetamines/methamphetamine (n=1), powder cocaine (n=1), or poppers and other drugs (n=3).

3.3 Retention/adherence and substance use

Among the 964 participants, 170 (18%) missed a clinic visit and 78 (8%) terminated early from clinic follow-up. For those studies with more than one vaccination time point (n=774), 75 (10%) did not complete the study vaccination schedule. Neither frequency of alcohol use, binge drinking, marijuana, nor other drug use reported at the screening visit were associated with any of these three adherence/retention measures. Alcohol use when coded as none versus some was inversely correlated with missing at least one clinic visit ($p=0.03$). Of those who did not complete their vaccine schedules, 60 (80%) reported some alcohol use, 24 (32%) reported binge drinking, 14 (19%) used marijuana, and 1 (1%) used other drugs. There were no statistically significant differences in the three retention measures between male and female participants. By region, participants in the Northeast and the Southern US were most likely to have missed visits, 21% (n=84) and 20% (n=52) respectively. ($p=0.003$ for comparison of all regions).

3.4 Screening and Follow-up Behavioral Risk Assessment (FUBRA)

The analysis comparing the screening and FUBRA included 765 participants. Excluded were 148 participants from the 2 protocols with no follow-up assessment, 30 participants who terminated from their respective study prior to the risk assessment follow-up visit, and 21 who missed the visit. There were no appreciable changes in the frequency of alcohol use or binge drinking between the two assessment time points. While frequency of marijuana use was similar at both time points, a slightly higher percentage of participants reported other drug use at follow up (2% (n=17) at screening vs. 4% (n=32) at follow-up, $p=0.01$). Six participants reported other drug use at both time points.

3.5 HIV Acquisition

In the trials included in these analyses, three participants became HIV infected during clinic follow-up. With 854 person years of follow-up, the HIV incidence rate was 0.35% (95% Poisson confidence interval 0.07%, 1.03%). The infected participants were enrolled at different study sites. Their substance use patterns were similar to other participants. On the screening BRA, two reported alcohol use of less than once a week and one less than once per month. All reported binge drinking less than once per month and none reported

unprotected sex while drunk. One reported daily marijuana use and having unprotected sex while high with his only partner. No other drug use was reported.

Discussion

Our findings indicate that engaging in binge drinking behaviors is associated with higher rates of unprotected sex among phase 1 preventive HIV vaccine trial participants, which may have implications in the risk of acquiring HIV [11, 12]. To our knowledge, the implications of binge drinking on HIV risk for individuals with lower HIV risk profiles has not been explored. Currently binge drinking is not listed as a topic for discussion in the RRC training provided to CRS staff for counseling trial participants. During RRC, staff explore the potential risk for HIV/STI acquisition related to alcohol and drug use with a focus on injection practices and sex while under the influence of alcohol and/or illicit substances, and a review of the changes the participant has attempted since the last clinic visit. Although we did not observe an association between binge drinking and HIV infection during follow-up of these phase 1 trials, a focus on binge drinking and increased HIV/STI risk during the RRC sessions even for populations with lower risk profiles may be beneficial in preventing HIV infection over a longer time period.

Given our focus on clinical trial participants with lower risk profiles, it was not surprising that we did not find significant retention issues. Our sample population may explain the discrepancy between our findings among people at lower risk of HIV infection and the literature reporting statistically significant effects of substance use on reductions in retention and medical compliance among HIV infected populations. [3, 6] Several efforts to identify factors that contribute to higher HIV risk have provided valuable guidance in determining the appropriate assessment of high-risk substance use. [13–15] The screening data and the low infection rate of participants during the trial period indicate that the selected eligibility criteria, the screening process and the RRC utilized by the HVTN have largely been successful in enrolling and retaining individuals with lower risk profiles into phase 1 preventive HIV vaccine clinical trials.

