COLLECTION
SCIENCES SOCIALES
ET SIDA

Recrutement-engagement dans des essais cliniques en prévention

Contextes, logiques sociales et médiations

Sous la direction de
Caroline Ollivier-Yaniv et Mathilde Couderc

anrs France REcherche Nord & sud Sida-hiv Hépatites
Agence autonome de l'Inserm

VRI VACCINE RESEARCH INSTITUTE

COMITÉ ÉDITORIAL

Yoann Allier, ANRS
Mathilde Couderc, Vaccine Research Institute, CEDITEC, UPEC
Véronique Doré, ANRS
France Lert, ANRS
Caroline Ollivier-Yaniv, CEDITEC, Université Paris-Est Créteil

COMITÉ DE LECTURE

Alice Desclaux, IRD
Jean-Daniel Lelièvre, Inserm/Université Paris-Est Créteil
Vinh-Kim Nguyen, Collège d'études mondiales/FMSH
Marie Préau, GREPS Lyon 2 University
Yves Souteyrand, World Health Organization
Bruno Spire, Inserm

Pour citer cet ouvrage :
Ollivier-Yaniv C et Couderc M, Eds. *Recrutement-engagement dans des essais cliniques en prévention. Contextes, logiques sociales et médiations*. ANRS, Collection Sciences sociales et sida, Paris, 2018.

Pour citer un chapitre, par exemple :
Durier C, Desaint C, Launay O. Conséquences socio-comportementales de la participation à un essai vaccinal préventif contre le VIH dans la cohorte ANRS COHVAC. In Ollivier-Yaniv C, Éd. *Recrutement-engagement dans des essais cliniques en prévention. Contextes, logiques sociales et médiations*. ANRS, Collection Sciences sociales et sida, Paris, 2018, p. 71-91.

Exceptional risk: healthy volunteers' perceptions of HIV/AIDS clinical trials

Marci D. Cottingham[1], Julianne M. Kalbaugh[2], Teresa Swezey[3], Jill A. Fisher[4]

Abstract

As with all early-stage testing of investigational drugs, clinical trials targeting HIV/AIDS can pose unknown risks to research subjects. Unlike sick participants seeking a therapeutic benefit, the motivations and barriers for healthy volunteers are more complex and understudied. Drawing on interviews and clinical trial data from 178 healthy volunteers, we examine how they perceive HIV/AIDS studies in the early stages of testing. A subset of healthy volunteers see Phase I HIV/AIDS studies as particularly risky for reasons ranging from fears of catching the disease to long-lasting and uncomfortable side effects or even inexplicable fears that they cannot articulate. Some participants have had past negative experiences in such trials that inform these views, but others cite information from staff and other participants as influential. Healthy volunteers' general fears concerning AIDS also shape their views of participating in Phase I HIV/AIDS clinical trials.

Key words: HIV, AIDS, Phase I studies, healthy volunteers, risk, fear

Since the 1990s, clinical trials have become a global industry. As part of efforts to speed up drug development, the pharmaceutical industry increasingly outsources the clinical testing of its products to contract research organizations (CROs) and other for-profit research companies [1, 2]. Companies have also expanded recruitment for clinical trials to more countries around the world, especially those that are relatively resource poor [3-5]. In spite of these massive changes in the organization of clinical trials, recruitment of research participants continues to be a major challenge that is said to delay drug development by months and sometimes years [6, 7].

As part of the clinical trials industry, not only are more companies engaged in the research enterprise, but a "professional" class of healthy volunteers has emerged to support that research [8]. In the United States (US), attention to such participants stems from the 1996 launch of Philadelphia "zine" *Guinea Pig Zero*

[1] Department of Sociology, University of Amsterdam, REC B6.19, Nieuwe Achtergracht 166, 1018 WV Amsterdam, The Netherlands.
[2] Department of Social Medicine, Center for Bioethics, University of North Carolina, CB 7240, Chapel Hill, NC 27599-7240, USA.
[3] Duke Clinical Research Institute, Duke University, PO Box 17969, Durham, NC 27715, USA.
[4] Department of Social Medicine, Center for Bioethics, University of North Carolina, CB 7240, Chapel Hill, NC 27599-7240, USA. Corresponding author – email: jill.fisher@unc.edu

(*GPZ*) [9, 10] and more recently has been fueled by the informational website "Just Another Lab Rat" [11]. "Professional" healthy volunteers are those that continually enroll in Phase I clinical trials and use the compensation they get from their participation as their primary – if not sole – source of income. Many professional volunteers adopt a clinical trial "lifestyle" in which they adapt their behaviors, such as diet, exercise, and alcohol consumption, to increase their chances of qualifying for studies [12]. The US is a particularly accommodating place for healthy volunteers to treat clinical trials as work because there is a high volume of trials and no regulatory limits on how much compensation participants can earn per year. Additionally, there is no centralized registry of research participants, which means that healthy volunteers can easily circumvent restrictions that could otherwise limit their trial participation [13-15]. Compensation for these trials varies dramatically based on the overall length of the trial, number of days confined to the research facility, and number of outpatient visits. The average US Phase I trial typically pays between $2,000 and $4,000 [16]. Compensation is based primarily on time, and US regulation prohibits setting payment based on risk [17].

