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“Once Bitten, Twice Shy”: Participant Perspectives in the Aftermath of an Early HIV Vaccine Trial Termination

P.A. Newman^{*,a}, S. Yim^a, A. Daley^b, R. Walisser^a, R. Halpenny^c, W. Cunningham^d, and M. Loutfy, MD^{c,e}

^aUniversity of Toronto, Faculty of Social Work, Centre for Applied Social Research, 246 Bloor Street West, Toronto, Ontario, Canada M5S 1V4

^bYork University, School of Social Work, Toronto, Ontario, Canada M3J 1P3

^cCanadian Immunodeficiency Research Collaborative, Maple Leaf Medical Clinic, 70 Carlton St., Toronto, ON M5B 1L6

^dUniversity of California, Los Angeles, Departments of Health Services and Medicine, Los Angeles, CA 90095-1772

^eUniversity of Toronto, Department of Medicine, Suite RFE 3-805, 200 Elizabeth Street, Toronto, ON M5G 2C4

1. Introduction

The development of safe and efficacious prophylactic HIV-1 vaccines is one of the highest priorities in AIDS research. To that end, several large-scale trials have been completed, involving tens of thousands of volunteers. The Thai Phase III prime-boost trial (RV144) completed in November 2009 was the first in which a test vaccine had a moderate degree of efficacy, though not sufficient for public licensure [1,2]. Further basic discovery research, preclinical studies and clinical trials involving thousands of additional volunteers will be needed to support HIV vaccine development [3,4].

It is a broadly accepted tenet that clinical trials, many which do not result in an efficacious product, are part of incremental efforts to advance science. The tremendous financial and human resources required, however, suggest the importance of using large-scale trials to their full advantage in marshalling evidence to address the complex social science as well as basic science challenges of HIV vaccine development [5,6]. To that end, the Step Study phase IIB HIV-1 vaccine trial [7] affords a unique opportunity to explore the experiences and perspectives of volunteers in the aftermath of an early trial termination amidst unexpected risks, with implications for recruitment and implementation of future HIV prevention trials.

1.1. The STEP Study

From 2004 to 2009, Merck, the HIV Vaccine Trials Network (HVTN) and the National Institute of Allergy and Infectious Diseases (NIAID) conducted a multicenter, randomized, placebo-controlled phase IIB test-of-concept clinical trial (Merck Protocol V520-023/HVTN 502). The goal of the investigational vaccine was to decrease HIV acquisition and/or lower viral load set-point. The vaccine was administered to 3000 volunteers between 18 and 45 years of age at high risk for HIV infection [7].

^{*}Corresponding author at: University of Toronto, Faculty of Social Work, Centre for Applied Social Research, 246 Bloor Street West, Toronto, Ontario, Canada M5S 1V4, Tel.: +1 416-946-8611, fax: +1 416-978-7072. p.newman@utoronto.ca (P.A. Newman).

In September 2007, the trial sponsors discontinued vaccination and enrollment as interim efficacy analysis conducted by an independent Data Safety Monitoring Board (DSMB) indicated the vaccine would not reach its efficacy endpoints [8]. In November 2007, the trial sponsors announced that all volunteers would be told whether they received vaccine or placebo, warned of possible risks, and encouraged to follow up for risk reduction counseling and monitoring [9]. Further analysis of the study data showed that the rate of HIV acquisition was significantly higher for a subset of volunteers (uncircumcised men and those with pre-existing immunity to the adenovirus [Ad5] used in the investigational vaccine) who received the test vaccine than those who had received the placebo [7,10].

The objective of the present study is to explore the experiences and perspectives of HIV vaccine trial participants, as well as key informant service providers and clinical investigators, in the aftermath of the Step Study, and implications for future biomedical HIV prevention trials.

2. Materials and methods

We conducted a mixed methods investigation including a baseline survey upon enrollment, from October 2005 – October 2006, and in depth interviews after the unblinding of volunteers, from January – August 2008, at the Toronto site of the Step Study.

2.1. Participants and recruitment

The vaccine trial eligibility criteria were: 1) aged 18 – 45 years; 2) HIV-1 seronegative; and, 3) in the 6 months preceding enrollment: for men, had two or more anal sex partners or unprotected anal sex; for women, exchanged sex for money, used crack at least three times, or had unprotected sex with a man who uses injection drugs or known to be HIV-positive.

