



Willingness to volunteer in future HIV vaccine clinical trials: A literature review and evidence synthesis

[Disposición para ser voluntario en futuros ensayos clínicos de vacunas contra el VIH: Revisión de la literatura y síntesis de evidencia]

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Abstract

Context: Developing an effective vaccine for HIV/AIDS is a global endeavor requiring the participation of willing volunteers.

Aims: To evaluate the willingness of the global population to undergo vaccination and participate in clinical trials.

Methods: Following PRISMA guidelines, relevant studies published from January 2005 to December 2019 that reported quantitative, qualitative, and mixed analyses in peer-reviewed research papers were sought in the major databases. The inclusion criteria were that the studies be related to the willingness of participants to undergo HIV vaccination and submit to subsequent clinical trials, that they are in English, conducted in any geographic location, and published during the target period. The exclusion criteria were grey literature and studies involving the stakeholders, medical students or medical fraternities, seropositive parents with seronegative offspring, the vaccine's biochemical, immunological, or financial aspects, and participants below the age of 16. Systematic reviews, letters to the editor, and case studies were also excluded.

Results: The selected databases initially yielded 334 articles, of which 27 remained after applying the inclusion and exclusion criteria. Demographic data, motivating factors, and the volunteers' willingness levels were collected and analyzed.

Conclusions: This review offers guidance for future research, including a standardized scale to predict the willingness of potential volunteer groups.

Keywords: clinical trials; HIV; review; vaccination; volunteers; willingness.

Resumen

Contexto: Desarrollar una vacuna efectiva para el VIH/SIDA es un esfuerzo global que requiere la participación de voluntarios dispuestos.

Objetivos: Evaluar la disposición de la población mundial a vacunarse y participar en ensayos clínicos.

Métodos: Siguiendo las pautas PRISMA, se buscaron en las principales bases de datos estudios relevantes publicados entre enero de 2005 y diciembre de 2019 que informaron análisis cuantitativos, cualitativos y mixtos en artículos de investigación revisados por pares. Los criterios de inclusión fueron que los estudios estuvieran relacionados con la disposición de los participantes a vacunarse contra el VIH y someterse a ensayos clínicos posteriores, que estuvieran en inglés, realizados en cualquier ubicación geográfica y publicados durante el período objetivo. Los criterios de exclusión fueron literatura gris y estudios que involucraran a las partes interesadas, estudiantes de medicina o fraternidades médicas, padres seropositivos con hijos seronegativos, aspectos bioquímicos, inmunológicos o financieros de la vacuna, y participantes menores de 16 años. Revisiones sistemáticas, cartas al editor, y los estudios de casos también fueron excluidos.

Resultados: Las bases de datos seleccionadas arrojaron inicialmente 334 artículos, de los cuales quedaron 27 después de aplicar los criterios de inclusión y exclusión. Se recopilaron y analizaron datos demográficos, factores motivadores y niveles de disposición de los voluntarios.

Conclusiones: Esta revisión ofrece orientación para futuras investigaciones, incluida una escala estandarizada para predecir la disposición de los posibles grupos de voluntarios.

Palabras Clave: disposición; ensayos clínicos; VIH; revisión; vacunación; voluntarios.

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Abbreviations: AIDS: Acquired immunodeficiency syndrome, ART: antiretroviral therapy, CBO: Community-based organization, HAART: Highly active antiretroviral therapy, HIV: Human immunodeficiency virus, MSM: Men who have sexual intercourse with men, NA: Not available, SD: Standard Deviation, STI: Sexually transmitted infection, UNAIDS: Joint United Nations Program on HIV/AIDS, WTP: Willingness to Participate.

INTRODUCTION

According to global reports from UNAIDS (Joint United Nations Program on HIV/AIDS), an acquired immunodeficiency syndrome (AIDS) is a universal problem, affecting 37.9 million people worldwide, with an estimated incidence of 1.7 million in the year 2018 (Mahy et al., 2019). Several preventive measures are available to restrict and prevent the transmission of the human immunodeficiency virus (HIV), but the disease continues to claim numerous lives, instigating substantial morbidity on a global scale, and is a problem of considerable importance in public health (Bakari et al., 2013). Even though the advent of highly active antiretroviral therapy (HAART) has improved life expectancy and quality of life for HIV patients, the disease burden remains of considerable magnitude in both the adult and pediatric populations worldwide. In this scenario, the development of an effective and safe vaccine to counter the infection would be a significant solution to the challenges presented, as has been the case with other viral diseases such as the effective control of smallpox (Esparza and Bhamarapravati, 2000). Current efforts to control the spread of HIV include creating awareness, advocating safe sex practices, developing vaccines and microbicides, and employing preventive therapeutic and post-exposure prophylactic measures. Among these efforts, the development and implementation of vaccination is the most accessible and economical option, which has the advantage of being independent of the subjects' continual cooperation. Another factor that motivates the development of vaccination is the unavailability and unaffordability of HAART in certain countries, potential adverse effects, and the possibility of developing resistance to the drug (Joseph et al., 2005; Koff et al., 2013; Thabethe et al., 2018).

