Social harms and benefits reported by HIV Vaccine Trial Network(HVTN) participants across different countries.

Fredericka Albertina Sesay

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Michele Andrasik

Herbie Duber

Barbara Metch

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University of Washington

Abstract

Fredericka Albertina Sesay

Social harms and benefits reported by HIV Vaccine Trial Network(HVTN) participants across different countries.

Chair of the Supervisory Committee:

Michele Andrasik

Department of Global Health

HIV vaccine trials bring to the limelight socio-behavioural issues that extend beyond the borders of traditional vaccine trials but, there is a dearth of knowledge on these issues. This study employed a cross protocol approach, using data from 51 closed protocols across HIV Vaccine Trial Network (HVTN) sites in thirteen countries. A total of 937 social harms were reported by 789 (7.5%) of 10,483 participants. The most common reported event was problems with personal relationship (n=704, 75.1%). Issues with insurance, education, housing, travel/immigration, and military/government agencies were minimal (<10 events). Most events (n=656, 70%) were considered resolved by the end of study. Logistic regression analysis showed that sex and age were not significantly associated with reporting a social harm, whereas region, participants' study phase and treatment group were significant predictors. A total of 6,562 participants reported at least one benefit at first assessment and the most common benefit reported was helping others/altruism(n=3,100). Age and treatment group were not associated with reporting at least one benefit. However, there were significant differences by regions, sex and study phase. Our study showed that the reporting of social harms was low across HVTN sites while a high number of participants reported benefit.

INTRODUCTION

HIV EPIDEMIOLOGY

Human immunodeficiency virus (HIV) causes Acquired Immunodeficiency Syndrome (AIDS). HIV attacks CD4 cells in the immune system which are vital in fighting infections leaving the body susceptible to opportunistic infections and malignancies. There are approximately 36.7 million people worldwide presently living with HIV/AIDS, 34.5 million of whom are adults.[1]Females are more affected than males, accounting for 51% of people living with HIV/AIDS.[2] The vast majority of people affected are living in low and middle-income countries, particularly in sub-Saharan Africa. Sub-Saharan Africa accounts for two thirds of the global burden of new HIV infections and in 2015, there were 25.6 million people living with HIV in these countries. [3]At the end of 2016, there were 1.8 million new infections of HIV globally and 1 million deaths from AIDS related causes. AIDS-related illnesses are the leading cause of deaths among women aged 15-49 years globally.[1] The present way in which statistics are collected classifies adolescents 15 years old and older as adults which has been criticized by some arguing that adolescence is a unique period with significant differences from adulthood.[4,5]

Heterosexual transmission remains the principal route of transmission while maternal to child transmission is responsible for almost all new HIV infections in children.[4] In countries with a high prevalence of HIV, young women are at an alarming high risk of HIV infection. In countries with low prevalence of HIV, marginalized populations which include injection drug users, commercial sex workers, men who have

sex with men, racial and ethnic minorities, gender non-conforming individuals and incarcerated individuals are disproportionately impacted by the epidemic.[1]

Increase in the use of antiretroviral therapy (ART) has been the main reason for the almost 50% reduction in deaths from AIDS related causes in the past 11 years.[2] Although ART can control the virus and reduce risk of transmission, it does not eliminate the virus from an individual's system and does not cure the disease.[6] This underscores the importance of developing a vaccine that prevents individuals from acquiring the virus. Completely eliminating the HIV virus would be difficult if not impossible to achieve without a prophylactic vaccine component.[4]

HIV VACCINE TRIAL RESEARCH

All vaccines go through different phases of clinical trials before they are licensed for use. Phase 1 trials are done to test safety in a small number of healthy participants who exhibit low HIV risk profiles. Phase 2a trials involve a greater number of individuals, typically with low risk profiles, and test safety and immunogenicity. For HIV vaccine trials, phase 2b trials enrolling individuals with high HIV risk profiles are employed as small-scale efficacy studies with lesser power than phase 3; these are also called proof of concept trials. Phase 3 trials assess the efficacy of the vaccine in many individuals with high risk profiles and phase 4 involves post-marketing surveillance.[7,8]

HIV vaccine trials started in the United States (US) in 1987, since then over 100 preventive candidate vaccines have been through phase 1 clinical trials in different parts of the world.[4,9] Some candidates made it to phase 2a trials but only a handful have shown enough promise to progress to phase 2b or phase 3 trials for efficacy.[10] Many candidate vaccines were safe and produced immune responses against the HIV virus to varying degrees.[4,11] This made possible the first phase 3 HIV vaccine trials of

AIDSVAX in the US in 1998 and in Thailand in 1999 with other candidates following suit in the ensuing years.[11] However, only one candidate has showed modest efficacy while the rest did not show efficacy. In one trial, increased risk of HIV infection was observed.[4]

Different collaborating bodies have been formed that have played key roles in vaccine development to date. The AIDS Vaccine Evaluation Group (AVEG) sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) was established in 1988 and was the first network funded in the US to conduct HIV vaccine research.[12] The HIV Prevention Trials Network (HIVNET) was instituted in 1993 to oversee HIV prevention trials both in the US and internationally. In 2000 under a reconfiguration of NIH funding for HIV prevention research, the HIV Vaccine Trials Network (HVTN) was established to oversee most preventative HIV vaccine clinical trials funded by NIAID. Since its inception, the HVTN has significantly expanded trials within international territories. [11]

The race to develop the ideal HIV vaccine candidate has been fraught with numerous difficulties. The number of different viral strains pose a challenge in addition to limited knowledge on unequivocal immune correlates of protection in humans.[13] In recent years, HIV vaccine development has seen tremendous advances and data from preventive HIV vaccine trials has driven innovation in the vaccine field in general. Results showing that the pairing of two vaccines (ALVAC-HIV and AIDSVAX B/E) decreased HIV infection rates by 31% gives hope that an effective vaccine is scientifically possible and has led to enhanced efforts to develop the ideal vaccine candididate.[14]

WHY HIV VACCINE

In the face of new modalities like Pre-Exposure Prophylaxis (PrEP), Post-Exposure Prophylaxis (PEP) and microbicides coupled with HIV prevention programs already in place, some people wonder whether there is still a need for a vaccine.[4] There are many international bodies working in partnership with local institutions worldwide to stem the HIV epidemic and there has been remarkable progress.[1,15] The concerted effort towards HIV prevention and treatment has ultimately led to reduction in transmission of the disease. This drop in new HIV infection globally is, however, not on track to meet the target set by the United Nations general assembly of less than 500,000 new infections yearly by 2020. Moreover, in eastern Europe and central Asia, the number of new infections between 2010 and 2016 rose by a shocking 60%.[1] In addition, there is no success story in any country where the epidemic has been contained or eliminated.[4] In the scientific community, there is a growing consensus that ART and prevention strategies dependent on behaviour change alone are insufficient to control the HIV epidemic and that vaccines provide the greatest prospect of stopping transmission and infection, making vaccine development a public health priority.[11,13,16]

We know that vaccines have achieved elimination[a] of a number of communicable diseases and even eradication[b] in the case of small pox. Therefore, it is possible that an effective HIV vaccine would be the most promising option of controlling the epidemic on a global scale.[4] Furthermore vaccines are the only prevention method that is not overly reliant on continuous behaviour modification.[4] It is not expected that initial HIV vaccines will be highly efficacious but even one that is

[a] Elimination-Reduction to zero of the incidence of a specified disease in a defined geographical area because of deliberate efforts; continued intervention measures are required.

