SciMedCentral

Clinical Research in HIV/ AIDS

Research Article

Socio-Behavioral Challenges to HIV Vaccine Trials: Literature Review

Joseph N. Inungu[1]*, Bonnie Bender[2], and Lisa Gieber[2]

[1]School of Health Sciences, Central Michigan University, USA
[2]International AIDS Vaccine Initiative, USA

*Corresponding author
Joseph N. Inungu, Master of Public Health Program, School of Health Sciences, Central Michigan University, Mt Pleasant, MI, USA; Tel: 989-774-4476; Fax: 989-774-2908; Email: inung1j@cmich.edu

Submitted: 19 December 2016

Accepted: 14 February 2017

Published: 16 February 2017

Keywords

- HIV
- Vaccines
- Clinical trials
- Social & behavioral factors
- Participation in HIV trials

Abstract

Introduction: Social and behavioral factors have the potential to affect and inform both the implementation of HIV vaccine trials and the uptake of an eventual HIV vaccine. The growing number of ongoing phase I/II HIV vaccine trials underscores the need for a review of factors affecting the conduct of these trials.

Methods: Major databases (PubMed, Cochrane, and Google Search Engine) were searched for relevant articles published in English in the last 10 years on social and behavioral issues affecting HIV vaccine trials. Key search terms applied included: HIV/AIDS, vaccine, microbicides, and recruitment, participation in trials, social harm, adolescent, community, ethics, consent, sexual behavior, acceptability, feasibility, motivation, key populations, vaccine-induced seropositivity, and vaccine trials. The review process was further informed by searches of the reference lists from publications of interest.

Results and discussion: In general participation in HIV trials was high among different populations around the world. Risk compensation during HIV trials was rarely observed or reported. Social harms were not a common occurrence in Western literature, and when they did occur they were not severe compared to reports from sub-Sahara Africa. Community engagement is critical for the smooth implementation of HIV trials. However, more examples of successful community engagement strategies from Africa are needed. A good understanding of key populations' risk behaviors is critical to inform the development of effective prevention strategies to control the spread of HIV. Social and behavioral factors have the potential to affect and inform both the implementation of HIV vaccine trials and the uptake of an eventual HIV vaccine.

Conclusion: The integration of basic, clinical, and social sciences research methods is critical in the search for an effective HIV vaccine. Innovative approaches to improve willingness to participate in HIV vaccine trials, prevent risk compensation, and shore the community involvement in HIV trials will not only contribute to the conduct of successful trials, but also ensure the uptake of the research products.

ABBREVIATIONS

AIDS: Acquired Immuno Deficiency Syndrome; ARV: Antiretroviral Drugs; ART: Antiretroviral Therapy; DNA: Deoxy Nucleic Acid; FSW: Female Sex Workers; GPP: Good Participatory Practice; HIV: Human Immunodeficiency Virus; HPTN: HIV Prevention Trials Network 052; ICT: Innovative Prevention And Care Technology; KAVI: Kenya AIDS Vaccine Initiative; MSM: Men who have Sex with Men; NSP: National Strategic Plan; PLH: People were Living with HIV/AIDS; PrEP: Pre-Exposure Prophylaxis; PEP: Post-Exposure Prophylaxis; RDS: Respondent-Driven Sampling; RNA: Ribo Nucleic Acid; STI: Sexually Transmitted Infections; TW: Transgender Women; WTP: Willingness To Participate

INTRODUCTION

Despite 30 years of efforts to fight HIV/AIDS, an estimated 2.1 million new infections occurred at the end of 2015 and1.1 million people died of AIDS in the same year [1]. A safe and effective HIV vaccine is needed to curtail the spread of the HIV epidemic. Several scientific challenges contribute to the extended

time-line in developing an effective vaccine against HIV infection. The number of circulating viral strains is one of the most intractable obstacles to vaccine development. Extremely rapid and error-prone replication yields a large number of mutant genomes, some of which are able to escape immune control [2]. Another major obstacle is the lack of clear immune correlates of protection in humans [3].