After enrollment at the Step Study's Toronto site, all volunteers were invited to participate in an adjunct sociobehavioral study. The sociobehavioral study included a brief, confidential, self-administered baseline questionnaire, which took approximately 10 – 15 minutes to complete. Seven questions assessed sociodemographic characteristics and 13 items (check as many as apply) assessed motivations for participating in the HIV vaccine trial. Concerns about participating (5 items), perceived HIV risk (2 items), HIV vaccine optimism (3 items), and trust in medical providers (5 items) and medical research (3 items) were assessed on a 4-point Likert-type response scale. Motivations, concerns, perceived HIV risk, and HIV vaccine items were based on our formative research [5,11] other published research on HIV vaccine trial participation [12,13], and a systematic review of the WTP literature [14]. Questions on trust in medical providers [15] and medical research [16] were based on items validated in national U.S. probability sample surveys.

Upon discontinuation of the Step Study and unblinding of volunteers, clinic staff handed out in person a letter of invitation to participate in a one-time, face-to-face, confidential one-hour interview. Trial participants who did not return to the clinic were mailed the letter of invitation. In the interest of confidentiality, all communication with trial participants was conducted by clinic staff. Due to IRB regulations, the sociobehavioral research team did not have access to a list of trial participants and all contact with the team had to be initiated by the participant. In order to encourage candor and mitigate any perceptions of coercion, interested trial volunteers were instructed to contact a research assistant who was independent of the clinical trial research team to inquire about or arrange an interview.

Interviews were conducted by trained research staff in a university setting off site from the clinic. We used a semi-structured interview guide with scripted probes to elicit volunteer's perspectives on their participation in the Step Study and the aftermath of unblinding and

learning that the experimental vaccine did not work. Open ended questions and probes were informed by a NIAID structured questionnaire developed for HIV vaccine trials [12], our formative research conducted in the context of the same trial [5], and published research on attitudes towards HIV vaccine trials [13,17]. Questions explored initial motivations for participating, experiences in the trial, and reactions upon hearing about the trial termination and to being unblinded.

We included key informants in order to solicit input on their experience with HIV/AIDS services and research with key populations at higher risk for HIV, such as the participants in the present study. Key informant interviews serve as a form of data source triangulation (i.e., informants and trial participants), which enhances the validity of qualitative findings [18,19]. Key informants were purposively sampled based on involvement with the trial or experience with populations eligible to participate. We asked key informants to reflect on trial implementation and termination, and volunteers' involvement.

Trial volunteers were given a \$40 honorarium, including transportation costs; key informants were not paid. The present study was approved by the University of Toronto Research Ethics Board and Merck, the trial sponsor. All participants provided informed consent.

2.2. Data analysis

We analyzed baseline survey questionnaires using descriptive statistics. Face-to-face interviews were digitally recorded, transcribed verbatim and uploaded into NVivo software (QSR International). We used thematic analysis to review transcripts, including line-by-line, in vivo and focused coding, and a constant comparative method [20,21]. First, two investigators (SY, RW) independently coded the same three transcripts and then met with the principal investigator (PN) to review codes and create a codebook. Next, we applied codes to analyze subsequent transcripts and generated new codes as they arose in an iterative process [19,20]. Differences in coding were resolved by consensus among three investigators. Data source triangulation (between trial volunteers and key informants), investigator triangulation (2 investigators independently coded the transcripts), and peer debriefing (investigators discussed emerging themes and interpretations with other researchers) enhance the validity of the findings [18,19]. Baseline questionnaires and post-trial interviews were strictly confidential and data were not linked.

3. Results

3.1. Participants

Eighty-seven percent (48/55) of trial volunteers completed the baseline survey. Participants' mean age was 37 years; all but one (n=47) were male, 98% (n=46) of whom identified as gay or bisexual. Nearly three-quarters (73%; n=35) identified as white, 8% (n=4) as Latino, and 19% (n=9) as Aboriginal, Asian or mixed. Median monthly income was \$1500 CAD.

Fifteen (14 men, 1 woman) trial volunteers participated in an in depth, face-to-face post-trial interview. Participants' mean age was 41 years. Most (n=12) identified as white, 2 as Aboriginal and 1 Latino, with a median monthly income of \$1200 CAD. All the men identified as gay or bisexual.

Key informants included three women and one man, one Caucasian, two African/Caribbean and one Aboriginal. Two were coordinators of HIV education and prevention projects, and two were clinical staff/investigators.

