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# Preparing for future European efficacy trials of interventions to prevent HIV and other sexually transmitted infections: Lessons on willingness to participate and barriers to participation from ten German clinics serving behaviorally vulnerable men who have sex with men

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ABSTRACT

Future efficacy testing of interventions to prevent HIV or other infections will require engagement of vulnerable populations. We characterized willingness to participate in a future HIV vaccine trial and barriers to participation among men who have sex with men in a 12-month German cohort study. Among 1015 participants at enrollment, 604 (60%) reported willingness, 60 (6%) were unwilling, 351 (35%) were unsure or refused to answer. Among those unwilling, the primary reason was fear of getting HIV. Among those willing, reasons included protection against HIV and furthering scientific knowledge. In a multivariable logistic regression model, higher odds of willingness to participate were seen among participants at the 12-month visit (aOR: 1.09, 95% CI: 1.04–1.15) and with prior knowledge of HIV vaccine research (aOR: 1.14, 95% CI: 1.06–1.23). Educating potential participants about vaccine research may facilitate recruitment and participation in future trials of HIV vaccine candidates and other prevention interventions.



## Introduction

Recruitment and retention of vulnerable participants is essential to the successful efficacy testing of any prevention intervention [1]. Trials that engage populations vulnerable to human immunodeficiency virus (HIV) and other sexually transmitted infections (STIs) face unique challenges since such populations may be marginalized and affected by comorbidities or substance use and mental health disorders that can interfere with research engagement [2]. The COVID-19 pandemic also highlighted and exacerbated vaccine hesitancy, which may complicate recruitment into trials of vaccine candidates for HIV and other STIs [3].

In the early 2000s, multiple HIV pre-exposure prophylaxis trials were canceled or stopped early due to community concerns about inadequate safety data, inadequate healthcare access, and a lack of community involvement in study design [4]. More recently the Imbokodo and Mosaico HIV vaccine trials were terminated early due to ineffectiveness, which may affect willingness to participate in future trials. Clinical trials for other STI vaccine candidates are in the pipeline including preclinical trials for syphilis, phase I trials for chlamydia, and phase II trials for gonorrhea, which will require strong community engagement as they move into larger phase III trials [5]. Recognizing the importance of community engagement in research, the Joint United Nations Programme on HIV/AIDS and AIDS Vaccine Advocacy Coalition released guidelines on good participatory practice in 2011 [6]. However, recent studies found more engagement is needed to meet guideline targets [7].

Community engagement needs to be tailored to individual target populations [8]. Previous studies found a wide range in reported willingness to participate in HIV vaccine trials across regions, with only 50% of youth in Tanzania reporting willingness compared to 99% of individuals from fishing communities in

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Uganda [9,10]. Characterizing potential barriers and facilitators to participation in HIV vaccine trials is key to ensuring successful conduct of such trials. Target populations for HIV prevention studies in the United States and Africa have been well-characterized, but there are limited data on factors associated with the potential engagement and participation of key populations in a European setting [7,11,12].

In Germany, men who have sex with men (MSM) have a high burden of HIV and other STIs with an STI prevalence of 40% among MSM on PrEP [13,14]. In 2020 41% of new HIV diagnoses in Germany were among MSM [15]. Therefore, it is important to test interventions that may reduce incidence in this population. We characterized willingness to participate in future vaccine trials to inform the design and conduct of future efficacy studies among MSM in Germany.

## Methods

The BRAHMS observational cohort enrolled behaviorally vulnerable MSM at 10 clinics in seven major German cities from June 2018 to July 2019, as previously described [14]. All clinics catered to sexual and gender minorities, had strong existing relationships with these communities, and had research experience and infrastructure prior to participation in BRAHMS, including experienced staff who participated in both clinical care and research activities. Individuals were eligible for enrollment if they had a non-reactive HIV test, identified as male, were 18–55 years of age, and self-reported condomless anal intercourse with at least two unique male partners or had an STI in the past 24 weeks [14]. Participants received HIV/STI prevention counseling and were tested for HIV and other STIs every three months for up to 12 months. The study was approved by institutional review boards of the Walter Reed Army Institute of Research, the University Duisburg–Essen, and all collaborating institutions. All participants provided written informed consent. Only questionnaire data were used for these analyses.

Participants completed a vaccine-related, sociobehavioral, and demographic questionnaire at enrollment and after 12 months. Participants were asked "If a preventive HIV vaccine candidate became available for testing to determine whether it could help prevent people from acquiring HIV, would you be willing to participate in such a study to receive vaccination?" Among participants who reported willingness to participate, reasons for willingness were solicited. Participants who reported unwillingness to participate were asked to provide reasons for unwillingness. Prior knowledge of vaccine research was assessed by asking participants if they had ever received education or information on HIV vaccine research. Participants were also asked to provide true/false responses to the following statements: (1) a vaccine is used to prevent illness, and (2) there is an effective vaccine to prevent HIV infection.