Vaccine technology has evolved significantly in the last decade, profoundly changing the future of vaccine development. Reports that the prime/boost combination of two vaccines (ALVAC (R) HIV and AIDSVAX (R) B/E) lowered the rate of HIV infection by 31 percent in a trial of more than 16,000 volunteers in Thailand, demonstrating that the development of an effective preventive HIV vaccine is scientifically possible. Recent advances in isolating broadly neutralizing antibodies and designing new tools and technologies for vaccine delivery have enhanced hope and reinvigorated vaccine discovery efforts [4]. Concomitantly, testing candidate vaccines in clinical trials is crucially dependent on the participation of individuals who reside in communities at high risk of HIV infection.

There is a growing recognition of the importance of integrating social and behavioral research into clinical trials. The advancement and integration of our best social, clinical, and biomedical science will optimize the likelihood of success for a safe and effective HIV vaccine that is widely acceptable and accessible to most-at-risk populations worldwide [5,6]. However, integrating biomedical and behavioral research within a preventive vaccine clinical trial has proven difficult.

Previous studies have identified several social and behavioral challenges related to HIV vaccine trials [7-9]. They include challenges in: recruiting and enrolling a large numbers of participants in all types of trials, getting community members involved in clinical trials, retaining participants over the life span of the clinical trial, preventing the risk of potential sexual disinhibition amongst trial participants, assessing HIV exposure accurately, developing innovative strategies to reduce the stigma and discrimination that trial participants may potentially have to endure, access to other HIV prevention tools, and ensuring the safety and ethical participation of volunteers from vulnerable populations.

Several conceptual frameworks depicting the intersection between individual, social, and contextual factors in all phases of HIV vaccine development have been developed to guide social scientists in designing socio-behavioral research [8,10,11]. These conceptual frameworks and models aid in addressing key gaps in understanding factors important to trial success, including trial participation and eventual vaccine uptake [8]. These conceptual frameworks, based on existing social and psychological theories, summarize relationships among social, behavioral, and biological determinants to describe strategic pathways that interventions could use to achieve the greatest impact. The purpose of this review is to summarize current knowledge about social and behavioral factors affecting the conduct of HIV vaccine trials worldwide to inform the design and implementation of future HIV trials.

METHODS

Search strategy and restrictions

Studies examining HIV vaccine trial participation including recruitment, enrollment, and retention published from 2005 to 2015 were identified by searching the following electronic databases: National Library of Medicine PubMed (PubMed), Cochrane, and Google Search Engine. Bibliographies of relevant reviews and eligible studies were examined for additional sources. Websites of professional organization were also reviewed for any relevant research published outside of peer-reviewed journals. Two librarians conducted the search using the terms: HIV/AIDS, vaccine, microbicides, recruit, willingness to participate, social harm, adolescent, community, ethics, consent, sexual behavior, acceptability, feasibility, motivation, key populations, vaccine-induced seropositivity, and vaccine trials. Peer-reviewed studies published in English were selected. Titles and abstracts of identified articles were first reviewed by each librarian before forwarding selected studies to the first author who further reviewed them for quality and relevance. Where possible, the author adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)statement [12].

Article review

The articles were classified per their relevance to the review (relevant, not relevant, and unclear). Studies deemed relevant were classified by type of socio-behavioral issue discussed. Each study was reviewed and the information extracted was entered into a predesigned form. The Quality Assessment Tool for Quantitative Studies [13], developed by the Effective Public Health Practice Project (EPHPP), guided our risk of bias assessment.

Inclusion criteria

Articles published in English and covering any of the following key topics regardless of the country were selected for this review:

a. Trial participation (recruitment, enrollment and retention)

b. Risk compensation during HIV trials

c. Social harms

d. Behaviors of most-at-risk populations*(key populations*) with emphasis on men-who-have-sex-with-men (MSM), and sex workers

e. Community engagement challenges

Exclusion criteria

Articles published in a language other than English and/or dealing with ethical issues such as informed consent, stigma, and discrimination were excluded for the review of literature. With few exceptions, the review focused mainly on articles dealing with HIV vaccine trials.

RESULTS AND DISCUSSION

Details of selected studies

After excluding duplicates, 3009 studies were identified

through the PubMed database, 2230 from Cochrane, 538 from Google, and 241 from recent international conferences. Of these, 208 studies were selected. Then47 studies were excluded for repetitive information. A total of 161 studies were included in this review.