A cadre of professional healthy volunteers is advantageous to Phase I researchers who can more easily recruit US participants for their studies than can researchers for later phase trials [18]. Moreover, US healthy volunteers tend to be drawn from more diverse sociodemographic groups than are research participants affected by illness [19]. Because of the financial compensation provided, healthy volunteers are often from disadvantaged minority groups that suffer economic and employment inequalities [20]. Healthy volunteers' social context as well as their serial participation also shapes their perceptions of the risks of clinical trials, leading to narratives in which risk is normalized as either an inescapable part of everyday life [20] or a transient and unremarkable part of study participation [16]. This is not to say that healthy volunteers are indiscriminate about the risks they might take in clinical trials. Indeed, they often describe studies in which they would refuse to participate due to their heightened sense of risk associated with specific drugs or procedures [21].

Given the availability of healthy volunteers in the US, one might expect that there would be few barriers to recruitment for HIV/AIDS clinical trials. Yet, our research suggests that a subset of US healthy volunteers see HIV/AIDS studies in particular as having more short-term and long-term risks than the average Phase I trial. They describe both credible and inexplicable fears about their participation in these trials and may assert their unwillingness to enroll in them. We find that some experienced or "professional" healthy volunteers are concerned about HIV/AIDS clinical trials because of a past personal experience with such studies or information obtained from fellow participants and staff. Other healthy volunteers highlight their trial inexperience or unsubstantiated fears as the basis for their negative views of HIV/AIDS studies. In the absence of direct or indirect experience, negative associations with the disease itself can fill the gap. Healthy volunteers, unlike participants in later phase trials, rarely invoke personal or social benefits of participating in HIV/AIDS clinical trials. Instead, such studies are seen as "serious" and "intense," and associated with feelings of concern, nervousness, apprehension, and fear.

Background literature

Clinical development is typically divided into three required phases for drugs to receive market approval in the US and elsewhere around the world [22]. Phase I trials are those that are designed to test the safety and tolerability of new products, typically using healthy volunteers as research participants. Additional testing in Phase II and III determines a product's efficacy by testing it on affected patients. HIV/AIDS clinical trials depart from many other therapeutic areas because the focus is not only on treatment but also on prevention. Specifically, healthy HIV-negative volunteers are needed to determine if vaccines or drugs can prevent HIV infection in people who are HIV negative [23]. In the realm of HIV preventative vaccine development, developing safe and efficacious vaccines requires recruiting "tens of thousands" of healthy HIV-negative volunteers over an extended period of time [24]. As a result, there has been a significant focus in the scholarly literature on managing the risks to which healthy volunteers are exposed and identifying barriers to and motivators for their participation in HIV vaccine trials [25].

There are always risks associated with participation in clinical trials. Generally, the risks to healthy volunteers in Phase I trials are relatively modest [26-28], with important exceptions such as the death of a participant in France in January 2016 [29]. Drugs being developed for HIV/AIDS are typically antiretroviral agents, which means that healthy volunteers are likely to experience transient impaired taste, rashes, gastrointestinal distress, and increased white blood cell counts [30-33]. For clinical trials conducted on healthy volunteers, unlike those with HIV-infected patients, these risks are not counterbalanced by direct medical benefits. Yet, as with any clinical trials on healthy volunteers, the expectation is that any physiological changes experienced by participants will be relatively short-term and their bodies will return to baseline [34].

HIV vaccine trials, however, have different risks to healthy volunteers than do drug trials. A systematic review of Phase I trials on healthy volunteers found that investigational vaccines have a statistically significant greater chance of producing severe adverse events than all other tested products [26]. One substantial risk unique to HIV vaccines is vaccine-induced sero-positivity or reactivity (VISP, VISR), meaning false positive-HIV tests for study participants [35, 36]. This may occur when participants who receive the active vaccine produce antibodies to HIV on standard HIV screening tests, making it appear as though they are infected when in fact they are not. While this might not affect the overall health of those participants, there could be potential social harms that result [25, 36]. A false positive test for HIV can have profound impacts on participants' personal relationships and also be a source of societal stigma. For example, individuals might face the possibility of discrimination in employment, inability to obtain insurance, inability to obtain a travel visa, ineligibility to serve in the US military, and exclusion from donating blood in some countries [35, 36]. A long-term study of VISP concluded that healthy volunteers in HIV vaccine studies should be informed of the potential that false positive results can last for almost 17 years [37]. Given the seriousness of VISP, researchers have recommended that data be collected about social harms such as stigma and discrimination experienced by HIV vaccine trial participants in the same rigorous manner that physical adverse events are recorded and monitored in clinical trials [38, 39]. This would allow for the provision of appropriate

support services to affected participants and would enable systematic evaluation of the impacts of social harm on study volunteers [38, 39].