[b] Eradication- Permanent reduction to zero of the worldwide incidence of infection caused by a specific agent because of deliberate efforts; intervention measures are no longer needed.[17]

moderately efficacious may prove beneficial in a population with high vulnerability to HIV.[18,19]

SOCIAL ISSUES ASSOCIATED WITH HIV VACCINE TRIALS

HIV vaccine trials are faced with unique challenges given the stigma and misconceptions of the disease worldwide. These trials bring to light social and behavioural issues that extend beyond the borders of traditional vaccine trials.[20] Even with licensed vaccines for diseases not plagued with stigma and discrimination, there is historical underutilization by those in need. The Human Papilloma Virus vaccine is a classic example of how a much anticipated vaccine can be underutilized when it is finally licensed.[21] Because HIV vaccine development is ongoing and will continue for many years requiring thousands of volunteers,[22] it is critical to explore barriers and facilitators to trial participation while researching associated social harms to ensure that they are addressed and highlighting social benefits to guarantee that the right information is provided and that trials are conducted in the most ethical way.[23]

Social harms related to HIV vaccine trial participation include impact on personal relationships and stigma or discrimination resulting from disclosure of vaccine trial participation and in rare instances loss of livelihood and insurance related to vaccine induced seropositivity (VISP).[24,25] Vaccine trial participants may also have a false sense of protection against HIV, leading them to engage in more risky sexual behaviors.[26-28] This potential for behavioural change is referred to as risk compensation. There have been mixed results regarding risk compensation reported in HIV prevention studies. Some studies have not observed it;[13,29] other studies have reported a decrease in risk behaviour;[13,30] whereas, risk compensation has been demonstrated among users of newer HIV prevention techniques like PrEP and male circumcision.[31] PrEP and male

circumcision can be a component of some HIV vaccine trials. In addition, the consent process for HIV vaccine trials has been questioned especially when it applies to vulnerable populations. Power dynamics between research agencies and participants, accompanied by communication barriers in some cases, make it difficult to know if participants fully understood the consent process.[32] Amidst all this it is important not to lose sight of the social benefits that arise for participants who may want to make a meaningful contribution to health.[13,33]

SOCIAL HARMS

The problems HIV vaccine participants face in different spheres of their lives related to trial participation are referred to by different terms including social harm, adverse social events and trial related discrimination. 'Social harm'[c] refers to negative trial-related experiences by a study participant which manifest in psychological, social or physical ways. These include, but are not limited to, stigma and discrimination.[34]

Social harms have been documented across different studies and are not limited to populations with increased vulnerability to HIV. Low risk participants in the US and developing countries have similarly been impacted. Although social harms are not frequently encountered and rarely life-altering,[13] the way they are dealt with when they do occur is important. One study found that participants' willingness to participate in HIV trials was influenced by what they hear about trial participation.[22] Meaning any social harm experienced can be a deterrent to the next person especially if not handled well. Across most studies assessing willingness to participate in an HIV vaccine trial,

[c] Social harm is used to refer to negative experiences throughout this work and social impact is used to refer to both positive and negative experiences.

the potential for social harms consistently ranks high as a deterrent from participation and may override altruistic motives.[19,20,35]

AIDS Vaccine Evaluation Group (AVEG) conducted a confidential survey in 1994 of HIV vaccine trial participants and found that over 20% reported a social harm many of which were not major.[36] A study done in Thailand among low risk participants similarly found that 20% of participants encountered negative reactions from loved ones due to trial participation. These reactions were often due to friends and family assuming that the participant was likely infected with HIV for participation in the trial and fear of the vaccine itself.[37] A later study done by AVEG in 2001 with a higher number of participants found that 5% experienced trial related discrimination with some participants having multiple encounters. Over 50% of these issues were marked as resolved by the end of the study.[38] Pitisuttithum et al (2007) researched social harms among 2,546 injection drug users enrolled in an HIV vaccine trial in Thailand. Participants were encouraged to report a social harm when it occurred although it was not actively solicited. An interview using a standard questionnaire followed each report of social harm. Thirty-seven participants reported at least one social harm, 85% of which were disruptions in personal life and the rest in employment and health. All of these issues were resolved by the end of the study.[9]

In Tanzania, Tarimo et al (2014) studied the persistence of social harms by conducting a longitudinal cohort study following participants 2-3 years after their second dose of HIV vaccine and found that low risk participants continued facing negative reactions even after completion of trial participation.[39] These reactions were related to stigma and discrimination from friends, relatives and colleagues. Another study conducted in Kenya, Uganda, Rwanda and South Africa which recruited low risk volunteers found that 42% of participants reported at least one social harm while the

majority reported social benefits in relation to their feelings about themselves and the HIV epidemic[40]

Although there are many studies on willingness to participate in HIV trials, there is a dearth of knowledge on social harms resulting from trial participation. This lack of information is even worse for certain regions like sub-Saharan Africa where most HIV cases are found.[35,41] Furthermore some of the studies conducted have been limited by small sample size and choice of study design (e.g., retrospective in nature, anonymous convenience sampling).[38] One of the recommendations put forward from an HIV Behavioural and Social Science (BSS) HIV vaccine clinical research conference report in 2011[23] was the monitoring of social harms and conducting post study analyses to add to existing knowledge and serve as a resource for future conduct of research. Documentation of these issues will facilitate better planning in anticipation of them and better management when they occur.[23]

HISTORY OF SOCIAL HARM DATA COLLECTION

Since the late 1980's when preventive HIV vaccine research started, social harm has been a worry for researchers and policy makers; therefore, NIAID in the US anticipated such issues and put mechanisms in place to address them when they arose. These measures included providing identification cards for participants to confirm their participation in an HIV vaccine trial if the need arises, a toll-free number to provide support, outreach to insurance companies and sensitization of the general public on the safety of the vaccine.[24,25]

There was no standardized tool for collecting data on social harms however until 1995 and until then only anecdotal reports on social harms were available. A tool was developed following recommendation from an external review of all HIV vaccine

networks that received funding from NIAID. It has gone through several amendments due to expanding knowledge on the topic of social harms. It is now standard practice to collect data on social harms for all NIAID, HVTN and Vaccine Research Centre (VRC) sponsored HIV vaccine trials. The frequency of data collection varies by protocol and reports are reviewed by NIAID medical officers and addressed on an individual basis.[24]

Social harms assessment instruments differ slightly across trials, but they all measure social harms in different areas of life, their impact on the participants' quality of life and the resolution status at the end of the study. Data across different trials can therefore be compared because of these similarities.[24]

TYPES OF SOCIAL HARMS

Classifying social harms is a challenge as there is a lot of overlap between them, Milford et al (2007) nevertheless categorized social harms as occurring due to (1) misperceptions and false beliefs of others; (2) trial participation itself; (3) misunderstandings of trial participants resulting in individual changes in risk behaviour; and (4) Vaccine Induced Seropositivity (VISP), a condition in which a participant has a positive HIV test result on a commercially available diagnostic test due to the presence of antibodies generated by an HIV vaccine. These categories are not mutually exclusive and social harms are not restricted to this list.[34]

Misperceptions and false beliefs of others

Misperceptions by others including the notion that all HIV trial participants are HIV positive or at high risk of infection and that VISP indicates true infection can strain personal and professional relationships and lead to stigma and discrimination. In extreme cases, stigma can lead to marginalisation and ostracism.[34,35,41]

There have been reports of participants being feared, treated with distrust and suffering negative reactions from friends, family and other acquaintances. In intimate relationships, reports of refusal to engage in sexual activities and general relationship stress have been documented and may affect the emotional well-being of participants.[42] Participants whose involvement in an HIV vaccine trial became known to friends and family have sometimes been assumed to be HIV positive and therefore criticized, avoided and/or treated differently.[35,42]

Trial participation itself

At any stage of HIV vaccine trial participation, participants may be exposed to increased levels of physical and emotional stress. They must make several visits to the trial site and undergo repeated HIV testing in addition to other minor procedures. Having to discuss personal details and health habits including risky behaviour in addition to repeatedly receiving HIV test results can be overwhelming and frightening especially for participants with higher risk profiles. Fear of HIV testing was one of the deterrents to trial participation in Kenya, largely because respondents feared possible disclosure of positive results to the community would result in stigma.[41] Furthermore, vaccine trial participation may continue for many years taking a toll on participants, causing distress and potentially leading to participation fatigue.[34]

Trial participants are required to attend visits on their own time and this may interfere with their normal work schedule. Experiences of complaints from superiors for missing work and job termination have been reported.[34,38]

Misunderstandings of trial participants resulting in individual changes in risk behaviour

Concerns about increased risk behaviour have been a contentious topic. Many have hypothesized that participants who believe that the HIV vaccine has been

administered to them and that it is effective will engage in risky sexual practices. It is believed that although trial participants receive ongoing risk reduction counselling and go through a thorough informed consent process, they may still disregard the advice because of a false sense of protection. [27,28,43]

In the Phambili study which was the first efficacy study done in sub-Saharan Africa, the risk behaviour of participants was tracked throughout the study and there was no evidence of increased risk behaviour post unblinding.[28] A study done in the US similarly found no evidence of risk compensation among trial participants enrolled in a phase 2b HIV trial when compared to participants who were screened but ineligible for trial participation.[27]Also, several other studies have not found risk compensation to be true among participants in HIV vaccine trials.[39,44,45] Nevertheless, the threat still looms as risk-reduction counselling may not impact all participants enrolled in trials. Moreover, there have been a few reports of some increases in individual risk behaviour in HIV vaccine trials including both participants with high and low vulnerability to HIV making it still an important issue to be explored.[34,44,46]

Vaccine-Induced Seropositivity - VISP

The ultimate goal of candidate HIV vaccines is to produce antibodies that can protect an individual against future infection. However, this comes with its own drawbacks as trial participants may develop VISP. To distinguish between VISP and true positive test results, specific tests may need to be used, such as nucleic acid tests.[24,47] In addition, commercially available tests have different sensitivities to antibodies generated by an HIV vaccine depending on the test kit and vaccine HIV inserts. Testing for VISP within the HVTN uses three or more distinct antibody-based test kits commonly used for HIV testing. However, it is possible that a participant who

tested negative for VISP at the end of a trial participation could test positive for VISP based on another test kit.