Data were entered directly into the ArcGIS Survey123 platform (Esri, Redlands, US) and final data were stored in OneDrive (Redmond, US).

### *Statistical analyses*

Chi-squared tests were used to compare demographic characteristics at enrollment between participants who were willing, unwilling, and unsure about participating in future trials. Top reasons for willingness and unwillingness to participate were tallied. McNemar's test was used to calculate change in pre-post responses from enrollment to the 12-month visit.

Generalized estimating equations were used to identify factors associated with the main outcome of willingness to participate in future HIV vaccine trials. For this analysis, the "unsure" and "unwilling" groups were combined. Visit (enrollment or 12-month) was included as an independent variable to assess change over time. Other independent variables were included a priori based on existing literature.

## Results

Of 1,017 participants enrolled, 1,015 completed the enrollment vaccine questionnaire, and 900 completed the 12-month questionnaire. There were no significant differences in demographic characteristics between those willing, unwilling, and unsure about participating in future trials (Table 1). Among all participants, 420 (41.4%) had ever received information on HIV vaccine research and those who had received information were most likely to be willing to participate in future trials (p = 0.02). Among participants who had ever received information on HIV vaccine research, the main sources were the internet (n = 226, 53.7%) and hospital, clinic, or health workers (n = 223, 53.0%).

Vaccine knowledge varied significantly by willingness to participate. The misconception that there is an effective vaccine to prevent HIV was reported by 79 (13.1%) participants who were willing to participate, 3 (5.0%) unwilling, and 24 (6.8%) who were unsure (p = 0.009). Most participants knew that a vaccine is used to prevent illness, including 574 (95.2%) willing to participate, 57 (95.0%) unwilling, and 329 (93.7%) unsure (p = 0.01).

Among 1015 participants who completed the enrollment questionnaire, 604 (60%) reported willingness to participate in future vaccine trials, 60 (6%) were unwilling, and 351 (35%) were unsure or refused to answer. Among 900 participants who completed the 12-month questionnaire, 587 (65%) reported willingness (Fig. 1a). The majority of participants who were willing to participate at enrollment remained willing to participate at the 12-month visit (n = 451, 85.6%) while a lower percentage of initially unwilling participants remained unwilling (n = 28, 50.9%, p < 0.001; Fig. 1b). Among those unsure about participating at enrollment, 125 (40.8%) became willing, 33 (10.8%) became unwilling, and 148 (48.4%) remained unsure at the 12-month visit (Fig. 1b).

Among participants who reported unwillingness to participate at enrollment, reasons included fear of getting HIV (n = 42, 70.0%), fear of side effects (n = 32, 53.3%), fear of getting a placebo (n = 17, 28.3%), fear of needles (n = 4, 6.7%), fear of death (n = 4, 6.7%), fear of testing HIV-positive (n = 4, 6.7%), fear of pain (n = 3, 5.0%), and time required for a visit (n = 2, 3.3%). Reasons for unwillingness to participate at the 12-month visit were similar, except for an increase in the number of participants reporting fear of testing HIV-positive (n = 16, 19.7%,) and 3 (3.7%) participants newly reporting spouse or partner refusal as a barrier.

Among those willing to participate at enrollment, reasons included possible protection against HIV (n = 532, 88.1%), to further scientific knowledge (n = 425, 70.4%), to do something positive for their health (n = 389, 64.4%), for possible access to an HIV vaccine (n = 367, 60.8%), access to HIV testing and counseling (n = 211, 34.9%), access to free healthcare (n = 180, 29.8%), and financial compensation (17.2%, n = 104). Responses were similar at the 12-month visit.

In the adjusted model, higher odds of willingness to participate were observed among participants who had prior knowledge of HIV vaccine research (aOR: 1.14, 95% CI:1.06–1.23; Table 2) and participants who had completed 12 months of study participation (aOR: 1.09, 95% CI:1.04–1.15).