While there is a sizeable literature on factors influencing people's willingness to participate in HIV vaccine trials, much of this research focuses on later phase trials that enroll high-risk HIV-negative participants [40]. Research on the challenges of recruiting and retaining volunteers in Phase I/II vaccine trials nonetheless provides insights into some of the factors influencing volunteers' willingness to participate in these studies [24, 38, 40-44]. With drug trials in particular, a systematic review of barriers to HIV patients' participation in HIV drug trials identified several major themes: safety (fear of side effects), distrust of researchers and the research process, concerns and misunderstandings about the research study design, impact of clinical trial participation on daily life and responsibilities, and social discrimination [45]. Many of the same barriers to trial participation emerge in vaccine trials as in HIV drug trials with the addition of participants expressing concern about the vaccine causing HIV/AIDS or resulting in false positive HIV tests [25].

In addition to barriers to participation, there have also been studies of participation motivators. For example, a recent systematic review of motivators for participating in HIV vaccine trials showed that the benefits of trial participation varied based on phase of the trial [46]. Specifically, it was common for studies to find participants motivated both by societal benefits, such as helping society or contributing to science, and personal benefits, such as protecting oneself from HIV, having current information on the disease, and financial compensation [46]. Additionally, research has found that volunteers' willingness to participate may change over the course of the screening and enrollment process with attrition occurring in the steps between prescreening and enrollment [24, 41, 42].

While the literature on HIV/AIDS vaccine trials contributes to our understanding of HIV-positive and/or high-risk volunteers' willingness to participate in these trials, the barriers and facilitators to recruiting healthy HIV-negative volunteers to Phase I trials is understudied. In particular, there is a dearth of information about how healthy volunteers at low risk for HIV infection perceive the risks and benefits of participation in HIV drug and vaccine trials. In part, this reflects a general bias in the published literature that tends to focus more on Phase III efficacy trials than on early-phase testing [19]. Yet, healthy volunteers who participate in clinical trials across diverse therapeutic areas might have important insights to share on their perceptions of the differential risks of such trials.

Methods

As part of a longitudinal, mixed-methods study of healthy volunteers' participation in Phase I clinical trials, this paper draws upon data collected in 570 semi-structured interviews and 878 clinical trial surveys with 178 healthy volunteers. Participants were recruited to our study from May to December 2013 while they were participating in a Phase I clinical trial at one of seven US clinics. Our recruitment method ensured that the participants would have participated as healthy volunteers in at least one clinical trial. However, participants' experience as healthy volunteers was broad at enrollment: approximately 21% were participating in their first clinical trial, 28% were enrolled in their second through fourth study, 25% were enrolled in their fifth through tenth study, and 26% reported participating in more than 11 studies and upward to 200 clinical trials (see *table 1*).

Our sample shows consistency with typical Phase I trial participants [16,19], with a majority consisting of men (74%) and racial and ethnic minorities (68%). Specifically, 40% self-identified as black, 32% as non-Hispanic white, 21% Hispanic, 7% as more than one race, 5% as Asian, Native Hawaiian or Pacific Islander, and 1% as Native American.[5] Almost 20% of our participants were born outside of the US, coming from countries in Africa, Asia, Europe, and the Americas. More than 60% of our sample were between the ages of 30 and 49, and 22% were between the ages of 18 and 29.

Table 1
Demographics of study participants (N=178)

	n	%
Sex		
Female	47	26.4%
Male	131	73.6%
Age		
18-21	6	3.4%
22-29	34	19.1%
30-39	58	32.6%
40-49	54	30.3%
50+	26	14.6%
Race/ethnicity		
Non-Hispanic white	57	32.0%
Black	72	40.4%
American Indian	2	1.1%
Asian	6	3.4%
Native Hawaiian or Other Pacific Islander	2	1.1%
More than one race	13	7.3%
Hispanic	38	21.3%
Foreign born	35	19.7%
Clinical Trial Experience		
1 study	38	21.3%
2-4 studies	49	27.5%
5-10 studies	45	25.3%
11-200 studies	46	25.8%

After their enrollment and participation in a baseline interview, participants were randomized using a 1:5 ratio into either the control arm or the full-participation arm of the study.[6] The control arm (n=33) involves interviews only at baseline

[5] As per US funding agency reporting requirements, ethnicity data were collected separately from race, which accounts for numbers not totaling 178.