Trial participation

Overview: Successful development and uptake of a safe and efficacious HIV vaccine depends on the extent to which members of communities most vulnerable to HIV are willing to participate in HIV vaccine research (WTP). Several vaccine preparedness studies have been implemented to examine the feasibility of HIV vaccine trials [14-16]. The majority of these vaccine preparedness studies found high reported trial participation in HIV vaccine trials among most-at-risk populations (key populations) across the world. Willingness to participate (WTP) in HIV vaccine trials among high-risk men who have sex with men (MSM) and transgender people varied between 70.9 % to 76.7% in China [17,18] compared to 31.6% to 73.8% in Thailand [19]. A high acceptance rate of 93% was reported among commercial female sex workers (FSWs) in Rio de Janeiro [20] compared to 88.9% in the Caribbean [21]. Even among injecting drug users (IDU), long considered unreliable for research and therefore underrepresented in previous clinical trials, reported WTP in preventive HIV vaccine trials was as high as 91% among people who use drugs and residing in rural communities in the USA [22] compared to 74.3% in China. Although adolescents girls and young men aged 15-24 years account for 20% of new HIV infection among adults worldwide [1], they have not always been included in clinical research for HIV vaccines. HB Jaspan, JR Berwick, L Myer, C Mathews, AJ Flisher, R Wood and LG Bekker [23] found that the majority of adolescents aged 11-19 years from a peri-urban community near Cape Town (79%) were willing to participate in an HIV vaccine trial compared to 50.6%among young adults in Dar es Salaam, Tanzania [24]. Despite concerns over the safety of HIV vaccine trials, C Farquhar, GC John-Stewart, FN John, MN Kabura and JN Kiarie [25] found that a high percentage (97%) of pregnant women presenting to a antenatal clinic in Nairobi for routine care reported that they would vaccinate their infant against HIV-1 and 91% reported willingness to enroll their infant in a research study. High acceptance to participate in HIV vaccine clinical trials was also documented among fishing communities along Lake Victoria in Uganda where the reported WTP in the hypothetical HIV vaccine trial was 99.4% [26]. Reported WTP in HIV vaccine trials was also high among high sexually diverse aboriginal people in Canada [27]. It is worth noting that methods used to collect the information on WTP as well as how much information about the trials is provided to participants vary widely among studies limiting the comparability of the results.

Following the discontinuation of the HVTN 503/ Phambili trial, public health experts were concerned about the negative impact of the information disseminated in the public arena on the future participation in HIV vaccine studies. However, PM Frew, MJ Mulligan, SI Hou, K Chan, and C del Rio [28] reported greater enrollment intention among men-who-have-sex-with-men (MSM) and transgender groups recruited from community settings in Atlanta in the wake of negative efficacy findings from the STEP Study. KN Otwombe, KJ Sikkema, J Dietrich, G de Bruyn, M van der Watt, and GE Gray [29], also found a high willingness to participate in biomedical HIV prevention studies (75%) after the HVTN 503/Phambili trial.

In addition to examining WTP in HIV vaccine trials among key populations, vaccine preparedness studies also investigated the difference in WTP in HIV vaccine trials by selected demographic characteristics such as educational level and gender. Unfortunately, the results showed inconsistencies among studies. With regard to education, Frew et al., (2009) found that educational level was a positive predictor of enrollment in HIV vaccine trial, whereas, S Dhalla and G Poole [30] and FH Priddy, AC Cheng, LF Salazar, and PM Frew [31] found no relationship between WTP with educational level. Furthermore,T Mbunda, M Bakari, EA Tarimo, E Sandstrom, and A Kulane [24] reported that young adults who had some knowledge about HIV vaccine studies were more likely than those without knowledge to enroll in HIV vaccine trials. G Giocos, A Kagee, and L Swartz [32], on the other hand, found that knowledge of HIV vaccines and HIV vaccine trials was not associated with WTP in HIV trials. Finally, WTP in hypothetical vaccine trials was higher in men than women in fishing communities along Lake Victoria in Uganda [33]. However, in a study conducted in Mozambique, Meque et al. (2014) [34], found that WTP in HIV trials was higher among women compared to men. In a second round of studies in fishing communities along Lake Victoria, N Kiwanuka, J Mpendo, A Nalutaaya, M Wambuzi, A Nanvubya, PK Kitandwe, E Muyanja, J Ssempiira, A Balyegisawa, and A Ssetaala [35] found that WTP in HIV trials was higher among women compared to men. In a large community-based HIV vaccine trial in Thailand from 2003 to 2009, J Kaewkungwal, P Pitisuttithum, S Rerks-Ngarm, S Nitayaphan, C Khamboonruang, P Kunasol, P Suntharasamai, S Pungpak, S Vanijanonta, V Bussaratid, et al. [36], found that more women (88%) completed 42 months follow-up compared to men (85%).