Developing vaccines for the prevention of HIV could be advantageous in several ways: vaccine therapy has the potential to enhance the immunological response, which can focus on the sequence sites different from the target sites for antiretroviral therapy (ART) (Das and Arnold, 2013; Lieberman-Blum et al., 2008; Métifiot et al., 2013; Puls and Emery, 2006; Wensing et al., 2010). When utilized in combination with HAART, vaccines possess the potential to act in synergy with the drugs in ART, resulting in an intensified therapeutic ability to restrict viral replication, and consequently leading to enhanced drug efficacy and inhibiting the development of resistant organisms (Garcia et al., 2013). Another beneficial effect of developing a vaccination is that the immunization ther-

apy could be utilized for a "shock and kill" therapy. When a combination therapy of vaccination and ART is implemented, the vaccine stimulates CD8⁺ T cells and acts in synergy with the ART drugs to induce cytotoxicity in latent HIV-infected cells, which are pharmacologically reactivated, thus aiding in eliminating the viral reservoir (Garcia et al., 2013).

Research involving the development of an effective HIV vaccination requires the implementation of clinical trials in various phases; this requires the participation of healthy volunteers from a representative population for optimal study designs and unbiased results. The results of the first phase III clinical trials for an HIV vaccination were reported in 2003 (Francis et al., 2003), and the first systematic review regarding the barriers to trial participation was published in 2004 (Mills et al., 2004). Since then, numerous clinical trials examining the results of vaccination trials and studies on the barriers or willingness of volunteers have been reported, while systematic reviews of these studies have been very few in number (Detoc et al., 2017; Dhalla and Poole, 2011a; Mills et al., 2004; Newman and Logie, 2010), but these include the studies published by Newman and Logie (Newman and Logie, 2010) in 2010 and two reviews by Dhalla and Poole in 2011 (Dhalla and Poole, 2011a; 2011b). The review by Newman and Logie (2010) presented acceptability of 35.2 to 94, with a mean of 65.6 on a 100-point scale, and reported vaccine efficacy, safety concerns, fear of adverse effects, and perceived benefits as factors that affect the vaccine's acceptability. Dhalla and Poole published two reviews in 2011 (Dhalla and Poole, 2011a; 2011b), that dealt with the motivators and barriers to participation in HIV vaccine trials. The authors reported that personal risk of adverse effects and vaccine-induced seropositivity were the most common barriers reported in the reviewed studies, along with barriers like social stigma and discrimination, personal costs, and logistical difficulties (Dhalla and Poole, 2011a). In another review, the authors reported that the positive motivators to participate in HIV vaccine trials were altruism and protection from HIV, along with factors like incentives and health care benefits (Dhalla and Poole, 2011b). The aforementioned reviews focused more on the factors influencing the acceptability of the vaccine and willingness to enroll in trials than on the varying degrees of willingness to participate in trials. To the best of our knowledge, a systematic review that includes studies from all geographic locations has not been published in recent times. The current study focuses on a review of studies published since 2005 in an attempt to

bridge this knowledge gap and facilitate research on HIV vaccination.

The researchers involved in such clinical trials may face a unique challenge regarding recruiting volunteers because of the significant stigma associated with the disease and the lack of awareness or understanding of it. Previous literature reveals a discrepancy between the projected requirement for an effective vaccine for AIDS and its actual implementation due to access and acceptability hurdles (Doshi et al., 2017; Esparza and Bhamarapravati, 2000; Gellin et al., 2003; Moher et al., 2015; Newman and Logie, 2010; Starace et al., 2006). This situation necessitates the identification and evaluation of a population that is willing to undergo vaccination or to volunteer for clinical trials involving HIV vaccination, with a comprehensive awareness of the HIV/AIDS entity and its possible adverse effects.

The current systematic review is an attempt to evaluate the willingness of global populations to undergo vaccination or to volunteer for the clinical trials involved and to review the results presented by various studies on the subject, in order to enable the development of an effective vaccine that may eventually lead to control of the expanse, morbidity, and mortality associated with the disease.

MATERIAL AND METHODS

Study design

The present study was designed as a systematic review under PRISMA guidelines (Page et al., 2021). The research focused on the willingness of specific adult populations to undergo vaccination for HIV and to volunteer in clinical trials involving HIV vaccination.

Search strategy

The PubMed, Ovid, Science Direct, and Google Scholar databases were searched for articles published from January 2005 to December 2019. The search strategy in PubMed was used. To search other databases, the search strategies were modified according to each database's searching protocol using the keywords: willingness; HIV; vaccination; volunteers; clinical trials.