[6] The purpose of having two study arms was to determine if the additional interviews and clinical trial data collection might unintentionally have an effect on the volunteers' perceptions, behaviors, or decisions about clinical trials during the study.

and three years after enrollment, with no other data on trial participation collected throughout the study. The full-participation arm (n=145) involves participating in three additional semi-structured interviews on top of the baseline and 3-year interviews, as well as providing real-time information about their clinical trial participation. Clinical trial data were collected through the "clinical trial diary" (CTD), filled out by participants online or by a staff member over the phone [18]. Ongoing participation in Phase I clinical trials was not a requirement of our study; however, the full-participation arm of the study was required to fill out a CTD for every Phase I study for which they screened. Most of these trials were those conducted by private companies on behalf of a pharmaceutical company. Our findings are based on interview data from participants in both the control and full-participation arms and the CTD data from participants in the full-participation group.

Baseline interviews were conducted in person at the clinic at the time of enrollment. Subsequent follow-up phone interviews occurred at 6-months, 1-year, and 2-years for the full-participation arm, and with both arms at 3-years.[7] The interviews concentrate on participants' experiences participating in Phase I trials, perceptions of the risks and benefits, assessments of different types of studies and/or procedures, and decision-making about trial enrollment. Interview questions do not focus on any therapeutic area because we are interested in the range of clinical trials in which healthy volunteers participate. Therefore, participants' thoughts about and experiences in HIV/AIDS studies are all unprompted. All interviews were transcribed in full, verified for accuracy, and coded using Dedoose qualitative software by two members of the study team.

Results

Direct comparison of the *actual* risks of HIV/AIDS studies to other types of clinical trials is complex because Phase I trials are conducted on all investigational drugs and have different scientific goals. From our interviews with US healthy volunteers, however, HIV/AIDS studies emerged as an exceptional type of clinical trial – along with studies of cancer and psychotropic drugs – that 38 participants (21%) directly referenced. Participants varied in their views of HIV/AIDS studies, but in general, volunteers see these Phase I studies as particularly risky for reasons ranging from fears of catching the disease, to long-lasting and uncomfortable side effects, or fears that they cannot articulate. Some participants base their views on past experiences in such trials, but others cite staff and other participants as shaping their beliefs about these studies.

Participants who were fearful of HIV/AIDS studies vacillated in their rationale. Some were concerned about actually contracting the disease itself or falsely testing positive for the disease after participating in a study. For example, Blake,[8] a black man in his 30s, asserted:

I've heard people talking about a AIDS [long pause] AIDS study, you know, where they take a-a small percentage of HIV or something like that, or like. 01% and inject it in your body and see how a body-. But you could receive tens of thousands of dollars. I don't know if that's true. Some things I hear are a myth,

[7] At the time of this writing, we have concluded data collection but have not yet analyzed data from the 3-year interviews, so they are not included here.

[8] We use pseudonyms to protect the confidentiality of our participants.

but, you know, they say, they say it's a, it's-it's less than 1% of 1% of a chance that you can catch AIDS, or HIV or whatever, doing the study, you know. But I don't, I don't want to take a risk like that.

Blake had participated in about a dozen studies as a healthy volunteer over the course of eight years, and his experience with AIDS studies is limited to what he has heard from other participants. Even though he acknowledges that a risky study like this could be an urban legend, he nonetheless asserts that he would not take the risk of enrolling in HIV/AIDS trials for fear of catching the disease. Similarly, Ray, a black man in his 20s, also explicitly identifies AIDS as an example of a "crazy" study that he would not participate in:

But depending on like what you're doing the study for, to me personally, I don't see like-, I mean, for Tylenol [acetaminophen], we didn't really have no long-term effect, you know, down the line, or yeah. So I think, you know, me personally, I just wouldn't do no crazy studies; as far as like AIDS medicine and all that crap, I'm cool.

Overall, Ray sees clinical trials as generally risky and contrasts a common pain medication to "crazy," higher risk studies such as those for AIDS medication.[9] Comparing Tylenol to AIDS medicine allows Ray to make sense of the unknown harms of Phase I testing. Anita, a Mexican immigrant in her 50s, also identifies AIDS as particularly high risk: "There are, are, are [studies] for AIDS, or I think that those are more, more intense, more risky."[10] Notably, the sources of these participants' views were not always clear. In the case of both Ray and Anita, each was enrolled in their first study when we interviewed them, suggesting that they had little personal experience or specific information on which to assess the differential risks of AIDS trials.

In contrast, ten participants, 26% of those who discussed HIV/AIDS trials, expressed their willingness to participate in such studies or even believed they might gain direct, positive therapeutic benefits. For example, Travis, a black man in his 40s, notes that he has done an AIDS study and dismisses any concerns about it. Comparing his experience to other types of studies he perceives as riskier, he says:

I actually run the other way from [some drug trials], especially when it says "investigational," [or] "schizophrenia." Anything that has anything to do with them, I'm good [I don't need to do them]. I've done some AIDS stuff. They make you go to the bathroom. You know, that's about it, to be honest with you.

In other words, Travis seems to see both AIDS trials and the gastrointestinal adverse effects he experienced as fairly banal. His phrasing of "AIDS stuff" and "you know, that's about it" conveys a sense that AIDS studies have side effects that are inconvenient, but not necessarily dangerous or alarming. Having participated in over 50 studies, Travis is more worried about the phase of development ("investigational" drugs by which he might mean first-in-human trials) and psychotropic medications.