Hypothetical willingness to participate in an HIV vaccine clinical trial does not predict the populations' actual participation when offered enrollment in a study. SP Buchbinder, B Metch, SE Holte, S Scheer, A Coletti, and E Vittinghoff [37], compared hypothetical and actual willingness to enroll in a preventive HIV vaccine trial and identified factors affecting enrollment among high-risk HIV-uninfected former HIV vaccine preparedness study (VPS) participants in 8 US cities. Of the 2531 participants contacted for the vaccine trial, 13% enrolled, 34% were ineligible, and 53% refused enrollment. Only 20% of those stating hypothetical willingness during the VPS actually enrolled in this vaccine trial. Table (1) summarizes the findings about WTP for different populations.

Factors that influence acceptability and WTP in HIV vaccine trials:

Barriers to participate in HIV vaccine trials: Overcoming barriers to participation in HIV vaccine studies will improve trial outcomes. Several factors that hamper participation in HIV vaccine trials have been identified. Mistrust and fear of government, costs, transportation constraints, concerns about vaccine-induced seropositivity, and possible breaches in confidentiality were important barriers to enrolling participants in HIV vaccine trials [22,38]. Additional barriers to participating

Table 1: Willingness to participate in HIV vaccinetrials from different populations.

Population	Country	Authors [Reference #]	Willingness to Participate (%)
MSM and Transgender	China	Li et al., 2013 [16]	70.9-76.7
	Thailand	Newman et al. 2010, [18]	31.6-73.8
FSW	Brazil	Barroso et al. 2009. [19]	93.0
	Carribean	Deschamps et al. 2013 [20]	88.9
IDU	USA	Young et al. 2014. [21]	91.0
	China	Yin et al. 2008. [22]	74.3
Adolescent	South Africa	Jaspan et al. 2008. [23]	79.0
	Tanzania	Mbunda et al. 2014. [24]	50.6
Pregnant Women	Kenya	Farquhar et al. 2006. [25]	91.0
Fisher folks	Uganda	Asiki et al. 2013. [26]	99.4

in HIV vaccine include: resistance from significant others, the stigma of a positive HIV antibody test as the result of vaccination, and concerns about the social consequences of participating in HIV research [39-45]. Efficacy, side effects, duration of protection, out-of-pocket cost, and social saturation are also serious concerns to those contemplating enrolments in HIV trials [19,46].

The requirement to delay pregnancy (for females), larger blood draws, the possibility of receiving either candidate vaccine or placebo, monthly study visits, and trial duration longer than 2 years significantly reduce WTP in trials. E Ruzagira, S Wandiembe, L Bufumbo, J Levin, MA Price, H Grosskurth and A Kamali [47], found barriers to HIV vaccine acceptability differed between men and women. For women, barriers to HIV vaccine acceptability were related to their intimate relationships, negative experiences with health care providers, and anticipated difficulties procuring insurance. Studying HIV positive women in Canada, MR Loutfy, LK V, S Mohammed, W Wu, M Muchenje, K Masinde, K Salam, L Soje, S Gregorovich, and W Tharao [48] reported that the research topic, time/availability constraints, language barriers, HIV disclosure/ stigma issues, lack of trust of research personnel, fear of research and inaccessibility to child care, and transportation constituted important barriers for women to participate in research. These women felt that the most important personal attributes for recruitment were research personnel who were respectful, skilled, flexible, empathetic, and had good communication skills.