The Boolean search code used in PubMed was as follows: ("willingness"[All Fields] AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND ("vaccine"[MeSH Terms] OR "vaccination"[All Fields]) AND ("volunteers"[MeSH Terms] OR "volunteers"[All Fields] OR "volunteer"[All Fields]) AND ("clinical trial"[All Fields] OR "clinical trials as topic"[MeSH Terms] OR

"clinical trials"[All Fields]) AND ("2005/01/01"[PubDate]: "2019/12/31"[PubDate])). Search Date: 08 Sep 2020.

Inclusion criteria

Quantitative, qualitative, or mixed-method analyses and peer-reviewed research papers that studied the willingness of participants to undergo HIV vaccination and to volunteer in follow-up HIV vaccine clinical trials were systematically reviewed. The focus of the review was on studies with quantitative data collection regarding the willingness of an adult population to participate in vaccination trials. Studies in English conducted in any geographic location and published from 2005 to 2019 were included in this review.

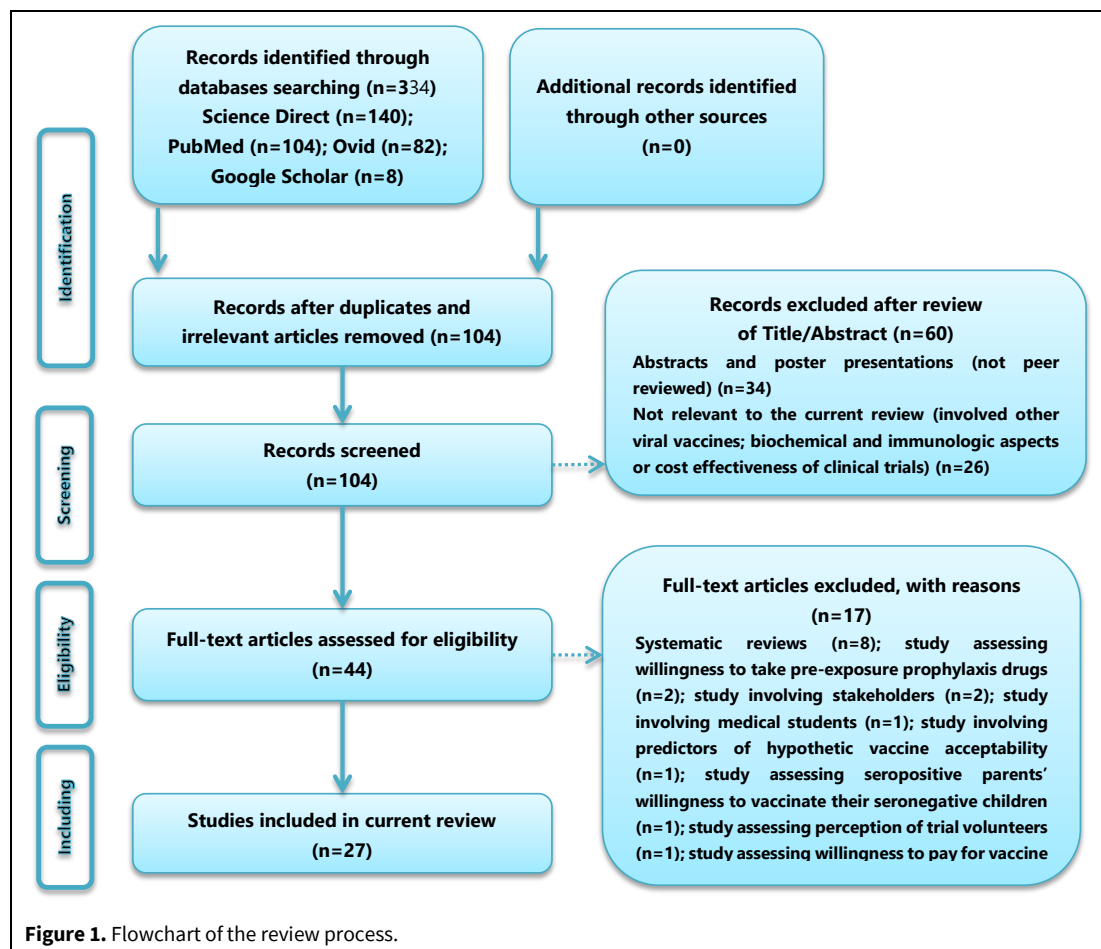
Exclusion criteria

Grey literature, including abstracts of poster presentations or meetings of scientific or medical bodies, studies involving the stakeholders, medical students, or a medical fraternity (to avoid bias, as they were not peer-reviewed), seropositive parents with seronegative offspring, studies exploring biochemical, immunological, or financial aspects of the vaccine, studies involving participants below the age of 16, systematic reviews of studies involving the willingness to participate in vaccination trials or undergo clinical trials, letters to the editor, and case reports were excluded from the study. Based on these inclusion and exclusion criteria, 27 studies were included in the current systematic review.