---

[9] Tylenol was not being tested in any of the clinical trials in which our participants were enrolled. They often made references to acetaminophen, however, as a way of describing clinical trials for pain or arthritis medications. We see this phenomenon as a mechanism for them to normalize the risks of certain clinical trials.

[10] Original Spanish: "*Hay, hay, hay del SIDA, o yo creo que esos son mas, mas fuertes, mas riesgosos.*"

More than minimizing the side effects, Esteban, a Mexican immigrant in his 30s, even emphasizes the potential *positive* effects of participating in an AIDS drug trial:

I've done one study for AIDS; it was very well paid... It paid $7,000 and some change... It was a study that really inspired a lot of confidence because it strengthened your immune system. If it strengthens the immune system of a sick person, it's even more so for a healthy person. It's logical, just a little common sense. So I really liked that study.[11]

Esteban interprets the risks and benefits of the AIDS study in a unique way. He uses his knowledge of AIDS as an immune system disorder and assumes that there is a benefit to his own immune system by consuming the investigational drug. Esteban's work installing satellite television antenna, which is very physical, might have made him more inclined to perceive positive health benefits. But Travis and Esteban appear to be outliers, as the majority of participants who mention HIV/AIDS studies stress that they are nervous or fearful of these types of studies and see them as stronger medications with higher risks and longer lasting side effects. This might, in part, be related to their overall Phase I trial experience. Both had actual experience participating in HIV drug studies, and not only did neither feel harmed, but also Esteban believed himself to have benefitted personally from the drug.

Clinical trial experience level may also play a role in how participants view HIV/AIDS studies. Five participants to date have enrolled in HIV/AIDS trials while participating in our study[12]. Their clinical trial experience at baseline ranged from 7 to 45 trials with an average of 27 clinical trials, and only one of these five participants had single-digit trial experience. In contrast, the 29 participants who expressed negative views of HIV/AIDS studies had a wider range of experience from one to 200 trials. More than half of these healthy volunteers had participated in fewer than ten clinical trials, with four first-time participants in this group. At the same time, however, there were a disproportionate number of participants with 11 or more trials who also held negative views of HIV/AIDS studies. Even though these participants make up only 25% of our overall sample, they constitute almost half of those with negative views. While the number of participants here is small, these figures suggest that first-time participants along with those who are highly experienced may be more likely to view HIV/AIDS studies in a negative light compared to those with mid-level experience. Overall trial experience may have a curvilinear relationship to negative views. This is modified by personal experiences in HIV/AIDS studies, such as in the case of Travis, for whom who not having been harmed in an HIV trial is more important than his overall trial experience.

In terms of the relationship between experience level and views of HIV/AIDS studies, Vanessa, who is a Columbian immigrant in her 50s and had participated

---

[11] Original Spanish: "*He hecho un estudio para el SIDA, está muy bien pagado... pagaba 7.000 y cacho dólares... Era un estudio que daba mucha confianza porque te fortalecía el sistema inmune, si a una persona enferma le fortalece el sistema inmune, a una persona sana pues con más ganas. Por lógica, un poquito el sentido común, entonces ese estudio me gusto mucho.*"

[12] CTD data for baseline through 2-year interviews is used for this analysis. It should be noted that many participants in our study have poor recall about the therapeutic purpose of the drug being tested in Phase I trials. Out of 509 CTDs for clinical trials in which our participants actually enrolled, they could not recall the therapeutic purpose of the study drug in 35 CTDs (7%).

in three trials at the time of her first interview, explicitly links her reluctance to enroll in HIV studies to her own lack of experience:

HIV and that, I won't do that. Or I've heard that the ones for schizophrenia or mental illness, I don't know. I've never done any of those, but they say that some of them have-. I don't know. Some people say they have side effect; other people say that nothing happen [sic]. But still, I don't-, like I say, I'm not a pro at this. I just kind of started.

After noting that she has heard mixed information from other participants, she highlights her Phase I trial inexperience as the reason for her avoidance of such studies.

Vanessa's quote also illustrates that other participants can serve as a source of information about HIV/AIDS trials. Bruce, a white man in his 40s with experience in 20 trials, has also received information on side effects from other participants:

I remember the HIV drugs that were coming out at some point in the 90s or early 2000s. I think those offered a lot of side effects that were overwhelming to some people. And so, you know, I realized that, and because of that, I just didn't do them. I mean, I didn't wanna have all those kinda side effects. I mean, people would tell me they'd be sick throughout the entire study, and I'm like, "Well, geez, that doesn't sound like fun; that doesn't sound like a vacation; that doesn't sound like anything I wanna do."