The study is not without limitations that need consideration. First, the current low risk criterion for enrollment limits the range of substance use we would see among phase 1 trial participants as self-reported chronic users would be screened out. Second, while all participants completed a BRA at screening, not all have subsequent FUBRA. Thus while we mainly assessed patterns based on the screening data, the cross-sectional nature of the screening BRA does not allow us to look at changes over time and how that may impact retention variables. The BRA itself also has several limitations; it does not differentiate between casual and main partners and the recall of 6 months is not ideal. A shorter recall period and the use of memory aids such as diaries have been found to increase the accuracy of HIV behavioral risk data.[16] In addition, stigma associated with sexual risk and substance use behaviors may limit willingness to disclose and result in underreporting of this sensitive information.[17, 18]

Given the low rates of drug use and multiple vaccine regimens evaluated in the trials included in our analyses, we were not able to evaluate the relationship between substance

use and immune response, a topic that warrants further study. The recreational use of legal and illegal drugs has been shown to have significant effects on immune responses and can thus potentially affect susceptibility to HIV infection. [19–21]. Therefore, drugs of abuse could have significant and potentially adverse effects on vaccination efficacy [19].

1. Conclusions

Our study supports the effectiveness of the screening protocols utilized across the HVTN to enroll individuals with a lower HIV risk substance use profile into phase I preventative HIV vaccine trials. Use of eligibility criteria that allow for light to moderate alcohol and marijuana use did not negatively impact adherence or retention. Following enrollment, the RRC procedures used throughout the trials seem to be effective in ensuring that these lower-risk individuals maintain low risk substance use behaviors while participating in the trial. In addition to continuation of the current RRC, our data supports the need for other supportive practices, specifically content and education regarding the link between binge drinking and HIV/STI risk.

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Abbreviations

HVTN	HIV Vaccine Trials Network
CRSs	Clinical Research Sites
RRC	Risk Reduction Counseling
BRA	Behavioral risk assessment
FUBRA	Follow-up Behavioral Risk Assessment

References

1. Dyer TV, Khan MR, Sandoval M, Acheampong A, Regan R, Bolyard M, et al. Drug Use and Sexual HIV Transmission Risk Among Men Who have Sex with Men and Women (MSMW), Men Who have Sex with Men only (MSMO), and Men Who have Sex with Women Only (MSWO) and the Female Partners of MSMW and MSWO: A Network Perspective. *AIDS Behav.* 2017; doi: 10.1007/s10461-017-1736-3
2. Zhang X, Wu L. Marijuana use and sex with multiple partners among lesbian, gay and bisexual youth: results from a national sample. *BMC Public Health.* 2017; :1–8. DOI: 10.1186/s12889-016-3905-0