Synthesis methods

The search yielded 334 results, of which 104 relevant articles were reviewed by their titles and abstracts, yielding 44 potential articles for review of the full text. From that group, 27 articles were selected for the present review that conformed to the inclusion and exclusion criteria (Fig. 1). The selected studies relating to volunteers' willingness to undergo vaccination were reviewed for demographics, sample size, geographic location, factors associated with acceptability of vaccination, socioeconomic status, and educational background of the participants.

In the first stage of article assessment, the screening was independently conducted by two reviewers. In case of discrepancy between the two, the decision was made by an unbiased third party. In the next step, four reviewers worked independently on full-text screening. Disagreements among the four researchers were resolved by a majority vote; in case of a deadlock, L.A. made the final decision.



Data analysis

Data from the studies were recorded, compared, and reviewed by the authors on a Microsoft Office Excel spreadsheet. Categorical variables in both qualitative and quantitative analysis were presented by frequency and percentage. Heterogeneity among study results and sensitivity analyses was not performed in this current study.

RESULTS

The Science Direct, PubMed, Ovid, and Google Scholar databases were searched for articles published from January 2005 to December 2019, yielding 140, 104, and 82 results from the first three, respectively, and eight articles were selected from Google Scholar.

The most common methods used for data collection in these studies were semi-structured computer-based or open-ended personal interviews (12 of 27 articles), four of which used quantified scales to assess willingness. Another method was self-reported or interviewer-administered questionnaires, including items scoring the likelihood of participation or vaccination, with scores indicating a range of responses

reflecting the degree of willingness to participate in trials (10 of 27 articles). Two studies used focus-group interviews and discussions for data collection, one used a telephone survey, one used a self-administered survey, and the last used a web-based survey for data collection.

Twenty-two of the twenty-seven studies provided quantitative results regarding the willingness or acceptability of vaccination for HIV, while five analyzed the qualitative aspects and provided results regarding the factors motivating or discouraging willingness. The geographic location of the studies included African countries - Uganda, South Africa, Togo, Kenya, and Tanzania (ten studies), United States (six studies), India (five studies), China (three), Spain (two), and Italy (one). The populations studied included homosexuals or men who have sexual intercourse with men (five studies), volunteers (five studies), drug users (four), sex workers (three), police officers and prison forces (two), college students (two), populations identified as having a high risk for HIV infection (two), a fishing community (one), transgenders (one), people at STI (sexually-transmitted infection) clinics (one), and seropositive patients (one). Sample sizes ranged from 20 to 924 participants, with a total of 8,676 par-

participants involved in this review. The age of the participants ranged from 16 to 41 years, and gender distribution ranged from 100% male to 100% female. The observed willingness to participate ranged from 19% to 97% among the 22 quantitative studies included. Six studies involved an African population with an estimated willingness to participate (WTP) ranging from 23% to 99.4%; the average of all six studies was 69.6%. The six studies of American populations revealed a WTP ranging from 17% to 93%, with an average of 63.89%. The four studies of Indian populations reported a WTP ranging from 48% to 90%, with an average of 67%. The three studies conducted on Chinese populations reported a WTP ranging from 35.8% to 91.5%, with an average of 67.2%. The two studies in Spanish populations averaged 88.5% WTP, and the study in Italy reported a WTP of 36.7%.

The observed positive motivators for willingness to undergo vaccination or clinical trials were mainly altruism in 13 studies, a desire for protection from HIV for oneself or their future offspring was named in 7 studies, and access to health care in 5 studies, along with the benefits to society - advancing research, insurance benefits, and accessible health care benefits. The reasons given for unwillingness or reluctance to participate were the fear of possible adverse effects (health, personal, professional, sexual, or social) mentioned in 19 studies, fear of contracting HIV infection from the vaccine (four studies), fear of partner rejection (four studies), cost (three studies), social stigma (three studies), doubts regarding the success of vaccination (three studies), travel to the venue of the trial (three studies), necessity to delay pregnancy (two studies), requirement of multiple procedures (two studies), prejudice or misconceptions (two studies), medical reasons (one study), and previous bad trial experiences (one study).

The quantitative and qualitative results are summarized in Tables 1 and 2. A summary of the factors influencing the willingness to participate is summarized in Tables 3, 4 and 5. The motivators and barriers for the WTP, as reported by the studies involved in the current review, are tabulated and categorized in Tables 6 and 7.

DISCUSSION

Immunization against disease has served humanity by saving more lives than any other medical intervention in recent centuries. It is one of the greatest scientific triumphs in modern medicine (Dhalla and Poole, 2011b). However, despite the health benefits and the protection afforded, the success of a vaccine depends entirely on social acceptance and public

opinion (Dhalla and Poole, 2011b). The current review is relevant in assessing the willingness of various populations to participate in the development and implementation of a vaccine and the factors influencing their willingness.