3.2. Pre-trial experiences

3.2.1. Motivation to enroll in the STEP study: “*Part of it was to protect myself*”

—All (100%; n=48) participants endorsed “to help end the HIV/AIDS epidemic” as a motivator for trial participation. About three-quarters (73%; n=35) also endorsed “because I think I am at risk for HIV/AIDS” and about half (48%; n=23) “to get extra protection against HIV/AIDS” as motivations for volunteering.

In post-trial interviews, the majority of participants (n=11) recounted their altruistic motivations for initially joining the trial: “A reason I got involved in it was for the greater good; I wanted to help people so people in the future wouldn't get sick and die” (43 y.o. gay man). Another participant explained:

I've had so many people, so many friends of mine die; I've watched so many people die. I used to volunteer at Casey House, at Bruce House (hospice and supportive housing for people living with HIV). I've seen so much and anything that I can do to help try and stop it, why wouldn't I? (41 y.o. gay man).

Protection motivation also emerged as a reason for joining the trial, reflecting multi-faceted motivations on the part of 8 volunteers: “Part of it was to protect myself...I was hoping that I would get this vaccine, hoping that it was something that would work so I would have it to protect myself as well” (40 y.o. bisexual man).

Key informants echoed participant accounts of compound motivations for joining the trial: “Why they would be enrolled? I think a couple of things: One, they were hoping to be protected I think, if they did get the vaccine; and then there was a big component of altruism and trying to further science.”

3.2.2. Informed consent and ethics: “*they never actually said that anything like this could possibly happen*”—Trial volunteers at baseline indicated near complete trust in the informed consent process and in their medical provider's advice and care. Volunteers (96%, n=46) nearly unilaterally *disagreed* with the statement, “I, or people like me, might be used as guinea pigs for medical research without my consent.” The majority (92%; n=44) agreed that, “If my doctor wanted me to participate in research, I trust that he or she would fully explain it to me.”

In post-trial interviews, most (n=9) participants expressed ambivalence about the clarity and transparency of the consent process and the ethics of the trial. A participant explained that he did not feel the consent process was adequate: “There was never anybody that sat down with me and said, ‘this could happen, we need you to know that just so that you're aware; that's part of your consent.’ I'm a little pissed off about that” (40 y.o. bisexual man). Similarly, another participant reported:

They never actually said that anything like this could possibly happen, but of course if they did nobody would take the trial. So it was in the back of my mind, wondering, did they know that this was ever a possibility? Because of course if they told anybody nobody would take it (43 y.o. gay man).

Another participant in retrospect questioned the integrity of the trial based on the unforeseen outcomes:

It's almost inherent in the study that in order for them to be able to really study the effects of the vaccine, they really, in essence, want you to contract HIV and that's why you're chosen for the study, because you're in a high-risk group for HIV infection. And so a small voice in my head is saying, well, this is kind of fucked up (45 y.o. gay man).

Alternatively, 6 participants indicated steadfast confidence in the informed consent process and acceptance of the possibility that the trial results were unexpected: “They were very clear that they didn’t know what was going to happen; but I think that that was a result maybe no one was expecting (gay man, no age reported [n.a.]).

Another participant explained that while he had held out hope for the test vaccine, he was nevertheless aware that it might not work; however, he expressed dismay that he was not aware of possible health risks of the trial:

I was hopeful it was going to work. But I also felt confident that my health was not in peril because I'm healthy and I certainly didn't want to become unhealthy to save the world. I'm no martyr (48 y.o. gay man).

Key informants expressed satisfaction with the informed consent process and volunteers’ comprehension: “They understood the consenting process...that we didn’t know what was going to happen.” Similarly, “The informed consent process for the study was so important... to say that, ‘we don’t know whether this vaccine is going to be beneficial or no help or cause harm.’”

Thus initial good will and nearly unilateral trust in medical providers appears to have been compromised for some participants, while others more readily accepted that unforeseen outcomes may occur. Additionally, divergent perspectives emerged between trial participants and key informants regarding the informed consent process.

3.3. In-trial experiences

3.3.1. Engagement in research and relationship with the research team: “I felt like an important part of the whole team...I wasn’t just a guinea pig, you know”—In addition to illustrating the multifaceted scope of reasons for volunteering based on personal and altruistic motivations (see 3.2.1), humanitarian motivations provide a helpful context for understanding volunteers’ expressed feelings about being part of an important scientific endeavor. Participants almost unilaterally (96%; n=46) indicated “to help my community” and “to benefit humanity” as reasons for volunteering.