## Discussion

Most participants in our study reported willingness to participate in future HIV vaccine trials, but a significant minority reported

**Table 1**
Participant characteristics and vaccine related knowledge at BRAHMS enrollment, by willingness to participate in potential future vaccine trials.

| | Willing N = 604 | Unwilling N = 60 | Unsure/refuse N = 351 | Total N = 1,015 | p-value |
|---|---|---|---|---|---|
| **Age (years)** | | | | | 0.51 |
| 18–29 | 194 (32.1%) | 21 (35.0%) | 110 (31.3%) | 325 (32.0%) | |
| 30–39 | 273 (45.2%) | 26 (43.3%) | 174 (49.6%) | 473 (46.6%) | |
| 40–49 | 112 (18.5%) | 12 (20.0%) | 60 (17.1%) | 184 (18.1%) | |
| 50+ | 25 (4.1%) | 1 (1.7%) | 7 (2.0%) | 33 (3.3%) | |
| **Education** | | | | | 0.66 |
| Less than Secondary School | 21 (3.5%) | 1 (1.7%) | 9 (2.6%) | 31 (3.1%) | |
| Secondary School | 269 (44.5%) | 27 (45.0%) | 156 (44.4%) | 452 (44.5%) | |
| Undergraduate Degree | 109 (18.0%) | 7 (11.7%) | 55 (15.7%) | 171 (16.8%) | |
| Master's or Doctorate | 205 (33.9%) | 25 (41.7%) | 131 (37.3%) | 361 (35.6%) | |
| **Number of sexual partners** | | | | | 0.65 |
| <=5 | 40 (7.7%) | 5 (8.9%) | 29 (9.5%) | 74 (8.4%) | |
| >5 | 479 (92.3%) | 51 (91.1%) | 275 (90.5%) | 805 (91.6%) | |
| **Prior awareness of HIV vaccine research** | | | | | 0.017 |
| Yes | 275 (45.5%) | 20 (33.3%) | 125 (35.6%) | 420 (41.4%) | |
| No | 291 (48.2%) | 34 (56.7%) | 193 (55.0%) | 518 (51.0%) | |
| Not sure | 38 (6.3%) | 6 (10.0%) | 33 (9.4%) | 77 (7.6%) | |

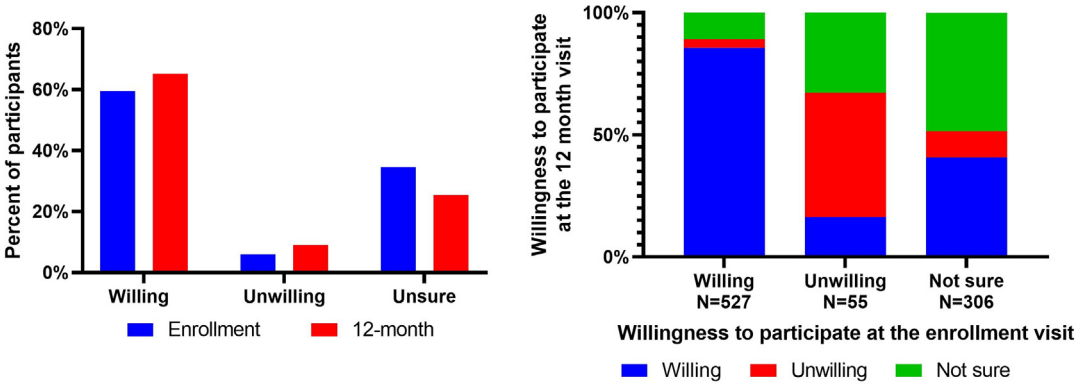


**Fig. 1.** Change in willingness to participate at enrollment and the 12-month follow-up visit. This figure presents the change in willingness to participate in future HIV vaccine trials at the enrollment visit and 12 month visit. In panel a, the percent of participants selecting each option by visit is presented. In 1b, the x-axis presents the response at the enrollment visit while the y-axis reflects the response at the 12-month visit. This analysis was restricted to participants who responded at both the enrollment and 12-month visit.

**Table 2**
Unadjusted and adjusted odds ratios for factors associated with willingness to participate in a future HIV vaccine trial.

| | Unadjusted | | Adjusted | |
|---|---|---|---|---|
| | Odds ratio | 95% CI | Odds ratio | 95% CI |
| **Age (years)** | | | | |
| 18–29 | Ref | | – | |
| 30–39 | 0.99 | 0.90–1.10 | 1.01 | 0.91–1.11 |
| 40–49 | 1.01 | 0.89–1.14 | 1.01 | 0.89–1.15 |
| 50+ | 1.18 | 0.98–1.42 | 1.18 | 0.98–1.42 |
| **Education** | | | | |
| Less than secondary school | Ref | | – | |
| Secondary school | 0.93 | 0.76–1.14 | 0.91 | 0.75–1.11 |
| Undergraduate degree | 0.92 | 0.74–1.15 | 0.92 | 0.74–1.15 |
| Master's or Doctorate | 0.86 | 0.70–1.06 | 0.85 | 0.69–1.04 |
| **Prior awareness of HIV vaccine research** | | | | |
| No | Ref | | – | |
| Yes | **1.15** | **1.06–1.24** | **1.14** | **1.06–1.23** |
| Not sure | **0.94** | **0.82–1.08** | **0.92** | **0.80–1.06** |
| **Visit** | | | | |
| Enrollment | Ref | | – | |
| 12-month visit | **1.09** | **1.04–1.15** | **1.09** | **1.04–1.15** |