The study observed that willingness or acceptability to participate in testing an HIV vaccine ranged from 17% to 97%, as reported in the 27 studies examined. The lowest percentage of willingness was observed in a study involving American college students, and the highest was observed in a study of high-risk groups of transgenders and female sex workers in Spain. The studies varied in their target populations, including high-risk groups (e.g., men who have sex with men (MSM), transgenders, drug users, and sex workers) and those in areas having a high prevalence of AIDS (e.g., Africa), which may have influenced the higher degrees of willingness to undergo vaccination reported in those studies. Similarly, in a systematic review done by Dhalla and Poole (Dhalla and Poole, 2011b), the observed willingness to participate in HIV vaccine trials ranged from 17% to 86%; the study exhibiting the lowest percentage involved Caucasians and the study exhibiting the highest percentage involved African Americans in the study in the United States.

The studies included in the current review utilized a range of methods to collect data, including questionnaires, structured or open-ended interviews, web-based surveys, and telephone surveys, that relied on subjective perceptions and self-reporting of variables. This diversity points to the fact that there is a lack of standardized, acceptable, and universal scales in this field of research - a fact to be addressed in future research.

Twenty of the twenty-seven studies in the current review analyzed populations at high risk in which pre-sensitization was performed before data collection. The factors that positively enhanced the willingness to participate were protection from HIV, altruism, incentives, vaccine efficacy, access to free health care, high perceived risk of infection, and engaging in high-risk behaviors like prostitution, injectable drug usage, or sexual intercourse with high-risk groups. The influence of these factors was also reported in various previous studies (Dhalla and Poole, 2011b; Doshi et al., 2017). As altruism was seen as a potential influencing factor, enhancing motivation to participate in trials was undertaken by various programs in previous studies (Buchbinder et al., 2004; Chakrapani et al., 2007; Dhalla and Poole, 2011a; 2011b; 2014; Doshi et al., 2017; Gellin et al., 2003; Perisse et al., 2000; Starace et al., 2006).

Table 1. Willingness or acceptability of HIV vaccination (n = 22 studies).

Study	Population	Country	Sample size	Gender distribution	Age range (years)	WTP (%)	Method of data collection
DEVELOPING COUNTRIES (n = 13 studies)							
(Mbunda et al., 2019)	Female sex workers	Tanzania	600	100% female	18-25	91	Self-reported questionnaire
(Kpanake et al., 2016)	Volunteers	Togo	363	56.5% male	18-62	49	Questionnaires
(Newman et al., 2014)	MSM	India	400	100% male	Median = 25	48.05	Interview-4-point scale
(Dong et al., 2014)	Seropositive patients	China	447	89.8% male	30-49	91.5	Self-reported questionnaire
(Asiki et al., 2013)	Fishing community	Uganda	328	62.2% male	18-49	99.4	Questionnaire-5-point scale
(Bakari et al., 2013)	Police officers	Tanzania	364	57% male	20-46	72.2	Interview
(Li et al., 2010)	MSM	China	550	100% male	20-33	35.8	Questionnaire
(Suhadev et al., 2009)	High risk groups	India	501	55% male	31-50	82	Semi-structured interview
(Middelkoop et al., 2008)	Volunteers	South Africa	200	26% male	16-40	83	Questionnaires
(Yin et al., 2008)	Drug users	China	401	88.3% male	26-33	74.3	Interview-4-point scale
(Suhadev et al., 2006)	High risk group- MSM, drug users, sex workers	India	112	62% male	Mean = 32.4 (SD: \pm 8.52)	90	Focus group and personal interviews
(Smit et al., 2006)	Volunteers	African countries	196	80% female	Mean = 23	23	Interviewer-administered structured questionnaire
		South Africa					
(Sahay et al., 2005)	Attendees of STI clinics	India	349	58.7% male	Mean = 29.9	48	Semi-structured interview
DEVELOPED COUNTRIES (n = 9 studies)							
(Young et al., 2014)	Drug users	-	433	55.2% male	29-41	91	Interviewer-administered questionnaires- 4-point Likert scale
(Etcheverry et al., 2013)	Female sex workers	-	251	72.7% female; 27.3% transgender	18-45	97- extended retention group 89-control group	Interview-4-point scale
(Etcheverry et al., 2011)	Drug users	Spain	735	76% male	21-44	80	Interview-4-point scale
(Ravert and Zimet, 2009)	College students	-	242	42.6% male	18-23	70.2	Web-based survey
(Kakinami et al., 2008)	Low socioeconomic & ethnically diverse groups	United States	126	59% male	Mean = 38	Males-61/100 Females-56/100	5-point Likert scale
(Newman et al., 2007)	Low socioeconomic strata	United States	123	69% male	18-50*	59	Computer assisted personal interview

Table 2. Willingness or acceptability of HIV vaccination (n = 22 studies) (continued...)