Trial participants are informed of the possibility for VISP during informed consent discussions before enrolment and during trial conduct and are asked to refrain from getting HIV tests outside of trial sites. However, outside testing cannot always be avoided as HIV testing can be a requirement for some employment opportunities, blood/tissue donation, life insurance, etc. Within the HVTN, site staff are trained to work with participants to provide HIV test results from the trial diagnostic lab to outside entities that require HIV testing.

The occurrence of VISP varies across different trials depending on the characteristics of the vaccine, delivery method, dosage and type of test being used. The duration of VISP is also not known but persistence of up to 17 years after completion of trial has been recorded.[48] A study of over 2000 volunteers who received different HIV vaccines found that over 40% of participants had VISP and that it was more common 'with vaccines containing both the HIV-1 envelope and group-specific core antigen gene proteins'.[47]Another prospective cohort study which followed healthy French volunteers from 16 trials since 1992, found the frequency of VISP to be 7.2% with persistence for up to 17 years. French participants were enrolled into the cohort 2-18 years after HIV vaccine trial participation and the vaccine candidates used were recombinant glycoproteins (rgp 160), canarypox vectors and HIV-1 lipopeptides.[48] It is critical to address VISP as it has been ranked the principal concern among social harms by study participants across different settings.[22,25,49]

Consequences of VISP

Participants can face potential challenges due to VISP. Some of these are listed below:

1. Employment- Reports on this are rare, but employers can deny jobs to individuals perceived as being HIV positive. Trial participants have reported 'troubles' with employment including not being allowed to start a new job assignment until trial participation ended.[25,50] Also, foreign service jobs and job corps participation require HIV testing as part of their employment process.[38,49]
2. Personal life- Family friends and colleagues may misunderstand VISP to be true HIV infection leading to stigma and discrimination.[25,51]
3. Insurance- Insurance companies may require HIV testing for different forms of insurance and participants could be denied insurance or be made to pay higher premiums based on their HIV results.[25]
4. Military career- In some countries, VISP can prevent enrolment in the military. In the United States, individuals with VISP cannot enlist in the military and if already enrolled, are exempt from deployment as they cannot donate blood in the field.[25,52,53]
5. Blood, organ, stem cell, sperm donor-VISP can prevent trial participants from being donors which can have psychological effects due to overwhelming disappoint and a sense of loss.[38] According to Red Cross guidelines even if VISP has been confirmed, the participant can still not donate blood.[25]
6. New-born HIV prophylaxis- In one instance outside the US, a baby was put on ART based on the VISP of the mother detected by a rapid test during labor. A similar incidence was only averted in the US because the trial site was contacted.[25]

SOCIAL BENEFITS/POSITIVE SOCIAL IMPACT

Social benefits associated with HIV vaccine trial participation have not been given as much attention as social harms. In willingness to participate studies, altruistic motives are most often cited as the reason why many volunteers would enrol in a vaccine trial and this remains true across all age groups.[16,51,54,55]

Benefits of trial participation have been reported in several HIV prevention studies. A study assessing the safety and efficacy of long term versus short term drug treatment in reducing HIV transmission, conducted in China and Thailand among 1,025 participants found that while 77% reported at least one social benefit, only 4 reported social harms.[56] A randomized trial assessing the effectiveness of a drug treatment intervention in reducing HIV infection rates among HIV negative injection drug users found a 45% decrease in drug use and a 3% decrease in cravings in the intervention group .[56] Due to the rigorous consent process and counselling required for participation, increase in knowledge is another benefit that often results from trial participation.[42] Trial participants also feel good about playing an important role in the race for an effective vaccine and view their participation as a means of giving back to society, ultimately leading to a world free of HIV.[42,56] In addition, participants who may know someone suffering from HIV or have lost loved ones to HIV, may view participation as a way to honour their loved ones. [51,55] Some participants have also enjoyed a positive recognition for their role increasing their feeling of importance.[24]

While there is hope for an efficacious HIV vaccine, the length of time that will take to happen is still unknown indicating that HIV vaccine trials will continue for many years. In that light, it is important to characterize the experiences reported by HIV vaccine trial participants and put mechanisms in place to amplify the positive ones whilst reducing the negative ones. It is important that when negative experiences occur, they are handled in the best possible way by trial staff. The only way this could be

achieved is by greater understanding of these social impacts through research and documentation.

This study aims to broaden understanding of social impacts associated with HIV vaccine trials and serve as a resource to other researchers and stakeholders. This study eliminates some of the restrictions ascribed to other social impact studies like small sample size, retrospective data collection and limitations in generalization by including over 10,000 participants in 13 countries. This study seeks to explore all social impacts, describe the most common ones, highlight differences in the reporting of these events and provide recommendations for future HIV vaccine trials based on our findings.

RESEARCH QUESTIONS

1. What are the different types of social harms reported by HVTN participants across all completed/closed protocols?
2. What is the frequency of reporting a social harm among HVTN participants across all completed/closed protocols?
3. Are there differences in the reporting of social harms by demographic characteristics, region and treatment arm?
4. What are the different types of benefits reported by HVTN participants across all completed/closed protocols?
5. What is the frequency of reporting a benefit among HVTN participants across all completed/closed protocols?
6. Are there differences in the reporting of benefits by demographic characteristics, region and treatment arm?

METHODS

STUDY TYPE

A cross protocol approach was employed, using data from fifty-one closed/completed protocols across HIV Vaccine Trial Network (HVTN) sites. All the trials included in the study were HIV vaccine trials except for one that enrolled 88 participants to assess human response to an antibody against HIV in healthy participants HVTN 104 (Monoclonal Antibody Study [mAb]).

STUDY SETTINGS

The HVTN is the world's largest publicly funded international collaboration working to develop an effective HIV vaccine. The HVTN conducts phase 1, 2a, 2b and 3 clinical trials among HIV uninfected adults at study sites located in different parts of the world. This study utilized data from a total of 54 HVTN sites in Australia, Botswana, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, South Africa, Switzerland, Trinidad and Tobago and the United States of America. The sites were predominantly located in large and medium-sized cities with accessible means of transportation in the participating countries.

Data on social harms and benefits were collected at different time periods depending on the protocol but across all protocols between 27 March 2001 to 12 September 2017.

SELECTION OF SAMPLE SUBJECTS

The HVTN data base was the source of all data used in this study. The trials included were a mix of phase 1, 2a and 2b, therefore participants with both higher and lower vulnerability to acquiring HIV infection were represented. The one phase 3 study conducted by the HVTN is ongoing and data are not included in these analyses. Participants and site

staff were blinded to a participants' treatment assignments during conduct of the trials. Participants were not informed of their assignment until after the last visit for their study occurred.

Inclusion criteria were:

- Participants enrolled in HVTN vaccine trials and HVTN 104 (mAb study) who completed the final clinic visit and were unblinded as of 1 Oct 2017.
- Statistical center for HIV/AIDS research and prevention (SCHARP) was the statistical and data management center for the trial
- For inclusion in the analysis of benefits of trial participation, the participant needed to have a study visit at which the assessment of benefits was administered.

DATA COLLECTION

Social Impact Assessment and Reporting

All participants enrolled in the study were assessed for social harms at time of enrolment as the period leading to enrolment is often marked by discussions and interactions with family members, colleagues, community members or others and may influence the decision to enrol in a trial.

Trial participants were asked about social harms at each subsequent study visit and instructed to call the clinic staff if an incident occurred between scheduled visits. A Social Impact Log (SIL)(Appendix 1) was completed for all reports that detailed the incident. At specific time points during each study, (which varied by protocol but was for most studies every three months post-enrolment), clinic staff also administered a Social Impact Assessment (SIA) questionnaire (Appendix 2) that asked participants yes/no questions about

whether the participants had experienced any “adverse” events related to trial participation during the assessment period. The number of times the SIA was administered varied by protocol from two to six. Separate questions asked specifically about problems with family, friends, significant others; travel; education; medical or dental treatment; health or life insurance; housing; military or other government agency; and other issues not specified. For each affirmative answer, a SIL form was completed if the social harm had not been previously reported. These multiple opportunities to report events established confidence that data were collected on events of interest and significance.