3. Knox J, Reddy V, Lane T, Hasin D, Sandfort T. Substance Use and Sexual Risk Behavior Among Black South African Men Who Have Sex With Men: The Moderating Effects of Reasons for Drinking and Safer Sex Intentions. *AIDS Behav.* 2016; doi: 10.1007/s10461-016-1652-y
4. Harawa NT, McCuller WJ, Chavers C. HIV risk behaviors among Black/African American and Hispanic/Latina female partners of men who have sex with men and women. *AIDS Behav.* 2013; 17:848–55. doi:1007/s10461-012-0138-9. [PubMed: 22290608]
5. Center for Behavioral Health Statistics and Quality. [Last accessed April 2017] Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health. HHS Publ No SMA 16-4984, NSDUH Ser H-51. n.d. <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.htm>
6. Pecoraro A, Royer-Malvestuto C, Rosenwasser B, Moore K, Howell A, Ma M, et al. Factors contributing to dropping out from and returning to HIV treatment in an inner city primary care HIV clinic in the United States. *AIDS Care.* 2013; 25:1399–406. DOI: 10.1080/09540121.2013.772273 [PubMed: 23428205]
7. Zweben A, Fucito LM, O'Malley SS. Effective Strategies for Maintaining Research Participation in Clinical Trials. *Ther Innov Regul Sci.* 2009; 43:459–67. DOI: 10.1177/009286150904300411
8. Novak RM, Metch B, Buchbinder S, Cabello R, Donastorg Y, Figoroa J-P, et al. Risk Behavior among Women enrolled in a Randomized Controlled Efficacy Trial of an Adenoviral Vector Vaccine to Prevent HIV Acquisition: the Step Study NIH Public Access. *AIDS* July. 2013; 17:1763–70. DOI: 10.1097/QAD.0b013e328360c83e
9. National Institute of Alcohol Abuse and Alcoholism. [Accessed November 2016] NIAAA council approves definition of binge drinking. NIAAA Newsl. 2004. No 3, P 3 n.d. <https://pubs.niaaa.nih.gov/publications/AlcoholFacts&Stats/AlcoholFacts&Stats.htm>
10. Centers for Disease Control and Prevention. Revised guidelines for HIV counseling, testing, and referral. *MMWR Recomm Reports Morb Mortal Wkly Report Recomm Reports.* 2001; 50:1–57. [Accessed November 2016] quiz CE1–19a1–CE6–19a1. <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5019a1.htm>.
11. Keen L, Dyer TP, Whitehead NE, Latimer W. Binge drinking, stimulant use and HIV risk in a sample of illicit drug using heterosexual Black men. *Addict Behav.* 2014; 39:1342–5. DOI: 10.1016/j.addbeh.2014.04.006 [PubMed: 24837758]
12. Wen XJ, Balluz L, Town M. Prevalence of HIV risk behaviors between binge drinkers and non-binge drinkers aged 18-to 64-years in US, 2008. *J Community Health.* 2012; 37:72–9. DOI: 10.1007/s10900-011-9418-y [PubMed: 21643823]
13. Balkus JE, Brown E, Palanee T, Nair G, Gafoor Z, Zhang J, Richardson BA, Chirenje ZM, Marrazzo JM, Baeten JM. An Empiric HIV Risk Scoring Tool to Predict HIV-1 Acquisition in African women. *J Acquir Immune Defic Syndr.* 2016; 72(3):333–43. [PubMed: 26918545]
14. Menza TW, Hughes JP, Celum CL, Goldern MR. Predution of HIV Acquisition Among Men Who Have Sex with Men. *Sexually Transmitted Diseases.* 2009; 36(9):547–555. n.d. [PubMed: 19707108]
15. Smith DK, Pals SL, Herbst JH, Shinde S, Carey JW. Development of a Clinical Screening Index Predictive of Incident HIV Infection Among Men Who Have Sex With Men in the United States. *J Acquir Immune Defic Syndr.* 2012; 60(4):421–7. [PubMed: 22487585]
16. Graham CA, Catania JA, Brand R, Duong T, Canchola JA. Recalling sexual behavior: a methodological analysis of memory recall bias via interview using the diary as the gold standard. *J Sex Res.* 2003 Nov; 40(4):325–32. [PubMed: 14735406]
17. Latkin CA, Mai NVST, et al. Social desirability response bias and other factors that may influence self-reports of substance use and HIV risk behaviors: A qualitative study in Vietnam. *AIDS Educ Prev.* 2016 Oct; 28(5):417–25. [PubMed: 27710083]
18. Rao A, Tobin K, Davey-Rothwell MLC. Social Desirability bias and prevalence of sexual HIV risk behaviors among people who use drugs in Baltimore, Maryland: Implications for identifying individuals prone to underreporting sexual risk behaviors. *AIDS Behav.* 2017 Jul; 21(7):2207–14. [PubMed: 28509997]

19. Ugen KE, Nyland SB. Injecting drugs of abuse and immunity: Implications for HIV vaccine testing and efficacy. *Springer Semin Immunopathol.* 2006; 28:281–7. DOI: 10.1007/s00281-006-0045-0 [PubMed: 17109182]
20. Friedman H, Newton CKT. Microbial infections, immunomodulation, and drugs of abuse. *Clin Microbiol Rev.* 2003; 16:209–219. [PubMed: 12692094]
21. Friedman H, Pross SKT. Addictive drugs and their relationship with infectious diseases. *FEMS Immunol Med Microbiol.* 2006; 47:330–342. [PubMed: 16872369]

Table 1

HVTN protocols and clinical trial details.