Study	Population	Country	Sample size	Gender distribution	Age range (years)	WTP (%)	Method of data collection
(Starace et al., 2006)	General population	Italy	924	80.5% male	Mean = 30.2	36.7	Telephone surveys
(Lally et al., 2006)	Prisoners	United States	153	65% male	-	93	Structured interviews
(Priddy et al., 2006)	College students	United States	226	71% female	73% <30	17	Self-administered survey

MSM: Men who have sexual intercourse with men; CBO: Community-based organization; STI: Sexually transmitted infection; WTP: Willingness to participate; SD: Standard Deviation.

Table 3. Factors affecting willingness for vaccination (n = 5 studies).

Factors affecting willingness for vaccination		Study	Population	Country	Sample size	Gender distribution	Age range	Method
POSITIVE	NEGATIVE							
Improved health status Improved awareness Access to healthcare Altruism	Stigma Misconceptions Bad experiences from trials	(Tarimo et al., 2019)	Police and prison forces	Tanzania	67	53.7% Male	24-38	Focus group discussions
Altruism, seeking protection from HIV	Prejudice Doubt regarding the success of vaccination Previous bad trial experiences	(Doshi et al., 2017)	MSM	Kenya	70	100% Male	18-25	Personal interviews
Social benefits of advancing research, helping society Financial benefits Health benefits	-	(Nyaoke et al., 2017)	Volunteers	Kenya	281	38.4% Female	18-38*	Interviewer-administered questionnaires
Altruism Incentives Endorsements from government, CBOs, and Peers	Social stigma, prejudice, misconceptions, fear of side effects	(Chakrapani et al., 2012)	MSM	India	68	100% Male	20-46	Personal interviews
-	Potential side effects; Mistrust; Uncertainty of post-vaccination health care; Discouraging friends and family.	(Tarimo et al., 2011)	Volunteers in trials	Tanzania	14	50% Male	20-38	Personal interviews

MSM: Men who have sexual intercourse with men.

Table 4. Factors influencing willingness to undergo participation in trials.

Study	Study design	Reported percentage of WTP	Influencing factors	
			Positive	Negative
(Mbunda et al., 2019)	Quantitative	91	Efficacy of vaccine, altruism, wanting to contribute to a cure for HIV, and wanting to learn about vaccine trials	Need for permission
(Tarimo et al., 2019)	Qualitative	NA	Improved health status; improved awareness; access to health care; altruism	Stigma; misconceptions; bad experiences from trials
(Doshi et al., 2017)	Qualitative	NA	Altruism, seeking protection from HIV	Prejudice, doubts regarding the success of vaccination, previous bad trial experiences
(Nyaake et al., 2017)	Qualitative	NA	Social benefits of advancing research, helping society; financial benefits; health benefits	-
(Kpanake et al., 2016)	Quantitative	49	Free vaccines, effective vaccines, family encouragement, awareness of the severity of AIDS	Higher costs, higher income
(Dong et al., 2014)	Quantitative	91.5	Seropositive patients: to delay or reduce ART and thereby to avoid ART side effects, to delay disease progression, increasing immune response, to suppress opportunistic infections, preventing drug resistance, reducing the potential transmission, earning economic reimbursement, and family support for participation	Concern about the safety of vaccine, less knowledge about the vaccine, satisfaction in ART
(Newman et al., 2014)	Quantitative	48.05	Distance from health centers (shorter travel) and shorter duration of trial, incentives, free health care, life insurance benefits	Distance to trial sites, side effects, trial duration
(Young et al., 2014)	Quantitative	91	Vaccine efficacy, incentives	Cost, multiple doses, travel, unsupportive partners
(Asiki et al., 2013)	Quantitative	99.4	Access to HIV counseling and testing services, HIV education, hope of being prevented from HIV infection, access to quality general health care services, desire to be among the first to participate in a vaccine trial and altruism	Requirement to delay pregnancy, drawing large volumes of blood
(Bakari et al., 2013)	Quantitative	72.2	-	Medical reasons, desire to have a child in two years
(Etcheverry et al., 2013)	Quantitative	97%-extended retention group 89%-control group	Education, behaviors with risk of infection	Prolonged trial duration
(Chakrapani et al., 2012)	Qualitative	NA	Altruism, incentives, endorsements from government, peers	Social stigma, prejudice, misconceptions, fear of side effects
(Etcheverry et al., 2011)	Quantitative	80	Injection drug use, intercourse with a partner who uses injectable drugs, under high risk of infection like sex workers	-
(Tarimo et al., 2011)	Qualitative	NA	-	Potential side effects; mistrust; uncertainty of post vaccination health care; discouraging friends and family

Table 5. Factors influencing willingness to undergo participation in trials (continued...)