Post-trial interviews reveal the sense of collaboration and camaraderie experienced by the majority of volunteers (n=8), who characterized their relationship with trial staff and investigators as a “very good rapport” (43 y.o. gay man) and the trial as “overall, a great experience” (44 y.o. gay man).

A volunteer explained:

Even though I was a participant, I felt like I was an important part of the whole team...They didn’t just treat me like a patient or a research study participant. I felt like I was part of the whole process and like an important part of the whole process. I wasn’t just a guinea pig, you know (45 y.o. gay man).

Again indicating a strong sense of engagement in the process of scientific discovery, another volunteer reported, “I felt a bit like a pioneer of sorts. It felt responsible and it felt I was actually quite proud to be part of something that could have some far-reaching impact” (48 y.o. gay man).

Additionally, volunteers expressed feeling welcomed and accepted as an important component of their trial experience: “I felt very, very welcomed. I really felt that I could trust them” (31 y.o. gay man); and, “A lot of the trial is talking about your sexual activity...I didn’t feel like they were judging me for the number of partners or whether I had been safe or not safe. So I guess that was helpful (40 y.o. bisexual man).”

Similarly, key informants acknowledged the importance of establishing personal relationships with the trial volunteers: “You have to have a couple of coordinators that can connect with the participants where the participants feel like they can trust them, that they have an ally.” Some participants sustained strong feelings of being partners in a vitally important scientific endeavor, even amidst the disappointing results and unexpected adverse effects.

3.3.2. Reactions upon study closure: “A worldwide disappointment, let's face it”—Two-thirds (n=32) of trial participants indicated at baseline that, “In the near future, HIV vaccines will reduce the threat of HIV/AIDS.” Twenty participants (42%) indicated that they believed the trial vaccine would prove to be at least 50% efficacious.

A majority (n=12) of those interviewed expressed negative reactions to learning of the trial closure and that the test vaccine made some recipients more susceptible to HIV infection. Participants expressed feeling “disappointed,” “angry,” “pissed off,” “worried about my health” and “sick.” A participant elaborated on his feelings and regret:

I felt sick. I'm sure it's not like finding out that you are HIV-positive but it was that similar kind of feeling. I didn't want to think about it...it's like there's something foreign in your body that you wish wasn't there. I just wish I hadn't done it (40 y.o. bisexual man).

Another participant echoed this feeling, indicating both comprehension of the difference between increased susceptibility and vaccine-induced infection, and a sense of trepidation about being “high risk” already and potentially having that risk exacerbated: “And even though it didn't technically give anyone HIV, when you're in a high-risk category to begin with you feel like, ‘oh great’” (n.a., gay man).

Nevertheless, 4 participants expressed very clearly that while they were disappointed, they realized the trial outcome was within the realm of possibility. For example,

It was a damn shame it didn't work out, but I can't say I was shocked. This is a scientific trial and it's not a bioequivalent, generic deal and it's not a cure-all. It's not a magic bullet...it's an experiment” (48 y.o. gay man).

Key informants expressed feeling “worried” about the trial participants: “Who would have thought we would have been involved in a harmful trial?” Key informants also indicated being pleasantly surprised at “how understanding and mature...the participant population was.” A key informant reported, “no one was angry, nobody was upset,” and related this to the very transparent informed consent process.

Thus a majority of participants expressed feeling distressed and upset, while others were disappointed yet cognizant and accepting of the uncertainties involved with the investigational vaccine. Key informant investigators may have had greater experience with the latter participants or sustained a more positive perspective, but participant and investigator perspectives were divergent.

3.4. Post-trial experiences

3.4.1. Study termination and unblinding: “Just a little bit more information throughout that process would have made a huge difference”—At baseline, volunteers nearly unilaterally (96%; n=46) endorsed, “I can freely ask my doctors any questions I have.” The vast majority (94%; n=45) responded accurately that, “People who join an HIV vaccine trial might not get the study vaccine.” About half (46%; n=22) indicated as a motivation for volunteering, “to get more information about HIV/AIDS vaccines.”

Open communication between trial investigators, sponsors, pharmaceutical companies and participants was identified as vital by participants and key informants alike. Nevertheless, divergences of opinion were revealed in participants' and key informants' assessments of the nature of communication as the closure of the Step Study unfolded. Four participants specifically described their perceptions of slow and sporadic communication, three of whom indicated they first heard of the trial closure through the media rather than from trial staff or investigators. An additional two participants first learned of the trial results from the present sociobehavioral study interviewers.