Protocol	Vaccine regimens ¹	Number of vaccinations	Vaccine schedule	Duration of clinic follow-up, LTFU	Regions ²
HVTN 076	DNA plasmid vaccine prime followed by an HIV-1 recombinant adenoviral type 5 (rAd5) vector boost	4	mo0, mo1, mo2, mo6	12mo, up to 5 yr LTFU	WC
HVTN 077	Recombinant adenoviral serotype 35 (rAd35) and serotype 5 (rAd5) HIV-1 vaccines given as a heterologous prime-boost regimen or as boosts to a recombinant DNA vaccine	Group 1: 2 Groups 2–4: 4	Group 1: mo0, mo6 Group 2–4: mo0, mo1, mo2, mo6	12mo, up to 18mo LTFU	NE, South, WC,
HVTN 083	Heterologous prime-boost regimens utilizing rAd35 with HIV-1 clade A Env insert and rAd5 with HIV-1 clade A or B Env inserts	2	mo0, mo3	9mo, up to 5 yr LTFU	NE, South, WC
HVTN 084	A comparison of rAd5 gag/pol Env A/B/C to rAd5 gag/pol	1	mo0	6mo, up to 5 yr LTFU	NE, South America, Switzerland
HVTN 085	Polytropic administration of VRC rAd5 gag-pol/env A/B/C vaccine	1	mo0	7mo, up to 5 yr LTFU	Midwest, NE, South, WC
HVTN 087	IL-12 pDNA enhanced HIV-1 multiantigen pDNA vaccine delivered intramuscularly with electroporation, with an HIV-1 rVSV vectored vaccine boost	Group 1, 3: 4 Group 2, 4: 4	Group 1, 3: mo0, mo1, mo3, mo6 Group 2–4: mo0, mo1, mo3, mo6	15mo, up to 3 yr LTFU	NE, South
HVTN 088	HIV-1 subtype C gp140 vaccine with moF59 adjuvant in healthy, HIV-1 uninfected adult participants previously primed or unprimed with HIV-1 subtype B envelope subunit vaccines with MF59	Group 1: 2 Group 2: 2	Group 1: mo0, mo6 Group 2: mo0, mo6	18mo, up to 5 yr LTFU	South, WC
HVTN 090	VSV _{IN} HIV gag vaccine	2	mo0, mo2	8mo, up to 3 yr LTFU	NE, South, WC
HVTN 092	3 DNA vaccine prime schedules followed by a NYVAC vectored vaccine boost	Group 1: 3 Group 2: 3	Group 1: mo0, mo0.5, mo1 Group 2: mo0, mo0.5, mo1	Group 1: 8mo, up to 5 yr LTFU Group 2, 3: 9mo, up to 5 yr LTFU	Midwest, NE, South, WC
HVTN 094	A prime-boost vaccine regimen of GEO-D03 DNA and MVA/HIV62B vaccines	Group 3: 3 Group 4: 4 Group 1: 5 Group 2: 5 Group 3: 4	Group 3: mo0, mo0.5, mo3 Group 4: mo0, mo1, mo2, mo5 Group 1: mo0, mo2, mo4, mo6, mo8 Group 2: mo0, mo2, mo4, mo6, mo10 Group 3: mo0, mo2, mo4, mo8	Group 4: 11mo, up to 5 yr LTFU Group 1, 3: 14mo, up to 3 yr LTFU Group 2: 16mo, up to 3 yr LTFU	NE, South, WC

Abbreviations: mo = month; LTFU = long term follow-up; NE = Northeast of US; WC = West Coast of US.