Drivers/Facilitators to participate in HIV vaccine trials: Competing factors motivate people to enroll/participate in HIV vaccine trials. They include: monetary incentives, convenience of participating in a study, sufficient and appropriate study information, personal benefits, altruism, and support from the researchers [49,50]. Trustworthy trial staff, convenient schedules and facilities, and involvement of trusted community groups in recruitment also motivated participants [44]. The other motivators of participation are access to HIV counseling and testing services, HIV education, and hope of being prevented from acquiring HIV health care [26]. G Giocos, A Kagee and L Swartz [32], found that subjective norms and attitude towards participation in an HIV vaccine trial were significant predictors of WTP among South African adolescents.

Strategies to enhance acceptability and WTP in HIV vaccine trials: Four strategies to improve WTP in HIV vaccine trials have been described in the literature. They include: (1) HIV vaccine recommendations from frontline health service providers taking ethics into account, (2) The integration and dissemination of combined behavioral and biomedical HIV prevention approaches, (3) Network-based HIV vaccine promotion [22], and (4) Strategies targeting organizations dealing with HIV [51].

Areas for further research: More studies are needed to better understand the discrepancy between WTP and actual enrollment into phase I/II trials in the same study population. We posit that the lack of a clear definition of the concept of "willingness to participate" as well as inconsistencies in information provided about the trials may explain the discrepancy. WTP may be understood as willingness to enroll in the study or willingness to vaccinate - this understanding, as well as how well the actual implications are described, affect the decision to participate. Furthermore, there is a need to examine how the presence of new prevention options and perception of end of AIDS affect WTP and actual participation [52].

Retention in Cohort Studies and Phase2 Trials:

Overview: The ability to retain large number of participants in clinical trials is a key concern in HIV vaccine efficacy trials since poor retention can reduce study power, possibly resulting in biased estimates of effect [53]. Existing evidence shows high retention (defined as completion of the trial) of participants in HIV prevention trials. Volunteers amongst police officers were enrolled in the first HIV vaccine trial in Dar es Salaam. They were primed with HIV-1 DNA vaccine at months 0, 1 and 3; and boosted with HIV-1 MVA vaccine at months 9 and 21. Out of 408 police officers who formed the core group, 364 (89.0%) attended the educational sessions. 263 out of 364 (72.2%) indicated willingness to participate in the HIV vaccine trial. 98% of those indicating WTP attended the pre-screening workshops. Retention into the schedule was: 98% for the 3 DNA/placebo vaccinations, while it was 83% and 73% for the first and second MVA/placebo vaccinations respectively [54]. Results from the phase 1, randomized, double-blind, placebo-controlled trial of ALVAC-HIV vCP1521 in infants born to HIV type 1-infected women in Uganda reported a 98% retention at 24 months [55]. HB Jaspan, AJ Flisher, L Myer, C Mathews, K Middelkoop, D Mark, and LG Bekker [56], reported a retention of 82% at 1-year follow-up among HIV-negative adolescents aged 14-17 years from Cape

Town enrolled into a cohort study for HIV, Syphilis, pregnancy testing, and sexual risk. Studying women participating in a phase III community HIV vaccine trial in Thailand from 2003 to 2009, J Kaewkungwal, P Pitisuttithum, S Rerks-Ngarm, S Nitayaphan, C Khamboonruang, P Kunasol, P Suntharasamai, S Pungpak, S Vanijanonta, V Bussaratid, et al. [36], found that more women (88%) completed 42 months follow-up compared with men (85%).

Uganda has long been successful in controlling the HIV epidemic but there is evidence that HIV prevalence and incidence are increasing again. E Ruzagira, S Wandiembe, A Abaasa, J Levin, A Bwanika, U Bahemuka, MA Price, and A Kamali [57], estimated the prevalence and incidence of HIV transmission in a rural community-based HIV vaccine preparedness cohort in Masaka, Uganda. Between February and July 2004, they carried out a house-to-house HIV sero-prevalence survey among consenting individuals aged 18–60 years. Participants were interviewed, counseled, and asked to provide blood for HIV testing. HIV uninfected participants were enrolled in a 2-year HIV sero-incidence study. Medical evaluations, HIV counseling and testing, and sample collection for laboratory analysis were done quarterly. Sexual risk behavior data was collected every 6 months. The HIV point prevalence was 11.2%, and was higher among women than men (12.9% vs. 8.6%, P=0.007). Twenty-one seroconversions were recorded over 2025.8 person-years, an annual HIV incidence of 1.04%. Cohort retention after 2 years was 87%.