A participant attributed his negative feelings not to the results *per se* but to inadequate communication throughout the study termination process: "My negative reaction...is based more on the handling of the dissemination...than it is on the actual findings" (n.a., gay man). Other participants described the months they spent waiting to hear from the clinic for unblinding as "scary," highly stressful and full of uncertainty: "When you want to find out if you're more susceptible to infection, you want to know like yesterday, not months in the future" (37 y.o. gay man).

Participants specifically discussed their fear and frustration at hearing initially about the study termination through the media:

The way I found out about this was through the media so initially there was some hostility on my part because I felt well, I'm in this study, if I'm finding out through the media that means that someone knew a week ago at least, you know what I mean? . . . It's very scary when you find out about something that you're involved in, not from the people that you were working with but from outside source (n.a., gay man).

They should be on top of that and they should tell people before that's released to the media. You know, I read it first and, but it was months before anybody told me. . . I would definitely caution people against that in the future. To make sure they're letting you know what's going on with this stuff. . . It's not fair that they hold it back on people (37 y.o. gay man).

A participant who was told she had received the test vaccine struggled with articulating her understanding of the complex results revealed in the unblinding process (enhanced susceptibility to HIV infection among those with high Ad5 [adenovirus] neutralizing antibody titers): "They had a hard time talking to me about it. They basically said I was in a higher level group, which is the 500 something, and if I get a common cold from someone that is sick it could trigger something in my system that would make me get HIV/AIDS" (35 y.o. woman).

She further described her reaction to the news and waiting for her HIV test results:

I was dumbfounded. It hit me in a way where I'm worrying about getting AIDS. And I definitely don't want to die that way. This is my first blood test and I just hope it comes out negative. If it comes out positive, I don't know; I'm going to lose it. It certainly changed my outlook of the trials...I'm pretty scared and I want to find out the results right away. I wish I would never have entered it because I didn't have a perfect life. But now I just feel like a sick person (35 y.o. woman).

Participants spoke of the need to "open that line of communications" between trial sponsors, investigators and volunteers. Further, they attributed what they perceived to be an unwarranted delay to trial sponsors' protecting their own interests: "They went into defense mode and were protecting their interests; and that meant, 'no comment,' which is not what you want to hear when you're like, 'I may have that vaccine in me'" (n.a. gay man).

Two volunteers who had dropped out of the trial were among those who contacted research staff of the present study and were interviewed. (After completion the interviewer provided contact information and urged them to follow up with the research clinic for their own safety.) These volunteers indicated complete surprise upon hearing about the results: “I didn’t receive anything; this is the first I’ve heard of it” (47 y.o. gay man).

That information was never passed on to me. I didn’t know there was any risk; I don’t recall that being discussed with me. It was my understanding that...they believed it would issue a false-positive...but other than that it would have no risk to your immunity at all” (43 y.o. gay man).

Key informants praised the efficiency of the pharmaceutical company and HIV Vaccine Trials Network (HVTN) in responding to the study findings, stating that they were “fantastic in terms of communication...rolling out the results.” Another key informant reported, “I’m a proponent of as soon as you have data and information, you put it out there” and “two months is not bad” (referring to the interval between initial results and beginning to unblind all volunteers). Thus different perspectives emerged between participants and key informants regarding the nature of communication in the process of early termination and unblinding.

3.4.2. Post-trial follow-up and support: “I’m in it for the rest of my life”—Among participants at baseline, nearly two-thirds (n=30) indicated “I think that I really could get HIV/AIDS.” One-fifth (n=10) indicated “concern about how my sexual partner or partners might react to my being in an HIV vaccine trial,” and nearly one-fifth (n=9) “concern that being in an HIV vaccine trial may lead to discrimination against me.”

Trial participants and key informants both emphasized the need for post-trial follow-up and support. Four participants described being left for long periods of time without contact from investigators. After the initial roll-out of results, a participant reported that follow-up subsided: “nobody’s talking.” Another participant reported, “I felt very much like they were completely at a loss about what to do” (n.a., gay man,). A participant who had received the test vaccine expressed “...fear that we’re just going to be abandoned” (40 y.o. bisexual man).

Though “not affected” in the same way as those who received the vaccine, participants who reported receiving the placebo expressed “camaraderie” with volunteers in the experimental vaccine group and viewed follow-up as an opportunity to learn more about the study findings, “how they came to this conclusion” and its impact on study participants:

Did a lot of these people in this clinical trial actually contract HIV while they were doing the trial and what percentage? Are they being even more safe or are they more depressed or are there any suicidal rates? What’s their life like now, are they being compensated or anything? (43 y.o. gay man).