¹ All included studies are phase I studies conducted in healthy HIV seronegative individuals at low risk of HIV acquisition.

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Region “South America”, included study sites in Iquitos, Peru; Lima, Peru; and Sao Paulo, Brazil. Region “West Coast”, included study sites in San Francisco, California and Seattle, Washington. Region “Midwest” had one study site in Chicago, Illinois. Region “South”, included study sites in Atlanta, Georgia; Birmingham, Alabama; Nashville, Tennessee. Region “Northeast” included study sites in Boston, Massachusetts; New York and Rochester, New York; and Philadelphia, Pennsylvania.

Table 2

Participant characteristics by sex

	Female	Male	Total	p-value ^I
Total	467	497	964	
Age				0.02
18–21	120 (25.7%)	99 (19.9%)	219 (22.7%)	
22–25	131 (28.1%)	117 (23.5%)	248 (25.7%)	
26–35	117 (25.1%)	150 (30.2%)	267 (27.7%)	
36–54	99 (21.2%)	131 (26.4%)	230 (23.9%)	
Race²				0.003
Asian	23 (4.9%)	18 (3.6%)	41 (4.3%)	
Black	56 (12.0%)	89 (17.9%)	145 (15.0%)	
Multiracial	23 (4.9%)	18 (3.6%)	41 (4.3%)	
Native American/Alaskan	1 (0.2%)	1 (0.2%)	2 (0.2%)	
Native				
Native Hawaiian/Pacific Island	1 (0.2%)	2 (0.4%)	3 (0.3%)	
White	319 (68.3%)	348 (70.0%)	667 (69.2%)	
Other	44 (9.4%)	21 (4.2%)	65 (6.7%)	
Hispanic				0.003
Yes	77 (16.5%)	50 (10.1%)	127 (13.2%)	
No	390 (83.5%)	447 (89.9%)	837 (86.8%)	
Region				<0.0001
US, Northeast	163 (34.9%)	239 (48.1%)	402 (41.7%)	
US, Midwest	16 (3.4%)	17 (3.4%)	33 (3.4%)	
US, South	122 (26.1%)	134 (27.0%)	256 (26.6%)	
US, West Coast	87 (18.6%)	92 (18.5%)	179 (18.6%)	
South America	33 (7.1%)	5 (1.0%)	38 (3.9%)	
Switzerland	46 (9.9%)	10 (2.0%)	56 (5.8%)	

^I All p-values are from chi square test² For chi square statistical analysis, “Native American/Alaskan Native” and “Native Hawaiian/Pacific Island” were merged into “Other” to make the test valid

Table 3Sexual risk behaviors by sex¹

	Female	Male	Total	p-value ²
Total	467	497	964	
Total Partners				0.34
0	128 (27.5%)	130 (26.2%)	258 (26.8%)	
1	293 (63.0%)	313 (63.1%)	606 (63.1%)	
2	32 (6.9%)	47 (9.5%)	79 (8.2%)	
3	10 (2.2%)	5 (1.0%)	15 (1.6%)	
4	2 (0.4%)	1 (0.2%)	3 (0.3%)	
Missing	2	1	3	
Unprotected Sex				0.61
Yes	234 (50.4%)	240 (48.8%)	474 (49.6%)	
No	230 (49.6%)	252 (51.2%)	482 (50.4%)	
Missing	3	5	8	
Unprotected Sex while Drunk on Alcohol				0.02
Yes	75 (16.2%)	110 (22.2%)	185 (19.3%)	
No	387 (83.8%)	385 (77.8%)	772 (80.7%)	
Missing	5	2	7	
Unprotected Sex while High on Drugs				0.02
Yes	12 (2.6%)	28 (5.7%)	40 (4.2%)	
No	453 (97.4%)	467 (94.3%)	920 (95.8%)	
Missing	2	2	4	
Anal Sex				<.001
Yes	44 (9.5%)	152 (30.6%)	196 (20.4%)	
No	420 (90.5%)	344 (69.4%)	764 (79.6%)	
Missing	3	1	4	
Anal Sex with Male Partner				<.001
Yes	44 (9.5%)	132 (26.6%)	176 (18.3%)	
No	420 (90.5%)	364 (73.4%)	784 (81.7%)	
Missing	3	1	4	