The SIL included a description of the social impact, onset date, the participant’s rating of the effect of the event on his or her quality of life (minimal, moderate, or major disturbance), action taken by the participant, clinical site staff, and others to resolve the event, resolution status, whether the situation involved disclosure of HIV vaccine trial participation (and how participation was disclosed); and whether HIV testing was an issue (and if an HIV test was performed). Participants rating of the effect of the events on their quality of life were subjective interpretations as determined by the participants themselves. HVTN Clinical Research Site (CRS) staff were provided with instructions and an internet-based training module on completing the SIA questionnaire and SIL. Staff followed the status of social harm events until resolution and, if requested by the participants, provided assistance in efforts to resolve events. Social harms were monitored by the protocol team for each protocol and across all protocols by National Institute of Allergy and Infectious Diseases (NIAID) medical officers.

The SIA questionnaire also asked participants if they had experienced any benefits from their participation in the study. Response categories were yes, no, don’t know. In earlier protocols, the type of benefit a participant mentioned was an open-ended response captured in a text field. In later protocols, the form was modified, and staff coded the benefit into check box

categories (i.e., personal relationships, feel good helping others, medical care, risk reduction counseling, or other). For the response category of 'other,' text describing the benefit was collected. Due to this difference in data collection, a new codebook was developed with expanded categories for the different types of benefits and all text answers to the benefits question were coded using the new codebook.

In 20 protocols (HVTN 042, 044, 045, 048, 049, 054, 055, 056, 057, 059, 060, 063, 064, 065, 067, 068, 069, 071, 072 and 204) SCHARP did not enter the complete text for benefits into the data base and would enter 'Y' to indicate that text was present on the Case Report Form (CRF) image in the data management system. These data were included in the analysis, with 'unknown' indicating that a specific benefit, was not recorded in the data base. At each assessment, participants could report multiple harms or benefits.

BASIC ANALYSIS PLAN

PRIMARY HPOTHESES

1. Social harms will be minimal and will not differ significantly by region or demographic characteristics
2. Benefits will be experienced across regions and demographic characteristics

OUTCOMES TO BE MEASURED

Reporting a social harm related to study participation- This was assessed by whether or not a participant had a SIL in the database.

Reporting a benefit related to study participation- This was assessed by individual responses to the question "Has participation in the study had a beneficial impact on your life?"

The social harm characteristics as captured on the SIL and types of benefits were also explored.

SAMPLE SIZE

A total of 10,495 participants were eligible for the study. There were only 12 participants from Thailand and they were removed from the analysis as Thailand was not similar to any of the other countries in terms of culture and standard of living to facilitate grouping. In addition, these participants did not report any social harms or benefits. Therefore, the study considered 10,483 participants who were included in the dataset assessing social harms. Slightly fewer participants (N= 10,266) were included in the benefits analysis as social harms were assessed at all visits but benefits were only assessed at visits at which the SIA questionnaire was administered. The first SIA administration was typically at the first visit following the enrolment visit.

ANALYSIS

Demographic and other participant characteristics including sex at birth, country, race/ethnicity, age at enrolment, trial phase, and whether the participant received an HIV vaccine or control product were analysed showing numbers and percentages of the total participants. The countries were grouped into three regions based on geographic locations: Africa, Caribbean, and South America. A fourth country group containing North America, Switzerland and Australia was created based on similarities in cultures and standards of living.

Reporting of a benefit was limited to specific study visits specified in the protocol at which a SIA questionnaire was administered. This introduces problems in comparing benefits across protocols and time as the SIA schedules varied by protocol, some participants missed their assessment visits, and participants might feel more pressure to report a benefit the

longer they were on study. For these reasons, analyses of benefits were done using the participants' first assessment. For the analysis, participants who answered, "don't know" and "no" to the question asking about benefits were classified into one group and participants who answered 'yes' were classified into another group.

Participants could report multiple benefits or social harms at each assessment and these are presented in tables showing both numbers and percentages of participants.

Descriptive data are provided for the number of social harms events reported, impact on quality of life (minimal, moderate and major) and resolution status (unresolved at end of study, unable to resolve and resolved).

Logistic regression was used to assess whether participant characteristics (sex, age, region, study phase and treatment group) were associated with reporting a benefit or a social harm. Ethnicity/race was not included in the model because of its collinearity with participants' region. Separate logistic regression models were constructed for social harms and benefits. The reporting of a social harm and reporting of a social benefit were the dependent variable for the harms and benefits regression model respectively. Confidence intervals and odds ratio are reported with the groups used as references indicated. Africa was used as the reference group for regions as it was important in this study to observe the differences in reporting social harms and benefits between Africa and other regions given its disproportionate burden of people living with HIV. The age group 18-24 years was used as the reference group for age as these were the youngest participants and also the largest age group. For treatment group, control was the reference group to aid interpretation of the impact of receiving vaccine. Depending on the follow-up time of a protocol, participants had varying lengths of time in which to experience and report a social harm. To account for this, the logistic modelling for social harms controlled for a participant's length of follow-up time.

Interviewer was not captured in the database so could not be controlled for in the analysis.

All statistical analyses were performed using R version 3.4.3.

RESULTS

SOCIAL HARMS RELATED TO STUDY PARTICIPATION

STUDY PARTICIPANTS

Among the 10,483 participants, 66.3% were male. The majority self-identified as either white, non-Hispanic (49.8%) or black, non-Hispanic (30.0%). The median age was 27 (range; 18-60) and 71.7% of participants were below the age of 35 years at time of enrolment. The majority of participants were from the US (70.9%). Approximately half (51.2%) were enrolled in phase 2b efficacy trials that recruited participants at high vulnerability of acquiring HIV (Table 1).

Table 1. Demographic and other characteristics of vaccine trial volunteers in social harms analysis

Characteristic		**Number of participants (N=10,483)**	**%**
Sex			
Male		6952	66.3%
Female		3531	33.7%
Age (years)			
18-24		3817	36.4%
25-34		3702	35.3%
35-44		2163	20.6%
45 and over		801	7.6%
Median, IQR, Range		27, (23,36) (18, 60)	
Ethnicity/race			
American Indian/Alaskan Native		23	0.2%
Asian/Hawaiian/Pacific Islander		164	1.6%
Black, non-Hispanic		3147	30.0%
Hispanic		1554	14.8%
White, non-Hispanic		5224	49.8%
Multiracial		255	2.4%
Other		111	1.1%
Unknown		5	0.0%
Region	**Country**		
Africa		1435	13.7%
	Botswana	24	0.2%

	South Africa	1411	13.5%
Caribbean		505	4.8%
	Dominican Republic	179	1.7%
	Haiti	198	1.9%
	Jamaica	34	0.3%
	Puerto Rico	54	0.5%
	Trinidad and Tobago	40	0.4%
South America		774	7.4%
	Brazil	196	1.9%
	Peru	578	5.5%
North America/Europe/Australia		7769	74.1%
	Australia	11	0.1%
	Canada	75	0.7%
	Switzerland	248	2.4%
	United States	7435	70.9%
Study Phase			
Phase 1		4009	38.2%
Phase 2a		1109	10.6%
Phase 2b efficacy		5365	51.2%
Treatment Group			
Vaccine		6858	65.4%
Control		3625	34.6%

REPORTED SOCIAL HARMS

Among the 10,483 participants, 789 (7.5%) reported a total of 937 social harm events (Table 2). On a participant level, 59 (0.6%) participants reported a major impact on the participant's quality of life (QoL) while 580(5.5%) had a minimal impact.

Table 2. Social Harms by Type and Maximum Impact on Quality of Life*

Type of social Harm	**Number of social harm events**	**Number of participants reporting social harms**		**Maximum impact on quality of life***					
				Minimal		**Moderate**		**Major**	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
All social harms	937	789	7.5	580	5.5	150	1.4	59	0.6
Personal relationships	736	644	6.1	510	4.9	105	1.0	29	0.3
Travel/Immigration	4	4	0.0	2	0.0	1	0.0	1	0.0
Employment	60	58	0.5	30	0.3	13	0.1	15	0.1
Education	3	3	0.0	2	0.0	1	0.0	0	0.0

Medical/dental	45	44	0.4	28	0.3	10	0.1	6	0.1
Health Insurance	2	2	0.0	1	0.0	1	0.0	0	0.0
Life Insurance	23	23	0.2	14	0.1	7	0.1	2	0.0
Housing	2	2	0.0	0	0.0	0	0.0	2	0.0
Military/other gov. agency	6	6	0.1	2	0.0	1	0.0	3	0.0
Other	56	56	0.5	31	0.3	22	0.2	3	0.0

The denominator for all percentages is the number of participants. For participants reporting multiple events within a type category, the event with the maximum impact on quality of life is reported. Likewise, for the all social harm row, the event with the maximum impact is reported.

Table 3 shows the different types of social harm events and the impact on participants' QoL. Sixty-three events (6.7%) in total were reported as having a major impact on the participant's QoL, while the majority (704, 75.1%) were reported as having a minimal impact. Among the 937 reported social harm events, the majority (736, 78.5%) involved personal relationships where family, partners, or coworkers disagreed with the participant's decision to join the trial, were worried about the side effects of the vaccines, or thought the participant was HIV infected because of his/her involvement in a vaccine trial. Most (80.6%) of the personal relationship social harms were considered by the participant to have a minimal impact on QoL, 15.4% a moderate impact and 4.1% (30 events) a major impact.