Trial participants and key informants both discussed counseling for volunteers, beyond the traditional risk reduction counseling conducted in HIV prevention trials. A participant explained: “They could have counseled us more on the possible emotional reactions to the possible results, I guess. Having been involved in something for two years, three years, and then at the end of it, it didn’t really help...” (40 y.o. gay man). Key informants reinforced that counseling should be offered “in any prevention study” and should be “mandatory” in research trials; and also support to “arrange a whole counseling and psychotherapy piece” in light of the Step Study outcomes.

A key informant also explained broader challenges and disappointment regarding post-trial dissemination of information in HIV vaccine and other biomedical prevention trials:

The information has not been in favor of big pharma or small pharma coming up with solutions...because of the trials not having the kind of outcomes that are appropriate to continue with. But no one's managing message or creating a level of understanding.

3.4.3. Trust: “*you’re putting a lot of trust in the clinician...the researchers...Merck.*”—

At baseline, the majority (92%; n=44) of participants agreed that, “I completely, or mostly trust my primary doctor or clinic to put my health above all other concerns”; 92% (n=44) disagreed with the statement, “I suspect that doctors have on some occasions given me treatment as part of an experiment without my permission.” Eighty-eight percent (n=42) agreed that, “My doctor would not ask me to participate in medical research if he or she thought it might harm me.”

In post-trial interviews, about half of participants (n=8) stated that they didn't attribute any malice or negative intentions to the investigators. These participants largely agreed that researchers “seem like people who are there for the right reasons” (46 y.o. gay man). “The thing is they didn't intentionally put those people at risk; it surprised everyone, what happened” (45 y.o. gay man). Two of these participants further empathized with investigators' likely feelings of disappointment:

I can't imagine, I mean, the people putting this test together always sound very professional and very interested and very goal-oriented, so I'm sure that they felt just crushed the way the study must have ended. I mean, so I can't imagine anybody purposely putting me at risk. Research is research. It's not always easy; it's not always plain and simple (46 y.o. gay man).

I don't think that they were malicious and I don't think they saw this as a possibility. I don't think that they thought, well It won't give you HIV but it might increase the chances. I don't think that ever occurred to them because this is the first study of this kind so they didn't know that. So I don't fault them for that..I'm assuming they did due diligence and went through these things beforehand. So I think that they were surprised too and I honestly don't, think they intended to try and find the vaccine so if this happened they were also very disappointed (n.a., gay man).

However the unforeseen termination of the study led four participants to specifically express mistrust of clinical trials:

I'm just not as confident in the process. The pharmaceutical company, I think that they in many ways tied the hands of the researchers. But I think that there were things that could've been done better by everyone involved (n.a., gay man).

Another participant indicated fear, even after unblinding, that he may have actually received the test vaccine: “Even though I was told that I had got the placebo...of course then your mind wanders and thinks well maybe they're just saying that for now (43 y.o. gay man).

Key informants discussed the challenges involved post-trial in maintaining participant trust, particularly in the context of high-profile trials that don't achieve desired endpoints, which are then scrutinized by the media and the public. A key informant described the Step Study aftermath in light of perceived gaps in post-trial information dissemination and follow-up among volunteers in the wake of the Vaxgen (AIDSVAX B/B) North American phase III trial, completed in 2003, in which Toronto was also a study site: “when they [investigators/ trial sponsors] don't follow up, it creates that sense that ‘Oh, I'm being used again’” on the part of vulnerable populations.

3.4.4. Willingness to participate: “Once bitten, twice shy”—In contrast to the universal altruistic motivations reported upon volunteering for the trial, post-trial interviews revealed mixed reactions as to how participants’ experience in the Step Study might affect their willingness to participate in future HIV vaccine trials. Six participants reported that enrolling in another HIV vaccine trial would elicit “too much anxiety”; “I’d be very reluctant” (43 y.o. gay man). “I don’t think I could personally commit to one again” (n.a., gay man).

These participants explained that the unexpected harms from the trial would discourage them from volunteering for future trials, because it “could happen again” (40 y.o. gay man), even as they described this outcome as unfortunate:

I am more aware of what can happen in a trial and the risks of it. So now I would not, just for my own self and health and protection, I wouldn’t get involved in something like that again...that’s I guess what I’ve come out with. Smarten up and don’t do this again, unfortunately (40 y.o. bisexual man).