Bold = $p < 0.005$.

uncertainty. The percentage of participants reporting willingness was lower than in other studies conducted in countries with a higher prevalence of HIV or among other key populations who may have a higher perceived risk of acquiring HIV [10,16]. Our

study provided knowledge that can be leveraged to increase participation in future trials.

The top reasons for willingness to participate were related to future benefits to the participant's health or scientific advancement as opposed to immediate, more tangible benefits such as financial compensation or access to free healthcare. These are in alignment with top reasons among varied populations such as young MSM in Kenya and Mozambique and older, predominately heterosexual men in the United States [16–18]. Other studies have found that health care access as a benefit of participation in a clinical trial may be a motivating factor [11]. However, this was not one of the top reasons in this study, which in part may be explained by routinely better access to health care in Germany as compared to other locations where willingness to participate has been evaluated. In a population of individuals with high levels of education and easier access to health care services, tangible incentives for participating such as financial or healthcare benefits may be less of a motivator and recruitment should instead focus on scientific advancements in future protection of individual and population health.

Among participants who reported unwillingness to participate in future trials, fear of getting HIV was a major driver. While a common misconception, some could interpret this as having been confirmed by the increased risk among vaccine recipients in the STEP study. Particularly among a well-educated population, some peripheral knowledge of this prior adverse experience from an HIV vaccine trial could do more damage to trust than in other communities where there is no such knowledge. Identifying sources of information, such as the internet or healthcare providers, and leveraging them to provide quality information is key. Other studies have similarly found that fear of getting HIV from the vaccine and fear of side effects are barriers for participation in HIV vaccine trials [11,12,19].

We found that prior awareness of vaccine research increased willingness to participate. This suggests there should be extensive education and community engagement long before actual recruitment into a specific clinical trial. This is especially notable as a significant proportion of participants reported they were unsure about participating at the enrollment visit and, among those participants, almost half became willing to participate by month 12. Engagement in an observational study may be a helpful way to introduce even reluctant participants to the research process and prepare a community for future interventional studies. Other studies, with varied populations including youth in Tanzania and MSM in the United States, have similarly found that prior knowledge of vaccine research was associated with an increase in willingness to participate in or favorability towards future HIV vaccine trials [9,20].

Strengths of our study included assessment of willingness at multiple time points and detailed responses to reasons for willingness or unwillingness to participate. However, the study has a few limitations. Only participants who reported willingness or unwillingness to participate were asked reasons why they selected this option, thus we do not have any rationale for participants selecting if they were unsure about participation. This likely represents a key population that may be persuadable to participate in future trials and understanding their motivations will be necessary for developing future education and recruitment tools. There was limited variability in responses for factors associated with willingness to participate in prior research, such as number of partners, engaging in transactional sex, and intravenous drug use, and thus we were unable to include these in our multivariable model. Additionally, we only assessed theoretical willingness to participate, which may not translate to actual future participation.

Given increasing vaccine hesitancy and distrust, it is important to understand the factors that play a role in decision-making surrounding vaccine trial participation, particularly among marginalized or stigmatized populations. Educating potential participants about ongoing vaccine research may reduce fears and increase willingness to participate in future efficacy trials of vaccine candidates and other prevention interventions.

## Disclaimer

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation. In the conduct of research where humans are the subjects, the investigator(s) adhered to the policies regarding the protection of human subjects as prescribed by Code of Federal Regulations (CFR) Title 45, Volume 1, Part 46; Title 32, Chapter 1, Part 219; and Title 21, Chapter 1, Part 50 (Protection of Human Subjects).

## Authors' contributions

AE and TAC conceived of the presented research idea. AE designed the statistical model, analysed the data and authored the first draft of the research manuscript. KJ and TAC helped to refine the statistical approach. JDS provided project management support and reviewed the collected data for quality and reliability. HS, KJ, TAC, and MLR contributed to the interpretation of the results. HS and MLR provided overall direction and planning for the BRAHMS study. All authors provided critical feedback and helped shape the research, analysis and manuscript, including review and approval of the manuscript in its final form.

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## Data availability

Data will be made available on request.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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