In addition to information coming from other participants, two healthy volunteers note they became concerned about HIV/AIDS studies as a result of information they received from Phase I clinic research staff. For example, Calvin, a black man in his 30s, says that a motherly staff member took him aside:

[She said,] "I don't want you doing, you know, anything with cancer or HIV; promise me." So, "Wow, okay." She was like, "Save your money, keep going to school, you know, but never do a cancer or an HIV medication drug." She was like, "I would not do too many [trials] at all anyway, but definitely don't do those two." So my apprehension towards those always was and always will be.

Calvin began participating in trials in 1999 and reported participating in over 100 clinical trials. Despite being quite experienced with clinical trials, though, he notes that he has avoided HIV studies because of the early warning he received from this staff member. Participants' relationships with research staff vary dramatically, but participants often speak of trusting *informal* information that staff give them about studies. Unlike the informed consent process, participants attribute staff's advice or insider knowledge to the rapport they develop over the course of the participant repeatedly returning to the same clinic.

Personal experience with long-lasting and uncomfortable side effects also corroborated participants' views. Steve, a white man in his 40s who was another experienced participant having done 70 trials, describes HIV studies in particular as scary.

If the informed consent [form] looked a little too scary, I'll pass on it, unless I'm really desperate. Like for example, I won't do HIV studies anymore because I did one back in "99, and it was the only one – it was the worst side effects I ever had in a study – it was the only one where I got sick and vomited.

Because of his negative personal experience with such a HIV study over a decade ago, Steve claims he would avoid such studies in the future.

Some participants, however, do not cite staff, other participants, or personal experience as a basis for their views of HIV/AIDS studies. Even with his experience participating in 16 trials, Leo, a black man in his 30s, lacked specific reasons for why he wanted to avoid AIDS studies:

Those are very, very-. I don't even know what word to use. Those are serious medications like that, that's used for, you know, serious illnesses. So I would assume that if [there were] any side effects, the side effects would be serious. And that's just the way my brain thinks... So, you know, the information that we have [about the studies] is basic information. And I'm sure, you know, it gets deeper. So I try to make sense of the information that I have and what makes, you know, whatever makes sense to me. I just try to follow my gut and just, you know, go about it in that form.

In such instances, without clear information on how to weigh the risks of studies, it seems reasonable to follow instincts and gut reactions to the different types of illnesses being targeted by investigational drugs. The problem with this strategy, though, is that it is likely to rely on unspoken and possibly even unconscious negative associations and stigma related to populations afflicted by different diseases. The HIV/AIDS epidemic was assumed in the 80s and 90s to affect only gay men and drug users, two populations already stigmatized as immoral among Christian conservatives in the US [47]. Negative media portrayals of AIDS, especially those from the 1990s, might also play a part in shaping participants' fears about HIV/AIDS studies [48]. For Leo, as with Ray and Anita above, there is the intangible feeling, regardless of the information provided about a clinical trial, that AIDS studies are riskier because the illness itself is such a serious one.

Conclusion

Overall, HIV/AIDS studies emerged from a subset of the interviews with healthy volunteers as examples of Phase I trials with exceptional risk. The reasons for this exceptional risk included fears of catching the disease, attempts to avoid long-lasting and uncomfortable side effects, as well as inexplicable fears that were difficult to articulate. Some participants have had past negative experience in such trials that informs these views, but others are influenced by information from staff and other participants. There were no differences based on gender or ethnicity in participants' views of these risks. However, our data suggest that blacks and participants in their 40s are more likely to hold negative views of HIV trials than are whites and younger healthy volunteers.[13] To date, five participants of the 145 in our full-participation group (those who are providing details on their trial participation) have reported actually enrolling in an HIV or AIDS-related study during that timeframe. Out of the 509 total clinical trials in which our participants enrolled, only 8 were HIV or AIDS studies (see *table 2*). This accounts for less than 2% of the studies participated in over a two-year period. All of these HIV/AIDS studies were sponsored by a pharmaceutical company and conducted in a clinic operated by that company or in a private, commercial research clinic. While our participants also enrolled in studies at universities or government clinics, none of these studies were related to HIV.

[13] Because of the unprompted nature of participants' reflections on HIV trials, we do not have data from nearly 80% of our total sample regarding their perceptions of HIV trials. Thus, we are hesitant to interpret these differences for race and age as study findings.

Table 2
Number of clinical trials participated in by aggregate illness (N=509)

	n	%
Brain-related (includes Parkinson's, Alzheimer's, and psych drugs)	70	13.8%
Pain	54	10.6%
Cancer and cancer-related	35	6.9%
Does not recall	35	6.9%
Liver-related (includes Hepatitis C)	34	6.7%
Cardiovascular Disease (includes hypertension and cholesterol)	34	6.7%
Autoimmune Diseases (includes multiple sclerosis)	34	6.7%
Blood-related	31	6.1%
Diabetes	28	5.5%
Arthritis	27	5.3%
Infectious disease (includes antibiotics)	21	4.1%
Gastrointestinal-related	19	3.7%
Kidney-related	13	2.6%
Lung-related	9	1.8%
Bone-related	8	1.6%
HIV	8	1.6%
Hormone-related	7	1.4%
Sexual-related	7	1.4%
Sleep-related	7	1.4%
Addiction	5	1.0%
Skin-related	5	1.0%
Allergies	3	0.6%
Anti-Fungal	3	0.6%
Immunosuppressant	3	0.6%
Muscle-related	3	0.6%
STI	3	0.6%
Anesthetic	2	0.4%
Pancreas-related	1	0.2%