The second largest reported category consisted of events related to employment (n=60, 6.4%). These events were usually due to participants altering their work schedules, taking time from work for study appointments and missing work due to symptoms of vaccine reactogenicity. Of the employment social harm events, 51.7% (31 events) were reported to have a minimal impact on the participants' QoL, while 25.0% (15) events were reported to have a major impact.

Table 3 Social harms events by type and impact on Quality of Life

Type of social Harm	**Number of social harm events**	**Impact on quality of life**					
		Mild N Row%*		**Moderate N Row %**		**Major N Row%**	
All social harms	937	704	75.1	170	18.1	63	6.7
Personal relationships	736	593	80.6	113	15.4	30	4.1

Travel/Immigration	4	2	50.0	1	25.0	1	25.0
Employment	60	31	51.7	14	23.3	15	25.0
Education	3	2	66.7	1	33.3	0	0.0
Medical/dental	45	29	64.4	10	22.2	6	13.3
Health Insurance	2	0	0.0	1	50.0	1	50.0
Life Insurance	23	14	60.9	7	30.4	2	8.7
Housing	2	0	0.0	0	0.0	2	100.0
Military/other gov. agency	6	2	33.3	1	16.7	3	50.0
Other	56	31	55.4	22	39.3	3	5.4

The denominators for percentages are the total number of events for a type/row.

The majority of events (656, 70.0%) were considered by participants to be resolved while they were on study; 158(16.9%) were considered not resolvable and the participant desired no further action be taken to resolve; 123(13.1%) were unresolved at the time the participant terminated from the trial (Table 4).

For 823 (87.8%) of all social harm events, others learned of the participant's involvement in an HIV vaccine trial, and the large majority of these events (758, 80.9%) were the result of voluntary disclosure by the participant. In 19 events (2.0%), someone learned of a participant's involvement in a trial by seeing study materials and in 5 events (0.5%) an entity required HIV status which led to disclosure.

Table 4 Social harm events by type and resolution status

Type of social harm	**Number of social harm events**	**Resolution status**					
		Unresolved at EOS		**Unable to resolve**		**Resolved**	
		N	**Row %***	**N**	**Row %**	**N**	**Row %**
All social harms	937	123	13.1	158	16.9	656	70.0
Personal relationships	736	83	11.3	134	18.2	519	70.5
Travel/Immigration	4	2	50.0	0	0.0	2	50.0
Employment	60	6	10.0	10	16.7	44	73.3
Education	3	0	0.0	0	0.0	3	100.0
Medical/dental	45	10	22.3	2	4.4	33	73.3
Health Insurance	2	2	100.0	0	0.0	0	0.0
Life Insurance	23	7	30.4	3	13.0	13	56.5
Housing	2	1	50.0	0	0.0	1	50.0
Military/other gov. agency	6	1	16.7	1	16.7	4	66.7
Other	56	11	19.6	8	14.3	37	66.1

The denominators for percentages are the total number of events for a type/row.

DIFFERENCES IN REPORTING SOCIAL HARMS BY PARTICIPANT CHARACTERISTICS

Table 5 shows the differences in reporting at least one social harm by participant characteristics. Percentages by region were: Africa-5.9%, Caribbean-5.7%, South America-4.3%, and North America/Europe/Australia- 8.3%.

Table 5. Participant characteristics by reporting of social harms

Characteristic		**Reported a social harm**	**Did not report a social harm**
		N (%*)	N (%*)
Sex			
Male		540 (7.8%)	6412 (92.2%)
Female		249 (7.1%)	3282 (92.9%)
Age			
18-24		279(7.3%)	3538 (92.7%)
25-34		301 (8.1%)	3401 (91.9%)
35-44		154 (7.1%)	2009 (92.9%)
45 and over		55 (6.9%)	746 (93.1%)
Ethnicity/race			
American Indian/Alaskan Native		2(8.7%)	21(91.3%)
Asian/Hawaiian/Pacific Islander		11(6.7%)	153(93.3%)
Black, non-Hispanic		180 (5.7%)	2967 (94.3%)
Hispanic		112 (7.2%)	1442 (92.8%)
White, non-Hispanic		452 (8.7%)	4772 (91.3%)
Multiracial		23 (9.0%)	232 (91.0%)
Other		9(8.1%)	102 (91.9%)
Unknown		0(0.0%)	5(100.0%)
Region			
Africa		85 (5.9%)	1350 (94.1%)
	Botswana	2(8.3%)	22(91.7%)
	South Africa	83(5.9%)	1328 (94.1)
Caribbean		29(5.7%)	476(94.3%)
	Dominican Republic	3(1.7%)	176(98.3%)
	Haiti	14(7.1%)	184(92.9%)
	Jamaica	4(11.8%)	30(88.2%)
	Puerto Rico	1(1.9%)	53(98.1%)

	Trinidad and Tobago	7(17.5%;)	33(82.5%)
South America		33(4.3%)	741(95.7%)
	Brazil	13(6.6%)	183(93.4)
	Peru	20(3.5%)	558(96.5%)
North America/Europe/Australia		642(8.3%)	7127(91.7%)
	Australia	3(27.3%)	8(72.7%)
	Canada	6(8.0%)	69(92.0%)
	Switzerland	11(4.4%)	237(95.6%)
	United States	622(8.4%)	6813(91.6%)
Study Phase			
Phase 1		302 (7.5%)	3707 (92.5%)
Phase 2a		89(8.0%)	1020 (92.0%)
Phase 2b efficacy		398(7.4%)	4967 (92.6%)
Treatment Group			
Vaccine		549 (8.0%)	6309 (92.0%)
Control		240(6.6%)	3385 (93.4%)
Total		789 (7.5%)	9694 (92.5%)

***The denominators for percentages are the number of participants in the level for the participant characteristic (i.e., row percentages).**

Table 6 shows the percentage of participants reporting specific types of social harms by participant sex, region and ethnicity/race. There were no large percentage differences by sex, region and ethnicity/race for each of the different types of social harms. North America/Europe/Australia had the highest percentage of participants reporting issues with personal relationships (6.8%) while South America had the least with 3.4%, Africa and the Caribbean had 4.7% and 4.1% participants respectively. The two participants who reported issues with housing were from South America and the Caribbean.

Table 6. Reporting a specific type of social harm by participants' sex, region and ethnicity/race

Characteristic	**Social harm**				
	Personal relationships	Travel/ immigration	Employment	Education	Medical/ Dental
Gender					
Male	438(6.3%)	2(0.0%)	39(0.6%)	3(0.0%)	27(0.4%)
Female	206(5.8%)	2(0.1%)	19(0.5%)	0(0.0%)	17(0.5%)
Region					
Africa	68(4.7%)	0(0.0%)	7(0.5%)	1(0.1%)	8(0.6%)
Caribbean	21(4.1%)	0(0.0%)	8(1.6%)	0(0.0%)	0(0.0%)

South America	26(3.4%)	0(0.0%)	6(0.8%)	0(0.0%)	2(0.3%)
North America/Europe/ Australia	529(6.8%)	4(0.1%)	37(0.5%)	2(0.0%)	34(0.4%)
Ethnicity/race					
Hispanic	93(6.0%)	1(0.1%)	12(0.8%)	0(0.0%)	3(0.2%)
White	368(7.0%)	2(0.0%)	27(0.5%)	1(0.0%)	27(0.5%)
Black	144(4.6%)	0(0.0%)	16(0.5%)	2(0.1%)	11(0.3%)
Other	39(7.0%)	1(0.1%)	3(0.5%)	0(0.0%)	3(0.5%)

***The denominators for the percentages are the total number of participants in the respective characteristic group**

Table 6. Reported Social harms by participants' sex, region and ethnicity/race cont.