Fishing communities (FCs) in Uganda are key populations for HIV/AIDS spread despite first noticing HIV more than two decades ago. FCs along Lake Victoria have an HIV prevalence of 22-29%, with an incidence of 3.4 -5 per 100 person years at risk [58]. A Ssetaala, J Nakiyingi-Miiro, S Asiimwe, A Nanvubya, J Mpendo, G Asiki, L Nielsen, N Kiwanuka, J Seeley, and A Kamali [59], explored factors affecting recruitment and retention of women from fishing communities in HIV prevention research. An HIV incidence cohort screened 2074 volunteers (1057 men and 1017 women) aged 13-49 years from five fishing communities along Lake Victoria using demographic, medical history, and risk behavior assessment questionnaires.1000 HIV negative high risk volunteers were enrolled and followed every 6 months for 18 months. A total of 382 (74%) women and 332 (69%) men completed all follow-up visits. Older women (> 24 years) and those unemployed, who had lived in the community for 5 years or more, were more likely to complete all study visits.

Factors affecting study retention: Since there is no published data on correlates associated with retention or non-retention in HIV vaccine clinical trials, we relied on few microbicide trials as a proxy. JM Marrazzo, G Ramjee, BA Richardson, K Gomez, N Mgodi, G Nair, T Palanee, C Nakabiito, A van der Straten, and L Noguchi [60], enrolled 5029 women in a randomized, placebo-controlled trial to assess daily treatment with oral tenofovir disoproxil fumarate (TDF), oral tenofovir–emtricitabine (TDF-FTC), or 1% tenofovir (TFV) vaginal gel as pre exposure prophylaxis (PrEP) against HIV-1 infection in women in South Africa, Uganda, and Zimbabwe. The rate of retention in the study was 91% during 5509 person-years of follow-up. PJ Feldblum, V Halpern, CC Lie, O Obunge, F Ogunsola, W Ampofo, and K Opoku [53] evaluated factors associated with non-retention in four trials of two candidate vaginal microbicides (1% C31G or SAVVY(R) and 6% cellulose sulfate or CS) conducted in multiple sub-Saharan African countries. Younger and less-educated women were more difficult to retain in these microbicide trials.

Strategy to enhance retention: In a systematic review of trials evaluating the effect of intervention strategies designed to improve recruitment to randomized controlled trials, S Treweek, P Lockhart, M Pitkethly, JA Cook, M Kjeldstrøm, M Johansen, TK Taskila, FM Sullivan, S Wilson, and C Jackson [61] found that a number of interventions including telephone reminders to non-responders [62], opt-out procedures requiring potential participants to contact the research team if they do not want to be contacted about a trial [63], a financial incentive with the trial invitation [64], and making the trial open rather than blinded [65] improved recruitment in high-quality studies involving real trials.

G Omosa-Manyonyi, W Jaoko, S Wakasiaka, J Bwayo, A Anzala, C Schmidt, M Oyaro, H Ogutu, B Farah, and J Nyange [66], described an innovative informed consent process that may have contributed to a high retention rate in HIV trials at Kenya AIDS Vaccine Initiative (KAVI). Since the year 2001, the KAVI team has conducted 4 Phase I/II clinical trials in healthy, adult, HIV uninfected volunteers in collaboration with the Medical Research Council and the International AIDS Vaccine Initiative (IAVI). These consisted of a phase I DNA trial, a phase I MVA trial, a phase I rollover trial in which those who had previously received DNA were boosted with MVA at least 32 weeks later and a phase IIA DNA prime MVA boost trial.