I don’t think I would participate in a vaccine study again because even when they explain to you all the risks that they expect, I mean in this case there was a risk they didn’t anticipate. It happened unfortunately to a lot of people who are going to have to deal with that (n.a., gay man).

A participant articulated his complex feelings and ambivalence, reflecting the widespread motivations based on altruism in conflict with fears for personal health and safety:

I feel very conflicted now more so than when I started in the trial because I still rationally believe that these trials are important and I understand that they need to happen. But at the same time I feel like, well I don’t want to be that guinea pig. I’ve dodged a bullet that I shouldn’t have taken. I’m gun shy; I don’t think I’d be comfortable taking that risk again (n.a., gay man).

Two participants specified their unwillingness to volunteer again for a vaccine trial rather than all clinical trials; for example, “I’d be very reluctant I would say to participate in any future trials where vaccinations are involved because of what had happened” (43 y.o. gay man).

Alternately, 9 participants described ongoing motivations to participate in HIV vaccine trials based on altruism, the memory of a friend and a desire for new HIV prevention technologies. When asked whether they would consider volunteering for a future HIV vaccine trial or not, these participants responded: “without a doubt” (45 y.o. gay man); “absolutely, in a second” (40 y.o. gay man); “...for the same reasons that I originally did it” (43 y.o. gay man); and, “I’m already involved in it and I don’t want to stop; I might find out if there is a real cure out there...and I’ll take the risk again (35 y.o. woman).

Participants also accurately articulated the need to include the results of the Step Study in future trial consent processes: “You would definitely need to tell them about what happened with this study...help them to make an informed decision and help them to know what the risks are of participation (45 y.o. gay man).

Key informants described reservations about future HIV vaccine trials as well, and their increased scrutiny of experimental vaccines: “In the next vaccine trial that comes out...I want to see the science; was there something in the science of the Merck vaccine trial that was missed to not know that this was a potential?” They also anticipated challenges for future HIV vaccine trial recruitment: “How hard does HVTN (HIV Vaccine Trials Network) want researchers to work to recruit participants, when I can’t blame people for not wanting to enroll?”

4. Discussion

This mixed methods investigation examined in depth the experiences and perspectives of volunteers, largely gay men, at one site of the Step Study Phase 2b HIV-1 vaccine trial upon the early termination of the trial. The experimental vaccine was not efficacious and a subgroup of test vaccine recipients were unexpectedly placed at increased susceptibility to HIV infection [7,9].¹ Results suggest critical dimensions of HIV vaccine trials that may impact volunteer perceptions and broader community support for future HIV vaccine research: 1) perspectives on the integrity and transparency of the informed consent process; 2) feelings of connectedness with trial staff and investigators, and sense of engagement in a shared mission; 3) perceptions of the clarity and efficiency of communications by investigators and trial sponsors upon termination of the trial; and, 4) post-trial follow-up information and psychosocial support.

As would be expected, trial participants and key informant investigators/service providers expressed similar as well as divergent perceptions in the wake of the Step Study. The most striking disparity was simultaneously what participants identified as the most troublesome aspect of their trial experience: perceived delays and lack of clarity in communications from trial investigators and sponsors once it became apparent that not only would the test vaccine not prove to be efficacious, but that it may have enhanced some recipients' susceptibility to HIV infection. Over half of participants interviewed went so far as to retroactively doubt the integrity of the informed consent process given the unexpected adverse effects of the test vaccine; however, many expressed acceptance of the fact that a clinical trial involves inherent uncertainties and reported that they had understood the possible risks of participation. Nevertheless, participants questioned and were upset by perceived delays and gaps in communication, particularly in waiting for the trial to be unblinded and in first hearing about the results from the media rather than from investigators.

The apparent lack of awareness among key informants as to the level of criticism and distress among some volunteers may be a result of participants' being less likely to express negative feedback directly to a physician or clinical investigator than to an outside researcher, or perhaps being less likely to follow up with the trial. Furthermore, what may constitute quick, efficient and transparent communication and decision-making in the complex world of clinical trials, among trial sponsors, data safety monitoring boards and investigators, may seem like protracted periods of uncertainty among participants. As participants may continue to engage in similar risk behaviors to those that initially made them eligible for the trial, they may understandably harbor reality-based fears that the test vaccine rendered their even unchanged level of risk behaviors more dangerous. The fact that the present sociobehavioral study succeeded in recruiting two participants who had previously dropped out of the trial and was the initial conduit for informing them of the overall trial results suggests that relatively low-cost community outreach efforts may help to mitigate loss to follow-up and enhance communication of results.