Characteristic	**Social harm**				
	Health Insurance	Life Insurance	Housing	Military/other gov. agency	Other
Gender					
Male	2(0.0%)	18(0.3%)	1(0.0%)	6(0.1%)	42(0.6%)
Female	0(0.0%)	4(0.1%)	1(0.0%)	0(0.0%)	14(0.4%)
Region					
Africa	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	5(0.3%)
Caribbean	0(0.0%)	1(0.2%)	1(0.2%)	0(0.0%)	0(0.0%)
South America	0(0.0%)	0(0.0%)	1(0.1%)	0(0.0%)	2(0.3%)
North America/Europe/ Australia	2(0.0%)	21(0.3%)	0(0.0%)	6(0.1%)	49(0.6%)
Ethnicity/race					
Hispanic	0(0.0%)	2(0.1%)	1(0.1%)	0(0.0%)	7(0.5%)
White	1(0.0%)	18(0.3%)	0(0.0%)	4(0.1%)	37(0.7%)
Black	1(0.0%)	2(0.1%)	1(0.0%)	1(0.0%)	10(0.3%)
Other	0(0.0%)	0(0.0%)	0(0.0%)	1(0.1%)	2(0.3%)

Logistic regression was used to analyse differences in reporting at least one social harm across all assessments. Since participants spent different time periods in the study across the different protocols, time spent in the study was controlled for. Sex and age were not significantly associated with reporting a social harm, whereas region and the participants study treatment group were significant predictors. Compared to participants from Africa, participants from North America/Europe/Australia had a 46% increased odd of reporting a

social harm (95% CI; 1.15, 1.88). Participants who received an HIV vaccine on study had a 21% increased odd of reporting a social harm compared to participants who received control product (95% CI; 1.03, 1.44). Participants who were enrolled in phase 2b trials had a 34% decreased odd of reporting a social harm compared to participants that were in enrolled in phase 1 trials. (Table 7)

Table 7. Multivariable logistic regression model of volunteer characteristics predictive of reporting a social harm*

Characteristic	**OR**	**95% CI**
Sex		
Male	1.07	0.90,1.26
Female	Ref	Ref
Age		
18-24	Ref	Ref
25-34	1.04	0.88,1.24
35-44	0.84	0.68,1.034
45 and over	0.78	0.57,1.05
Region		
Africa	Ref	Ref
Caribbean	0.99	0.63,1.55
South America	0.67	0.44,1.01
North America/Europe/Australia	1.46	1.15,1.88
Treatment Group		
Vaccine	1.21	1.03,1.44
Control	Ref	Ref
Study Phase		
Phase 1	Ref	Ref
Phase 2a	1.17	0.90, 1.49
Phase 2b	0.66	0.49,0.88

- **Model controls for time from enrolment to last study visit, the assessment period for social harms.**

BENEFITS

STUDY PARTICIPANTS

Among the 10,483 participants, 10,267 had at least one study visit at which they were administered the questionnaire asking about benefits of trial participation and are included in the benefits analysis. Table 8 provides a summary of demographic and study characteristics of the 10,267 participants. Characteristics were similar to those in the social harms analysis.

Table 8. Demographic and other characteristics of vaccine trial volunteers in benefits data analysis

Characteristic		Number of participants (n=10,267)	%
Sex			
Male		6811	66.3%
female		3456	33.7%
Age (years)			
18-24		3724	36.3%
25-34		3639	35.4%
35-44		2119	20.6%
45 and over		785	7.6%
Median, IQR, Range		(27, (23, 36), (18, 60))	
Ethnicity/race			
American Indian/Alaskan Native		21	0.2%
Asian/Hawaiian/Pacific Islander		161	1.6%
Black, non-Hispanic		3053	29.7%
Hispanic		1537	15.0%
White, non-Hispanic		5130	50.0%
Multiracial		250	2.4%
Other		110	1.1%
Unknown		5	0.0%
Region	**Country**		
Africa		1398	13.6%
	Botswana	24	0.2%
	South Africa	1374	13.4%
Caribbean		503	4.9%
	Dominican Republic	179	1.7%
	Haiti	196	1.9%
	Jamaica	34	0.3%
	Puerto Rico	54	0.5%
	Trinidad and Tobago	40	0.4%
South America		771	7.5%
	Brazil	195	1.9%
	Peru	576	5.6%
North America/Europe/Australia		7595	74.0%
	Australia	11	0.1%

	Canada	74	0.7%
	Switzerland	246	2.4%
	United States	7264	70.8%
Study Phase			
Phase 1		3905	38.0%
Phase 2a		1079	10.5%
Phase 2b, efficacy		5283	51.5%
Treatment Group			
Vaccine		6706	65.3%
Control		3561	34.7%

REPORTED BENEFITS

There were 6,562 participants (63.9%) who reported at least one benefit at the time of first assessment. Table 9 outlines the different types of benefits reported by participants. The benefits most commonly reported were helping others/altruism (30.2% of participants), risk reduction counselling (21.2%) and free access to medical care which included regular HIV testing (17.7%). Among participants who reported at least one benefit, 47.2%, 33.1% and 27.6%, respectively, reported these types benefits.

Table 9. Frequency of type of benefit reported at first assessment of benefits

Benefits	**Number of participants reporting a benefit***	**Percentage among all participants in the analysis (N=10,267)**
Any benefit	6562	63.9%
Help others/ altruism	3100	30.2%
Received HIV risk reduction or pregnancy prevention counselling	2176	21.2%
Received medical care	1815	17.7%
Improved Personal relationships	1053	10.3%
Received compensation	516	5.0%
Increased knowledge HIV	352	3.4%

Personal satisfaction	184	1.8%
Increased knowledge of clinical/scientific research	151	1.5%
Increased general knowledge	124	1.2%
Advanced science	88	0.9%
Facilitated conversation about HIV and other issues	54	0.5%
Beneficial interactions with counselling staff	50	0.5%
Other	58	0.6%
Benefit unknown**	1011	9.8%

***Participants could report more than 1 benefit**

****The specific benefit was not entered into the database**.

Table 10 shows the differences in reporting at least one benefit by participant characteristics. Percentages by region were: Africa-72.1%, Caribbean-79.5%, South America-69.8%, and North America/Europe/Australia- 60.8%. For each country, a greater number of participants reported benefits than those not reporting, except for Brazil and Switzerland where 47.7% and 48.4% of participants reported benefits respectively. The proportions of participants reporting benefits were similar across the different age groups (61.5%-64.4%) and sex (males 62.8%, females 66.1%).

Table 10. Reported social benefits at first assessment by participant characteristics*

CHARACTERISTIC	**Reported a benefit**	**Did not report a benefit**
	N (%*)	N (%*)
Sex		
Male	4276(62.8%;)	2535(37.2%)
Female	2286 (66.1%)	1170(33.9%)
Age		
18-24	2398 (64.4%;)	1326 (35.6%)

25-34		2320 (63.8%)	1319(36.2%)
35-44		1361 (64.2%)	758(35.8%)
45 and over		483 (61.5%)	302 (38.5%)
Ethnicity/race			
American Indian/Alaskan Native		13 (61.9%)	8(38.1%)
Asian/Hawaiian/Pacific Islander		84(52.2%)	77(47.8%)
Black, non-Hispanic		2063 (67.6%)	990 (32.4%)
Hispanic		1082(70.4%)	455 (29.6%)
White, non-Hispanic		3084 (60.1%)	2046(39.9%)
Multiracial		155 (62.0%)	95 (38.0%)
Other		77 (70.0%)	33(30.0%)
Unknown		4(80.0%)	1(20.0%)
Region	**Country**		
Africa		1008(72.1%)	390(27.9%)
	Botswana	19(79.2%)	5(20.8%)
	South Africa	989(72.0%)	385(28.0%)
Caribbean		400(79.5%)	103(20.5%)
	Dominican Republic	164(91.6%)	15(8.4%)
	Haiti	139(70.9%)	57(29.1%)
	Jamaica	21(61.8%)	13(38.2%)
	Puerto Rico	52(96.3%)	2(3.7%)
	Trinidad and Tobago	24(60.0%)	16(40.0%)
South America		537(69.6%)	234(30.4%)
	Brazil	93(47.7%)	102(52.3%)
	Peru	444(77.1%)	132(22.9%;)
North America/Europe/Australia		4617 (60.8%)	2978 (39.2%)
	Australia	7(63.6%)	4(36.4%)
	Canada	59(79.7%)	15(20.3%)
	Switzerland	119(48.4%)	127(51.6%)
	United States	4432(61.0%)	2832(39.0%)
Study Phase			
Phase 1		2366 (60.6%)	1539(39.4%)
Phase 2a		564 (52.3%)	515 (47.7%)
Phase 2b efficacy		3632 (68.7%)	1651 (31.3%)
Treatment Group			
Vaccine		4208 (62.7%)	2498(37.3%)
Control		2354 (66.1%)	1207 (33.9%;)

***The denominators for percentages are the number of participants in the level for the participant characteristic (i.e., row percentages).**

Logistic regression analysis showed that age and treatment group were not associated with reporting at least one benefit. However, there were significant differences by regions, sex and study phase. There was a 41% decreased odd of reporting at least one benefit for North

America/Europe/Australia participants (95% CI; 0.52, 0.68) compared to participants from Africa and male participants had a 16% decreased odd of reporting a benefit compared to females (95% CI; 0.77, 0.92). Using participants enrolled in phase 1 trials as a reference, participants in phase 2a trials had a 34% decreased odd of reporting a benefit (95% CI; 0.57, 0.76), while participants in phase 2b trials had a 38% increased odd of reporting a benefit (95% CI; 1.25, 1.52). (Table 11)