¹ Behaviors self reported as occurring in the six months prior to screening.² All p-values are from chi square tests

Table 4Substance use by sex and by age¹

	Sex		Age				p-value ²	Total	
	Female	Male	18–21	22–25	26–35	36–54			
Total	467	497	219	248	267	230		964	
Alcohol Frequency							0.01		
Never	63 (13.5%)	62 (12.5%)	35 (16.0%)	19 (7.7%)	27 (10.1%)	44 (19.1%)		125 (13.0%)	
< once/month	80 (17.1%)	61 (12.3%)	51 (23.3%)	25 (10.1%)	28 (10.5%)	37 (16.1%)		141 (14.6%)	
< once/week	142 (30.4%)	129 (26.0%)	72 (32.9%)	70 (28.2%)	76 (28.5%)	53 (23.0%)		271 (28.1%)	
>= once/week	182 (39.0%)	245 (49.3%)	61 (27.9%)	134 (54.0%)	136 (50.9%)	96 (41.7%)		427 (44.3%)	
Alcohol Amount³							< 0.001		
None	63 (13.5%)	62 (12.5%)	35 (16.0%)	19 (7.7%)	27 (10.2%)	44 (19.1%)		125 (13.0%)	
1–2 drinks	274 (58.8%)	232 (46.7%)	88 (40.2%)	129 (52.0%)	154 (57.9%)	135 (58.7%)		506 (52.5%)	
3–4 drinks	115 (24.7%)	159 (32.0%)	76 (34.7%)	81 (32.7%)	70 (26.3%)	47 (20.4%)		274 (28.5%)	
5 or more drinks	14 (3.0%)	44 (8.9%)	20 (9.1%)	19 (7.7%)	15 (5.6%)	4 (1.7%)		58 (6.0%)	
Missing.	1	0	0	0	1	0		1	
Binge Drinking⁴							< 0.001		
Never	326 (69.8%)	280 (56.3%)	131 (59.8%)	121 (48.8%)	162 (60.7%)	192 (83.5%)		606 (62.9%)	
< once/month	120 (25.7%)	129 (26.0%)	67 (30.6%)	85 (34.3%)	71 (26.6%)	26 (11.3%)		249 (25.8%)	
< once/week	20 (4.3%)	75 (15.1%)	18 (8.2%)	36 (14.5%)	31 (11.6%)	10 (4.3%)		95 (9.9%)	
>= once/week	1 (0.2%)	13 (2.6%)	3 (1.4%)	6 (2.4%)	3 (1.1%)	2 (0.9%)		14 (1.5%)	
Marijuana Use							0.001		
Yes	80 (17.2%)	130 (26.3%)	65 (29.7%)	74 (30.0%)	50 (18.7%)	21 (9.3%)		210 (21.9%)	
No	386 (82.8%)	364 (73.7%)	154 (70.3%)	173 (70.0%)	217 (81.3%)	206 (90.7%)		750 (78.1%)	
Missing	1	3	0	1	0	3		4	
Other Drug Use							0.16		
Yes	7 (1.5%)	14 (2.9%)	8 (3.7%)	7 (2.9%)	1 (0.4%)	5 (2.2%)		21 (2.2%)	
No	458 (98.5%)	477 (97.1%)	208 (96.3%)	238 (97.1%)	266 (99.6%)	223 (97.8%)		935 (97.8%)	
Missing	2	6	3	3	0	2		8	

¹ Substance use self reported as occurring in the six months prior to screening.