Study	Study design	Reported percentage of WTP	Influencing factors	
			Positive	Negative
(Li et al., 2010)	Quantitative	35.8	Perceived personal benefits of getting current information about HIV research, free counseling and HIV testing, incentive for participation, and motivation to avoid risky behaviors	Social risks like facing avoidance, fear of vaccine related problems
(Ravert and Zimet, 2009)	Quantitative	70.2	Perceived HIV susceptibility, psychological invulnerability, number of partners	High cost, danger invulnerability
(Suhadev et al., 2009)	Quantitative	82	Protection from HIV, altruism	Unknown efficacy or vaccines, adverse effects, effects on personal or professional life, less education
(Kakinami et al., 2008)	Quantitative	Males-61/100 Females-56/100	Women: ability to conceive a child without worrying about contracting HIV and support from their partners, family support Men: feeling safer with sex partners and social influence from friends to get vaccinated, family support	Women: Partner's reaction, negative experiences with health care providers, anticipated difficulties procuring insurance Men: vaccine would weaken the immune system or would affect HIV test results
(Middelkoop et al., 2008)	Quantitative	83	Awareness of vaccine, perception of risk	-
(Yin et al., 2008)	Quantitative	74.3	Sexual intercourse with injectable drug users, sharing syringes during drug abuse, family support, obtaining updated information about HIV/AIDS, free HIV counseling and testing, incentive for participation, and motivation to avoid risky behaviors.	Risk of social stigma, isolation for participation, fear of rejection from partners and fear of health problems
(Newman et al., 2007)	Quantitative	59	Vaccine efficacy, low socioeconomic status	Risk of vaccine-induced infection, perceived risks
(Lally et al., 2006)	Quantitative	93	Effectiveness of vaccine, high-risk perception	Fear of contracting infection from the vaccine, low perceived risk of AIDS
(Priddy et al., 2006)	Quantitative	17	Compensation	Possible adverse effects, Fear of being labeled HIV ⁺ , belief that HIV is not an important issue, fear of needles, distant location of health care facilities, and longer duration of trial
(Smit et al., 2006)	Quantitative	23	Incentives, altruism, protection from HIV, free medical care, awareness	Repeated injections, drawing blood, fear of infection and side effects
(Starace et al., 2006)	Quantitative	36.7	Altruism, protection from HIV	Social stigma, fear of infection and adverse effects
(Suhadev et al., 2006)	Quantitative	90	Altruism, protection from HIV, and support for the researchers	Efficacy, possible side effects, fear of being given placebos, impact on life, marriage prospects or professional life
(Sahay et al., 2005)	Quantitative	48	Awareness, efficacy of vaccine, incentives, altruism, insurance benefits	Partner rejection, concern regarding vaccine related issues

HIV: Human immunodeficiency virus; AIDS: Acquired immunodeficiency syndrome; NA: Not available.

Table 6. Frequent motivators and barriers in vaccine acceptability and WTP.

Characteristic of motivators	Number of studies that mentioned the factors		Top three reasons mentioned by the studies		Top reason mentioned in the studies		Characteristic of barriers
	Motivators	Barriers	Motivators	Barriers	Motivators	Barriers	
Altruism	13	19	9	19	6	15	Fear of possible adverse effects-health, personal, professional, sexual or social effects
Protection from HIV/AIDS	6	4	5	2	3	-	Fear of contracting infection from vaccine
Incentives	5	4	3	-	-	-	Partner rejection
Free health care, health education, and free vaccine	5	3	1	-	1	-	Doubt and unknown efficacy of vaccine
Effective vaccines	4	3	4	-	2	-	Travel and venue
Behaviors with risk of infection	4	3	1	2	-	2	Cost
ART related issues	1	3	1	2	1	-	Social stigma
Family support	3	2	1	-	-	-	Prejudice
High perceived risk of infection	3	3	-	-	-	-	Duration of trial
Access to HIV counseling and testing services, HIV education	2	2	1	2	1	2	Need for permission
Injection drug use or intercourse with a partner who uses injectable drugs	2	2	1	2	-	1	Necessity to delay pregnancy
Motivation to avoid risky behaviors	2	2	-	1	-	-	Multiple doses, injections, and procedures
Insurance benefits	2	1	-	1	-	1	Medical reasons
Ability to conceive seronegative children	1	1	1	-	1	-	Bad previous experience
Support research	1	1	-	-	-	-	ART related issues
Improved health status and improved awareness	1		-		-		
Desire to be among the first to participate in a vaccine trial	1		-		-		
Endorsements from Government, CBO, and Peers	1		-		-		

HIV: Human Immunodeficiency Virus; AIDS: Acquired immunodeficiency Syndrome; CBO: Community Based Organisation; ART: Antiretroviral Therapy; WTP: Willingness to Participate.

Table 7. Ranking of motivators and barriers in WTP.

MOTIVATORS	BARRIERS
Protection from HIV/AIDS	Fear of possible adverse effects- health, personal, professional, sexual or social effects
Altruism	Fear of infection from vaccines
Incentives	Fear of partner rejection
Vaccine efficacy	Cost
Access to/free health care	Multiple procedures
High perceived risk of infection	Longer trial duration
Engaging in high-risk behaviors	

HIV: Human immunodeficiency virus; AIDS: Acquired immunodeficiency syndrome; WTP: Willingness to participate.