Given volunteers' compound motivations—based on altruism and a desire for individual protection—it may be difficult to disentangle the extent to which initial stated motivations for participation (e.g., protection vs. altruism) may predict reactions upon trial termination (e.g., resentment and mistrust vs. disappointment) and willingness to participate in future trials. However, increasing integration of social science research, including both qualitative and quantitative methods, as an ongoing component of HIV vaccine trials may generate

¹Note: A follow-up observational study (HVTN 504) [22] that was implemented to monitor Step Study volunteers suggests that enhanced susceptibility to HIV infection due to adenovirus (AD5) immunity may have waned over time, but uncircumcised men who have sex with men who received the experimental vaccine continue to show increased risk [23].

evidence to improve our ability to successfully explain challenging concepts to trial participants. Facilitating increased volunteer comprehension of concepts such as random assignment and investigational vaccines may help to mitigate therapeutic misconception and undue expectations of the success of investigational products [11,14,24,25]. Nevertheless, this also raises questions as to how much detail researchers should include in the informed consent process. The mere addition of technical explanations and use of checklists to assess comprehension may not reveal the true extent of participants' understanding of complex scientific concepts [26]. Ultimately, increasing participants' meaningful engagement in HIV vaccine trials may help to sustain participant and community support for future trials [5,27].

An important theme revealed across participants and key informants was the significance of respectful, caring and collaborative relationships between trial staff and volunteers, which tended to be associated with volunteers' feeling a stake in the research as "collaborators" and "pioneers" more so than as mere research "subjects." These somewhat intangible yet positive experiences may serve as important buffers in clinical trials, many of which do not result in efficacious products; they also may support the longer term process of HIV vaccine development.

Limitations to this study include the small sample of participants from one Canadian site of a larger international HIV vaccine trial. Additionally, the subgroup that participated in post-trial interviews may not be representative of the larger trial population; and in adhering to strict confidentiality guidelines we were unable to match baseline survey data with post-trial interviews. It is possible that participants in the post-trial interviews may differ from those who did not participate: they may tend to be those more invested in the trial and HIV vaccines, those more dismayed by the outcome, or those more motivated by the financial incentive. However, the variety of nuanced perspectives expressed, neither unilaterally critical nor supportive, suggests we were successful in recruiting participants with a range of perspectives and opinions. Furthermore, the purpose of this mixed methods investigation was to explore in depth participant experiences and reactions rather than to generalize to the entire multi-site trial; we were successful in eliciting data about trial participants' experience of the process of the clinical trial, which is largely absent from published research on HIV vaccine trials..Future social science investigations in the context of large-scale HIV prevention trials are needed to assess the generalizability of the present findings.

5. Implications

This investigation has several implications for interventions to enhance participant experiences as well as for recruitment and retention in future HIV vaccine trials: 1) focus on improving and clarifying communication mechanisms between participants, trial investigators and trial sponsors; 2) emphasize training, support and recognition of trial staff to facilitate and reward their building camaraderie and a collaborative spirit with participants; 3) increase focus and reasonable resource allocation to support post-trial information dissemination in order to effect clear and timely communication of both negative and positive trial outcomes to trial volunteers, key populations at higher risk, the general public, and the media; and, 4) augment structures to provide informational and supportive post-trial follow-up for trial volunteers, including lay language debriefings, local community forums, and opportunities for referrals for psychosocial support.

Overall, this study suggests that we might conceptualize the interim data analysis that is routinely conducted in clinical trials as an opportunity to assess psychosocial and behavioral indices (e.g., therapeutic misconception) as well as biomedical markers. Similarly, trial endpoints might be consistently structured to comprise psychosocial measures (in addition to risk behavior assessment), including evaluations by participants of the conduct (i.e., process)

of clinical trials [27,28]. Extensive human and financial resources will be needed to support HIV vaccine and other biomedical HIV prevention trials for the foreseeable future. Systematic implementation of integrated (i.e., qualitative and quantitative) social science research among populations at higher risk for HIV [e.g., 11,13,14,17,26,29,30], and particularly in the context of HIV vaccine clinical trials [e.g., 5,12,31,32], may build evidence to support the highest standards of trial implementation and community engagement [6,27,33]. Incorporating social science research in HIV vaccine trials also may help us to prepare for the monumental challenges of future HIV vaccine dissemination [34,35].

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