Table 11. Logistic regression analysis of volunteer characteristics and reported benefit at first assessment

Characteristic	**OR**	**95% CI**
Sex		
Male	0.84	0.77, 0.92
Female	Ref	Ref
Age		
18-24	Ref	Ref
25-34	1.02	0.92, 1.12
35-44	1.10	0.98, 1.24
45 and over	1.08	0.92, 1.28
Region		
Africa	Ref	Ref
Caribbean	1.26	0.98, 1.62
South America	0.84	0.69, 1.03
North America/Europe/Australia	0.59	0.52, 0.68
Treatment Group		
Vaccine	0.98	0.89, 1.08
Control	Ref	Ref
Study Phase		
Phase 1	Ref	Ref
Phase 2a	0.66	0.57, 0.76
Phase 2b	1.38	1.25, 1.52

DISCUSSION

In this study, 7.5% of participants reported at least one social harm. This percentage is similar to a study previously done in the US to assess negative social consequences of participation in an HIV vaccine trial where 5% of participants reported at least one event.[38] Researchers associated with the study, hypothesized that the low occurrence may be due to the fact that only low risk participants were enrolled in that study. In another study conducted in the US and Canada among participants with high vulnerability to HIV, 18% of participants reported at least one event,[57] whereas, an HIV prevention trial among injection drug users in Thailand and China found that among 1,025 participants, only 4 reported a negative social impact.[56]

In our study, participants who were enrolled in phase 2b efficacy trials had a 34% decreased odd of reporting a social harm compared to participants that were in enrolled in phase 1 trials. Study phase was used as a proxy to determine participants' vulnerability to HIV. Participants enrolled in phase 1 trials had a low vulnerability to HIV infection, participants in phase 2a were a mix of both low and high vulnerability to HIV infection while participants in phase 2b had a high vulnerability to HIV infection. This study however, did not consider additional questions which can be used to establish vulnerability categories. It is reassuring that the occurrence of reported social harms is low in the majority of studies and this should be emphasized in recruiting volunteers for future trials as the fear of social harms has been highlighted as a deterrent for HIV vaccine trial participation.[58,59]

Problems in personal relationships accounted for 80.6% of the social harm events reported in this study which is consistent with several other studies in which negative reactions/experiences from family, friends, colleagues, community members and other acquaintances were the most common social harms reported.[38,39,57] This study did not break down personal relationships by category (family, friends, colleagues etc.). In one study wherein

personal relationships were teased out, Tarimo et al (2014) found that most negative reactions emanated from work colleagues and friends from their communities.[39] Future trials may want to report on the different categories of personal relationships affected to generate better understanding of the issue. While there were legitimate concerns about the safety of the vaccine and well-being of trial participants by their family, friends and colleagues, of a more worrisome nature was the assumption that participants may be either HIV infected or at high risk of HIV for enrolling in the trial or that administration of the vaccine trial products could lead to HIV infection of the participant. These are common misconceptions that have been expressed in other HIV vaccine trial studies exploring social harms[38,57] and willingness to participate in HIV vaccine trial studies exploring barriers and facilitators to participate in future HIV vaccine trials.[41,60,61] These false perceptions resulted in tensions in personal relationships with trial participants being treated differently by others. The manifestations included avoidance of sharing meals, refusal of sexual intercourse by partners and even dissolution of relationships. These occurrences highlight the deep-rooted issues of stigma and discrimination surrounding HIV/AIDS which are complex and multi-faceted. Moreover, they may also indicate mistrust of government and other institutions conducting vaccine trials which may be due to knowledge of past unethical research involving vulnerable populations.[62,63] Most importantly, these issues are strong reminders that education and sensitization about HIV/AIDS and the safety of HIV vaccine products, underscoring the point that a participant cannot get infected from vaccine products, is needed. Education should not be limited to trial participants only, larger community engagement, education and awareness efforts should be put in place so that trial staff can allay most fears and be one step ahead of problems that could arise without the right information. Community education is a priority at all HVTN sites with resources and specific times allocated for such activities.

Events related to employment made up the second largest category of social harms with 60 events reported by 58 participants. Fuchs et al (2007) also found events related to employment as the second most common reported negative social impact in their study,[57] while Jenkins et al (2005) assessed discrimination in employment among HIV vaccine trial participants and found no reports of such instances in Thailand.[42] Twelve participants lost their jobs as a result of trial participation mainly due to taking time off to attend scheduled visits; in eight (66.7%) of these cases, the impact on quality of life was major. Loss of employment may have dire consequences for participants especially if that job was their main source of income. In addition, participants who are paid hourly, may lose income by taking time off to attend study visits. Participants may not want to disclose their participation to employers and that makes it difficult to negotiate time off during work hours for trial visits. HIV vaccine clinical research sites (CRSs) work to schedule visits around participants' schedules to avoid problems with employment. Whenever possible, CRSs allow for visits in the evenings after work or early in the morning before work. However, some HVTN CRSs may not have the resources to expand hours. Also, CRS staff are acutely aware of the need to work efficiently so that participants spend the least possible time at trial sites; this is being enhanced by HVTN as part of a rapid improvement process.

Issues related to education, health insurance, housing, travel/immigration, and military and other government agencies were minimal which support findings from other studies.[36,38,57] Twenty-two participants reported problems with obtaining life insurance mainly because HIV testing was required, and participants had been advised against having an HIV test done outside of the site by trial staff to avoid the confusion of a reactive HIV test result due to VISP. Trial staff were actively involved in trying to solve the issues that arose upon request from participants. The minimal number of events related to insurance could be attributed to some of the structures already put in place by NIAID including providing insurance companies with

HIV testing results when requested by the participant and working with HIV test kit manufacturers to ensure that information about VISP is printed on their inserts.[38]

Age and sex were not significant predictors of reporting a social harm in our study; another study done in North America had found that among men who have sex with men (MSM), a younger age was associated with increased likelihood of reporting a negative social impact. [57] Participants from North America/Europe/Australia had a 46% increased odd of reporting a social harm compared to participants from Africa. This could be because certain social harms are more likely to be encountered in the West based on existing structures and way of life, like issues with obtaining health and life insurance, whilst in Africa participants may encounter these issues less frequently.

Participants who received an HIV vaccine on study had a 21% increased odd of reporting a social harm. We could not ascertain whether the increase in participants reporting social harms from the vaccine group compared to the control group was in any way related to VISP. The advice given to participants to limit HIV testing to trial sites may have curtailed some of the potential social harms related to VISP because while in 167 events HIV testing was an issue (insurance purposes, travel/immigration, job-related etc.), only in 33 events were tests actually performed out of study. It is therefore important to reinforce such messages and put modalities in place for participants when these issues occur.

In 88% of all social harm events, others learned of the participant's involvement in an HIV vaccine trial. This highlights the importance of informing participants ahead of time that their participation may become known, sometimes due to circumstances beyond their control. HIV vaccine CRS staff work with participants to devise disclosure strategies and prepare participants for that eventuality. Moreover, since many negative reactions towards participants can be tied to others knowing about their association with an HIV vaccine trial, CRS staff

discuss the importance of exercising caution in disclosing their involvement. HVTN currently addresses these issues during the informed consent process and as these issues arise.

Social harms may continue even after the conclusion of an HIV vaccine trial. A study conducted in Tanzania to assess social harms and changes in sexual behaviour after the completion of an HIV vaccine trial found the persistence of negative comments, stigma and ridicule a year after study completion[39]. With this in mind, vaccine trial agencies should have structures in place to provide support for participants beyond study completion as well as ongoing community engagement to reduce stigma and negative perceptions of HIV clinical trial research participation. HVTN provides HIV testing services for as long as participants need it even after trial sites have closed and continues to work with participants to mitigate social harms.

Even though the fear of potential social harms in HIV vaccine trials has been raised by many researchers, the occurrence of social harms throughout our study spanning 15 years was low. This may be due to the effort put in place by the HVTN, CRS staff and funders to mitigate some of these social harms. Counselling was an important component of all trials and CRS staff were perceived as a constant source of support and even friendship. Furthermore, some participants were not confronted with the need to disclose their involvement in an HIV vaccine trial, making them less likely to encounter social harms. NIAID plays an important role in liaising with insurance companies to increase awareness about VISP and prevent vaccine participants from being refused health/life insurance. NIAID also works with HIV test kit manufacturers to ensure that inserts have information on VISP. These reasons coupled with the advice given to participants to avoid outside HIV testing may have, no doubt, contributed to the general low occurrence of social harms we see in this study.