Participant recruitment at the beginning of vaccine trials involved holding seminars at a KAVI site in Nairobi during which basic information on the trials was presented. The attendees were given an opportunity to ask questions during and at the end of the presentations. Those who were interested in further information were invited to the Vaccine Trial Centre at Kenya AIDS Vaccine Initiative (KAVI) for a more detailed presentation. This approach was modified in the later trials to include the participation of peer-leaders chosen by the communities themselves. These peer-leaders were given basic training on vaccines and HIV in general, and in particular on HIV vaccines. They were then tasked to disseminate this basic information in their communities and to organize community seminars during which nurse/counselors or physicians from KAVI would give information on the vaccine trials, and invite those who were interested in participating or hearing more to come to KAVI for more detailed presentations. After each of the detailed presentations, individuals who showed interest in participating in the vaccine trials were booked to have individualized sessions with the nurse/counselors or physicians, during which they were counseled on how to maintain low risk behavior and contraception, among others, and given more opportunity to ask any additional questions.

A total of 250 volunteers were screened for the 4 studies conducted at KAVI between 2001 and 2003. Most of these volunteers (77%) were male and seventy-one percent of the volunteers were aged between 18 and 27 years. Most of the volunteers were single. The follow-up rate in all the 4 trials was good, ranging from 90% to 96%. The research team attributes

the high retention rate in all the trials to the informed consent process being employed at the center, and to repeated volunteer education on the trial procedures during their follow-up visits. The many contacts volunteers had with the study team prior to enrollment facilitated good rapport and trust between the volunteers and the study team, hence enhancing their retention in the study. It is also possible that the medical care given to volunteers for all the adverse events may have contributed to the good follow-up rate since health care in Kenya is not easily available.

Areas for further research: More cohort studies in key populations are needed to evaluate creative approaches to enhance recruitment and retention in these populations.

Risk compensation in HIV prevention:

Overview: The last ten years have witnessed an expansion in research for the development of new HIV prevention technologies including vaginal microbicide [67], oral antiretroviral pre-exposure prophylaxis (PrEP) [68], and the use of antiretroviral treatment as prevention [69]. Excitement about new HIV prevention technologies has been tempered by concerns that reductions in HIV transmission risks resulting from these new technologies may have the potential to simultaneously lower perceptions of risk which in turn may alter risk-behaviors. An inadvertent increase in risk behaviors following the introduction of new HIV prevention methods is often referred to as risk compensation [70,71].

The extant literature about risk compensation show mixed results. Some studies support the existence of risk compensation among users of new HIV prevention methods including male circumcision, microbicides, and pre-exposure antiretroviral prophylaxis (PrEP) [70,72], whereas others either failed to observe this phenomenon[73,74]or reported a marked reduction in risk behaviors after enrollment in trials [75,76].

Although syphilis rates in the United States declined steeply between 1990 and 2003, syphilis cases among MSM rose sharply after 2000. This increase is believed to be related to diminished concerns about the risk of acquiring and transmitting HIV as a result of optimism regarding highly active antiretroviral therapy [72]. In a study of 15 women and 10 men that examined the potential influence of a hypothetical HIV vaccine on sexual-risk behaviors in Santo Domingo, Dominican Republic,C Barrington, L Moreno, and D Kerrigan [77] reported that approximately half of the male study participants stated that they would increase their number of sexual partners and/or would not use condoms if they received an efficacious HIV vaccine. In contrast, female participants reported that they would be unlikely to change their own behavior, but stated that an HIV vaccine would allow them to worry less about the sexual-risk behavior of their male partners. A Tripathi, YO Whiteside, and WA Duffus [78] reported similar results after interviewing 89 seronegative partners in a Ryan White Clinic in South Carolina from 2010-2011. They found that 26% of the participants reported that they would be more likely to have unprotected sex with HIV-positive partner while using (PrEP). Studying HIV-negative gay and bisexual men (GBM) in HIV sero-discordant relationships in Los Angeles, RA Brooks, RJ Landovitz, RL Kaplan, E Lieber, SJ Lee, and TW Barkley [79] found that the adoption of PrEP could potentially contribute to a decrease or abandonment of condom use. However, a review of studies that examined the impact of wider access to ART on sexual risk behaviors among HIV-infected individuals in the developing world showed that ART was associated with a significant reduction in unprotected sex following treatment initiation [80,81]. In addition, the majority of studies that examined risk compensation following pre-exposure prophylaxis (PrEP) implementation showed no increase in sexual risk behavior or sexually transmitted infections[82-84].