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² p-values are from Chi-square tests³ A drink is considered: 12 ounces of beer (one can), 5 ounces of wine (one glass), or 1.5 ounces of hard liquor (one shot).⁴ Binge drinking is defined as 5 or more drinks in about 2 hours for men and 4 or more for women in 2 hours for women

Table 5

Substance use by ethnicity and race[/]

	Ethnicity		Race						p-value ²	Total
	Hispanic	p-value ¹	White	Black	Asian	Multiracial	Other			
Total	127		667	145	41	41	70		964	
Alcohol Frequency		< 0.001						< 0.001		
Never	20 (15.7%)		58 (8.7%)	37 (25.5%)	6 (14.6%)	10 (24.4%)	14 (20.0%)		125 (13.0%)	
< once/month	35 (27.6%)		71 (10.6%)	26 (17.9%)	12 (29.3%)	4 (9.8%)	28 (40.0%)		141 (14.6%)	
<once/week	33 (26.0%)		189 (28.3%)	40 (27.6%)	12 (29.3%)	14 (34.1%)	16 (22.9%)		271 (28.1%)	
>= once/week	39 (30.7%)		349 (52.3%)	42 (29.0%)	11 (26.8%)	13 (31.7%)	12 (17.1%)		427 (44.3%)	
Alcohol Amount ³		0.17						< 0.001		
None	20 (15.7%)		58 (8.7%)	37 (25.5%)	6 (14.6%)	10 (25.0%)	14 (20.0%)		125 (13.0%)	
1–2 drinks	58 (45.7%)		367 (55.0%)	63 (43.4%)	24 (58.5%)	18 (45.0%)	34 (48.6%)		506 (52.5%)	
3–4 drinks	37 (29.1%)		204 (30.6%)	31 (21.4%)	10 (24.4%)	12 (30.0%)	17 (24.3%)		274 (28.5%)	
5 or more drinks	12 (9.4%)		38 (5.7%)	14 (9.7%)	1 (2.4%)	0 (0.0%)	5 (7.1%)		58 (6.0%)	
Missing	0		0	0	0	1	0		0	
Binge Drinking ⁴		0.68						< 0.001		
Never	82 (64.6%)		378 (56.7%)	115 (79.3%)	32 (78.0%)	28 (68.3%)	53 (75.7%)		606 (62.9%)	
< once/month	32 (25.2%)		203 (30.4%)	16 (11.0%)	8 (19.5%)	8 (19.5%)	14 (20.0%)		249 (25.8%)	
<once/week	10 (7.9%)		79 (11.8%)	9 (6.2%)	1 (2.4%)	5 (12.2%)	1 (1.4%)		95 (9.9%)	
>= once/week	3 (2.4%)		7 (1.0%)	5 (3.4%)	0 (0.0%)	0 (0.0%)	2 (2.9%)		14 (1.5%)	
Marijuana Use		0.86						< 0.001		
Yes	27 (21.3%)		161 (24.3%)	26 (17.9%)	6 (14.6%)	8 (19.5%)	9 (12.9%)		210 (21.9%)	
No	100 (78.7%)		502 (75.7%)	119 (82.1%)	35 (85.4%)	33 (80.5%)	61 (87.1%)		750 (78.1%)	
Missing	0		4	0	0	0	0		4	
Other Drug Use		0.89						0.29		
Yes	3 (2.4%)		17 (2.6%)	1 (0.7%)	1 (2.5%)	2 (4.9%)	0 (0.0%)		21 (2.2%)	
No	124 (97.6%)		643 (97.4%)	144 (99.3%)	39 (97.5%)	39 (95.1%)	70 (100.0%)		935 (97.8%)	
Missing	0		7	0	1	0	0		8	

[/] Substance use self reported as occurring in the six months prior to screening;

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² p-values are from Chi-square tests;

³ A drink is considered: 12 ounces of beer (one can), 5 ounces of wine (one glass), or 1.5 ounces of hard liquor (one shot);

⁴ Binge drinking is defined as 5 or more drinks in about 2 hours for men and 4 or more for women in 2 hours for women.