In our study, 63.9% of participants reported at least one benefit at first assessment, this is less than what has been reported in other studies. Jenkins et al (2005) in a much smaller sample of 363 participants enrolled in an HIV vaccine trial (phase1/2) in Thailand found that on any given assessment, more than 98% of participants reported a benefit.[42] Sugarman et al (2015) found that in an HIV prevention trial in China and Thailand, 77% of participants reported at least one positive social impact over 104 weeks of follow up.[56] Our study differs from the ones mentioned above by only considering benefits reported at first assessment.

The most common reported benefit in our study was helping others/altruism which indicates that volunteers felt a genuine need to make a meaningful contribution in the life of others. This should be highlighted, and the message spread in communities where discrimination against trial participants occur to change the narrative and showcase participants as heroes. HVTN CRS sites in Peru employ a heroes' strategy which showcases participants to the public and raises awareness about the work that is being done in Peru. Receiving HIV risk reduction or pregnancy prevention counselling was the second most common benefit reported, signalling the importance of counselling as participants clearly appreciated the time spent talking with them and viewed it as important. It is refreshing to note that some participants indicated that they intend to keep relationships established with trial staff beyond trial participation and some even played important roles in recruiting new volunteers.

While age and treatment group were not predictors of reporting at least one benefit, there were significant differences by region, sex and trial phase. There was a 41% decreased odd of reporting at least one benefit for North America/Europe/Australia participants compared to participants from Africa. This could be due to cultural differences about perceptions as to what counts as benefits and could be attributed to the trial. For example, while participants from North America/Europe/Australia had a 46% increased odd of reporting a social harm compared to participants from Africa, the opposite holds true for benefits where a 41%

decreased odd was observed. In our study, male participants had a 16% decreased odd of reporting a benefit compared to females; the reason for this is not clear but could be that the females were more expressive about their benefits and found it easier to talk about benefits.

Benefits experienced by trial participants may play a role in offsetting some of the potential social harms associated with HIV trial participation therefore should be well documented and HIV vaccine trial agency should plan ahead of time how they could use this information to best design HIV vaccine studies.

LIMITATIONS

While our study was not restricted by sample size and region as it considered over 10,000 participants enrolled in phase 1, 2a and 2b HIV vaccine and mAb trials in 14 countries, and had procedures put in place to assure data quality, some limitations must be acknowledged. Our study is observational and therefore can only infer associations and not causation. The questionnaires were administered by different individuals across several countries which may have affected results. Our study also relied on self-reported data with no verification done. There may have also been social desirability bias in reporting benefits as trial staff administered questionnaires and participants may feel the need to report a benefit. In future studies, the option of external workers not directly related to the vaccine trial administering certain questionnaire should be explored. In addition, the tool used for data collection may not have been adaptive enough for all contexts across all countries. Improved tools for data collection that considers cultural-specific issues can prove beneficial in future research. Additionally, the participants in our study are from specific countries, so the findings may not be generalizable to other countries with different cultures and norms. Interpretation of results should also be done bearing in mind that our sample consisted predominantly of participants living in the US.

CONCLUSIONS

The occurrence of social harms was low in HIV vaccine and mAb trials conducted by the HVTN. Problems with personal relationships were the most common. Issues with insurance, education, housing, travel/immigration, and military/government agencies were minimal. Social harms mainly arose when participants' involvement in trial participation became known, but the majority of social harms were resolved before completion of study.

A high number of participants reported at least one benefit at first assessment with altruism/helping others being the most common benefit. Age was not a significant predictor of social harms or benefits, but significant differences were found in regions and study phase for reporting of both social harms and benefits.

Our study which should serve as a useful document to guide agencies that would embark in future vaccine research as well as policy makers to ensure that participants' welfare is best catered for. Awareness of the social harms dominant in certain cultures would enable researchers to better address them and possibly eliminate some.

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APPENDIX 1

HVTN ### ***Social Impact Log (SIL)***

(SIL) 151

Note: *Number pages sequentially (01, 02, 03) for each participant.* **Page #** ☐☐

Participant ID:

☐☐☐-☐☐-☐☐☐-☐

Site ID *Protocol* *Participant* *Chk*

Social Impact Log

Instructions: *Submit this form to DF/Net whenever a new social impact is recorded or information on this form is updated. Submit only pages with new entries or revisions.*

1 Concisely describe social impact

2 Onset Date ☐☐ ☐☐☐ ☐☐ (*dd* *MMM* *yy*)

3 Reported at visit ☐☐.☐

4 Social impact code ☐☐ *See back for codes and definitions.*

5 In this situation, did participation in the study become known to others? ☐ *yes* ☐ *no* *If no, go to item 6.*

5a. How did the participation become known? *Mark only one.*

- ☐ participant disclosed voluntarily
- ☐ someone disclosed it without participant's permission/ knowledge
- ☐ someone saw participant's ID card or other trial-related materials
- ☐ employer/agency/government official required information about HIV status
- ☐ other, specify _____

6 Was HIV antibody testing an issue in this situation? ☐ *yes* ☐ *no* *If no, go to item 7.*

6a. Was HIV antibody testing performed? ☐ *yes* ☐ *no* *If no, go to item 7.*

6b. Where was testing done? *Mark all that apply.*

- ☐ 6b1. protocol-specified HIV diagnostic lab
- ☐ 6b2. outside lab
- ☐ 6b3. clinical research site lab

7 ***Ask participant:***
What impact has this situation had on your quality of life?

- ☐ minimal disturbance
- ☐ moderate disturbance; no significant impact
- ☐ major disturbance with significant impact

8 Describe what was done by staff and participant to address social impact.

8a. Participant

8b. Staff

9 Record current status.

- ☐ unresolved
- ☐ unresolved at final clinic visit
- ☐ unable to resolve; no further action taken
- ☐ resolved

If unable to resolve or resolved, record closure date.

☐☐ ☐☐☐ ☐☐ (*dd* *MMM* *yy*)

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_____ *Initials/Date*

APPENDIX 2

HVTN ### ***Social Impact Assessment Questionnaire (SIA)***

(SIA) 150

Visit Code ☐☐.☐

Participant ID: ☐☐☐-☐☐-☐☐☐-☐ (*Site ID – Protocol – Participant – Chk*)

Date: ☐☐ ☐☐☐ ☐☐ (*dd MMM yy*)

Social Impact Assessment Questionnaire

Instructions: *Before administering this Assessment, update information about any unresolved, previously reported social impacts on a Social Impact Log (SIL). Complete a separate SIL for each new impact identified below.*

1 **Initial Assessment:** As a result of your participation in this study, have you...
Subsequent Assessment(s): As a result of your participation in this study, have you had any new social impacts that you have not previously told us about? Have you...

	yes	*no*	
1a. had any negative experiences with your family, friends, significant others, neighbors, community members or sex partners?	☐	☐	***(SIL Code = 01)***
1b. had problems with travel, securing documents, obtaining formal permission to travel to or enter another country, such as being denied a visa, or had a problem with immigration/ naturalization?	☐	☐	***(SIL Code = 02)***
1c. been turned down for a new job, lost a job, experienced other problems at work or had problems securing a job where HIV testing was a requirement?	☐	☐	***(SIL Code = 03)***
1d. been turned down by an educational program, told to leave an educational program, denied access to enrollment in a school or educational facility, or experienced other problems at school?	☐	☐	***(SIL Code = 04)***
1e. been told you have to have an HIV test by a health care provider, been refused medical or dental treatment, or treated negatively by a health care provider?	☐	☐	***(SIL Code = 05)***
1f. lost your health insurance, medical aid or a hospital plan, had problems getting new health insurance, medical aid or a hospital plan, or experienced other problems related to health insurance, medical aid or a hospital plan?	☐	☐	***(SIL Code = 06)***
1g. lost your life insurance policy or funeral cover policy, had problems getting new life insurance policy or funeral cover policy, or experienced other problems related to your life insurance policy or funeral cover policy?	☐	☐	***(SIL Code = 07)***
1h. had trouble getting or keeping housing, or had other problems related to housing?	☐	☐	***(SIL Code = 08)***
1i. had a problem with the military or any other government agencies?	☐	☐	***(SIL Code = 09)***
1j. had any other problems? Specify _____	☐	☐	***(SIL Code = 10)***

2 Has participation in this study had a beneficial impact on your life? *yes* ☐ *no* ☐ *don't know* ☐ → *If no or don't know, end of form.*

2a. Indicate the beneficial impact. *Mark all that apply.*

- ☐ 2a1. personal relationships
- ☐ 2a2. feel good helping others
- ☐ 2a3. medical care
- ☐ 2a4. risk reduction counseling
- ☐ 2a5. increased awareness and knowledge about HIV
- ☐ 2a6. increased awareness and knowledge about research
- ☐ 2a7. compensation
- ☐ 2a8. other, specify: _____

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_____
Initials/Date