While our dataset illustrates a broad range of therapeutic areas in which healthy volunteers enroll in trials, it is unclear how many Phase I HIV/AIDS trials were initiated by research facilities during the timeframe of our study or how many of our participants had the opportunity to participate in an HIV/AIDS trial. Based on the small number of our participants enrolling in HIV/AIDS trials, however, our data suggest – perhaps counter-intuitively – that professional healthy volunteers are not the most likely to participate in these studies. Future research could investigate more systematically healthy volunteers' perceptions of these studies by asking them directly about their views, sources of information, and opportunities for participating in HIV/AIDS trials. Our findings nonetheless suggest that fear concerning AIDS shapes the views of a subset of healthy volunteers who participate in Phase I trials. As participation from healthy volunteers is critical to the development of HIV/AIDS drugs and vaccines, future research should continue to explore the complex motivations of this subpopulation.

References

1. Fisher JA. *Medical research for hire: the political economy of pharmaceutical clinical trials*. New Brunswick: Rutgers University Press, 2009.
2. Mirowski P. *Science-Mart: privatizing American science*. Cambridge, MA: Harvard University Press, 2011.
3. Petryna A. *When experiments travel: clinical trials and the global search for human subjects*. Princeton: Princeton University Press, 2009.
4. Rajan KS. Experimental values: Indian clinical trials and surplus health. *New Left Review* 2007; 45: 67-88.
5. Shah S. *The body hunters: how the drug industry tests its products on the world's poorest patients*. New York: The New Press, 2006.
6. Allison M. Reinventing clinical trials. *Nat Biotechnol* 2012; 30: 41-9.
7. Fisher JA. "Ready-to-Recruit" or "Ready-to-Consent" populations?: informed consent and the limits of subject autonomy. *Qual Inq* 2007; 13: 875-94.
8. Abadie R. *The professional guinea pig: big pharma and the risky world of human subjects*. Durham, NC: Duke University Press, 2010.
9. Helms R. *Guinea Pig Zero: an anthology of the Journal for Human Research Subjects*. New Orleans: New Mouth for the Dirty South, 2005.
10. Weinstein M. A public culture for guinea pigs: US human research subjects after the Tuskegee study. *Sci Cult (Lond)* 2001; 10: 195-223.
11. Motluck A. Occupation: lab rat. *New Scientist* 2009; 203: 40-3.
12. Monahan T, Fisher JA. "I'm still a hustler": creative and entrepreneurial responses to precarity by participants in Phase I clinical trials. *Econ Soc* 2015; 44: 545-66.
13. Dresser R. Subversive subjects: rule-breaking and deception in clinical trials. *J Law Med Ethics* 2013; 41: 829-40.
14. Devine EG, Waters ME, Putnam M, *et al.* Concealment and fabrication by experienced research subjects. *Clin Trials* 2013; 10: 935-48.
15. Dickert NW. Concealment and fabrication: the hidden price of payment for research participation? *Clin Trials* 2013; 10: 840-1.
16. Fisher JA. Feeding and bleeding: the institutional banalization of risk to healthy volunteers in phase I pharmaceutical clinical trials. *Sci Technol Human Values* 2015; 40: 199-226.
17. Grady C. Payment of clinical research subjects. *J Clin Invest* 2005; 115: 1681-7.
18. Edelblute HB, Fisher JA. Using "clinical trial diaries" to track patterns of participation for serial healthy volunteers in US phase I studies. *J Empir Res Hum Res Ethics* 2015; 10: 65-75.
19. Fisher JA, Kalbaugh CA. Challenging assumptions about minority participation in US clinical research. *Am J Public Health* 2011; 101: 2217-22.
20. Cottingham MD, Fisher JA. Risk and emotion among healthy volunteers in clinical trials. *Soc Psychol Q* 2016; 79: 222-42.
21. Fisher JA. Stopped hearts, amputated toes, and NASA: contemporary legends among healthy volunteers in US phase I clinical trials. *Sociol Health Illn* 2015; 37: 127-42.

22. Fisher JA, Cottingham MD, Kalbaugh CA. Peering into the pharmaceutical "pipeline": Investigational drugs, clinical trials, and industry priorities. *Soc Sci Med* 2015; 131: 322-30.

23. Dubé K, Ramirez C, Handibode J, *et al.* Participation in HIV cure-related research: a scoping review of the proxy literature and implications for future research. *J Virus Erad* 2015; 1: 250-6.