According to Myers and Smith (2012), not just altruistic or non-altruistic personal motives affect the willingness to participate in trials. Dhalla and Poole (2011b) classified motivators into microsocial motivators - benefits to an individual's close social circle (helping a close or important person); mesosocial - to benefit a larger social circle (helping others and the community), and macrosocial - to benefit society at large (helping to find a cure for AIDS or aiding research). The motivators in the current study were largely mesosocial and macrosocial, with non-altruistic personal motivators as secondary factors. Another motivating factor considered is the vaccine's efficacy, along with incentives, financial benefits, and access to health care that were observed as motivators for participation in vaccine trials in developing countries and among individuals of lower socioeconomic status. The high perceived risk of infection for those engaging in risky behaviors would be a major impetus for willingness to participate in trials.

In the current review, barriers negatively influencing willingness were fear of possible adverse effects - health, personal, professional, sexual, or social - the social stigma, fear of being infected by the vaccine, the longer duration of trials, repeated injections, cost, partner rejection, fear of unknown vaccine efficacy, and multiple medical procedures. These are similar to observations found in previous systematic reviews (Galea et al., 2011; Kpanake et al., 2016; Mills et al., 2004; Newman and Logie, 2010; Zhou et al., 2012), for a lower degree of willingness to participate in trials. The barriers observed in the current review were principally rooted in misunderstandings and misconceptions. Barriers in the personal or sexual area included fear of rejection by a partner, the requirement to delay pregnancy, personal costs, travel, duration, and venue of trial, and previous bad experiences. The fear of social isolation, rejection, fear of being perceived as infected, and fear of damaging social prospects also can act as potential barriers to clinical trial participation. Knowledge of potential barriers is essential to tackle the possible shortage of participants

in future research. A previous review stated that "the health belief model" offers a theoretical foundation for the assessment of factors affecting the willingness to participate in clinical trials, which can be applied in the current scenario (Dhalla and Poole, 2011b). The health belief model proposes that the behavior or attitude of a community towards health-related research depends on factors, such as the presence of adequate motivation or concerns regarding health-related issues, to make it relevant, the perceived threat or susceptibility to health problems and their consequences, and the belief that abiding by a particular recommendation can result in alleviation of the threat at an acceptable cost. The cost mentioned refers to the various obstacles that must be overcome in order to follow the health recommendation, which includes but is not restricted to financial issues (Becker, 1974; Rosenstock, 1966; 1974; 1988). Thus, the ethics of the portrayal of trial participation as a positive behavior without risk must be questioned (Kafaar et al., 2007).

Another notable finding is that expressing a willingness to participate may not always predict actual participation, as demonstrated in a previous study (Buchbinder et al., 2004), in which 28.9% of people who expressed willingness ultimately refused to participate in trials. Poole (2012) suggested the use of psychosocial principles in studies assessing willingness and in the recruitment of volunteers. Stating the difference between willingness to participate and actual enrolment in trials, the author suggested that working along with impending trials, assessment of willingness with a scale that can differentiate between willingness and ability to participate and following up to assure participation can lead to reducing the gap between intention and implementation.

The clinical trials for HIV vaccination are prolonged, delicate, and complicated procedures, which include multiple medical procedures, and the target is a disease subject to high levels of stigma, commonly involving participants from marginalized populations

(Thabethe et al., 2018). In the current study, a higher willingness to participate in trials and undergo vaccination was observed in studies involving high-risk groups in the African, Asian, and Spanish populations, while the lowest degree of willingness was observed in studies involving American college students, thus providing an indication of the potential candidate population for clinical trials. The present systematic review included studies of high-risk populations utilizing diverse data collection methods and analytical measures. This can be an obstacle in reaching a consensus on the representation of the problem. Additionally, a high-risk population may be inherently biased, owing to the perceived personal risk. Nevertheless, the current study offers useful data regarding the attitudes of diverse populations toward HIV vaccines and factors affecting their testing.

CONCLUSION

Because AIDS is a universal problem facing communities all around the world, improved preventive measures and innovative research are necessary to discover solutions. This is possible only with informed public participation and cooperation, making the identification of volunteer groups a key prerequisite for research. The current review offers several pointers to facilitate future research, including the need for a standardized scale to be used in such studies seeking to alleviate the lack of studies involving a representative population, the prevalence of social stigma, fears of the vaccine, and the possibility of identifying potentially cooperative volunteer groups.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Huyen TNT	Pumtong S	Sanroongruangsri S	Anuratpanich L
Concepts or ideas	x			x
Design	x	x	x	x
Definition of intellectual content	x			x
Literature search	x	x	x	x
Experimental studies	x	x	x	x
Data acquisition	x			x
Data analysis	x			x
Statistical analysis	x			
Manuscript preparation	x			x
Manuscript editing	x	x	x	x
Manuscript review	x	x	x	x

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