24. Newman PA, Daley A, Halpenny R, Loutfy M. Community heroes or "high-risk" pariahs? Reasons for declining to enroll in an HIV vaccine trial. *Vaccine* 2008; 26: 1091-7.

25. Mills E, Cooper C, Guyatt G, *et al*. Barriers to participating in an HIV vaccine trial. *AIDS* 2004; 18: 2235-42.

26. Johnson RA, Rid A, Emanuel E, Wendler D. Risks of phase I research with healthy participants: a systematic review. *Clin Trials* 2016; 13: 149-60.

27. Emanuel EJ, Bedarida G, Macci K, Gabler NB, Rid A, Wendler D. Quantifying the risks of non-oncology phase I research in healthy volunteers: meta-analysis of phase I studies. *Br Med J* 2015; 350: h3271.

28. Sibille M, Donazzolo Y, Lecoz F, Krupka E. After the London tragedy, is it still possible to consider phase I is safe? *Br J Clin Pharmacol* 2006; 62: 502-3.

29. Hawkes N. French drug trial had three major failings, says initial report. *Br Med J* 2016; 352: i784.

30. Calabrese C, Berman SH, Babish JG, *et al.* A phase I trial of andrographolide in HIV positive patients and normal volunteers. *Phytother Res* 2000; 14: 333-8.

31. Hendrix CW, Flexner C, MacFarland RT, *et al.* Pharmacokinetics and safety of AMD-3100, a novel antagonist of the CXCR-4 chemokine receptor, in human volunteers. *Antimicrob Agents Chemother* 2000; 44: 1667-73.

32. Kraft WK, McCrea JB, Winchell GA, *et al.* Indinavir and rifabutin drug interactions in healthy volunteers. *J Clin Pharmacol* 2004; 44: 305-13.

33. Hawkins T. Understanding and managing the adverse effects of antiretroviral therapy. *Antivir Res* 2010; 85: 201-9.

34. Sibille M, Deigat N, Janin A, Kirkesseli S, Vital Durand D. Adverse events in phase-I studies: a report in 1015 healthy volunteers. *Eur J Clin Pharmacol* 1998; 54: 13-20.

35. VISR Working Group of Global HIV Vaccine Enterprise, Voronin Y, Zinszner H, Karg C, *et al*. HIV vaccine-induced sero-reactivity: a challenge for trial participants, researchers, and physicians. *Vaccine* 2015; 33: 1243-9.

36. Allen M, Lau CY. Social impact of preventive HIV vaccine clinical trial participation: a model of prevention, assessment and intervention. *Soc Sci Med* 2008; 66: 945-51.

37. Desaint C, Durier C, Poda A, *et al.* Long-term persistence of vaccine-induced HIV seropositivity in healthy volunteers. *J AIDS Clin Res* 2014; 5: 275.

38. Gray K, Legg K, Sharp A, *et al.* Participation in two phase II prophylactic HIV vaccine trials in the UK. *Vaccine* 2008; 26: 2919-24.

39. Sheon AR, Wagner L, McElrath MJ, *et al.* Preventing discrimination against volunteers in prophylactic HIV vaccine trials: lessons from a phase II trial. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; 19: 519-26.

40. Lucero MC, Diaz-Brito V, Murillo BT, *et al*. Reasons for not participating in a phase 1 preventive HIV vaccine study in a resource-rich country. *AIDS Patient Care STDS* 2012; 26: 379-82.

41. Sobieszczyk ME, Xu G, Goodman K, Lucy D, Koblin BA. Engaging members of African American and Latino communities in preventive HIV vaccine trials. *J Acquir Immune Defic Syndr* 2009; 51: 194-201.

42. Thapinta D, Jenkins RA, Morgan PA, *et al.* Recruiting volunteers for a multisite phase I/II HIV preventive vaccine trial in Thailand. *J Acquir Immune Defic Syndr* 2002; 30: 503-13.

43. Ellman TM, Hawkins K, Benitez J, *et al.* Representation of Latinos and Blacks in screening for and enrollment into preventive HIV vaccine trials in New York City. *Vaccine* 2015; 33: 6809-15.

44. Luzi AM, Gallo P, Colucci A, *et al.* Communication, recruitment and enrolment in the preventative and therapeutic phase I clinical trial against HIV/AIDS based on the recombinant HIV-1 Tat protein. *AIDS Care* 2011; 23: 939-46.

45. Mills E, Wilson K, Rachlis B, *et al.* Barriers to participation in HIV drug trials: a systematic review. *Lancet Infect Dis* 2006; 6: 32-8.

46. Dhalla S, Poole G. Motivators to participation in actual HIV vaccine trials. *AIDS Behav* 2013; 18: 263-277.

47. Chambré SM. *Fighting for our lives: New York's AIDS community and the politics of disease.* New Brunswick: Rutgers University Press, 2006.

48. Hart KPR. *The AIDS movie: representing a pandemic in film and television*. New York: Routledge, 2014.