Between July 2008 and November 2010, Baeten et al., (2012) enrolled heterosexual HIV-1 serodiscordant couples from 9 sites in Kenya and Uganda. At enrollment, participants were assigned to one of three study arms: once-daily TDF, FTC/TDF, or placebo. Of 7856 HIV-1 serodiscordant couples screened, 4758 were enrolled and 4747 eligible couples were followed: 1584 randomized to TDF, 1579 to FTC/TDF, and 1584 to placebo. Overall, baseline characteristics were similar across the three study arms. HIV-1 protective effects of FTC/TDF and TDF were not significantly different (p=0.23), and both study medications significantly reduced HIV-1 incidence in both men and women. The rate of serious medical events was similar across the study arms. At enrollment, 27% of HIV-1 seronegative partners reported sex without condoms with their HIV-1 seropositive partner during the prior month. This percentage decreased during follow-up (to 13% and 9% at 12 and 24 months) and was similar across the study arms. JL Marcus, DV Glidden, KH Mayer, AY Liu, SP Buchbinder, KR Amico, V McMahan, EG Kallas, O Montoya-Herrera, and J Pilotto [74], evaluated potential risk compensation among men-who-have-sex-with-men and transgender women who participated in the multinational Preexposure Prophylaxis Initiative (iPrEx) using biomarkers of sexual risk behavior. They found no increase in HIV or syphilis among study participants, and no increased engagement in receptive anal sex without a condom, all of which could be markers of increased risk-taking.

The concept of risk compensation behavior originates from the theory of "*risk homeostasis*" [85]. This theory suggests that each of us continually adjusts our risk-taking so that our perceived risk approaches a "target risk level", the level at which we see the most acceptable trade-off between risks and benefits. This level need not be static, and it may change due to factors such as time or social influences. However, at any given point, our target risk level represents what we perceive to be the optimal balance between risk-taking (e.g., sex without condoms) and the potential benefits of risky behavior (e.g., intimacy, sexual pleasure) [71]. Historically, similar arguments have been raised regarding risk compensation after introduction of other interventions that lessen the consequences of risky behavior. The extensive availability of female contraceptives has been criticized for promoting risky sexual behavior [86]. GM Secura, T Adams, CM Buckel, Q Zhao, and JF Peipert [87], found that giving women free birth control did not result in increased promiscuity. More recently, there was concern that earlier sexual debut and greater numbers of sexual partners would follow use of the human papillomavirus vaccination (HPV), but increased sexual activity has not been observed [88].

Factors affecting this phenomenon: The debates about

risk compensation will likely continue for quite some time since existing evidence cannot confirm or dispel its existence. More studies assessing this phenomenon are needed. Unfortunately, rigorous methodological designs for assessing risk compensation are not available. They would be ethically flawed and difficult to implement. K Underhill [71], posited that the most methodologically rigorous, externally valid, and ethically acceptable design for assessing risk compensation behavior is to take advantage of a naturally occurring experiment during roll-out and Phase IV testing. If this opportunity does not naturally arise, post marketing studies should continue using nonrandomized or simulation methods to link product use, perceptions of reduced HIV risk, and user behaviors. These designs presently account for most assessments of risk compensation behavior among product users, although they lack the methodological rigor of a randomized approach, external validity is a key strength [71].

Strategy to reduce risk-taking behavior: BA Koblin, S Bonner, DR Hoover, et al. [89], conducted a randomized trial of enhanced HIV risk-reduction and vaccine trial education interventions among HIV-negative high-risk women who use non-injection drugs. The UNITY study which includes an enhanced vaccine education intervention using pictures along with application vignettes and enhanced risk-reduction counseling, consisting of 3 one-on-one counseling sessions compared with standard conditions. During follow-up, the percentage of women reporting sexual risk behaviors declined significantly but did not differ significantly by study arm. Knowledge of HIV vaccine trial concepts significantly increased but did not significantly differ by study arm. To ensure optimal protection offered by HIV prevention technologies, brief risk reduction counseling should be concurrently implemented. Brief risk reduction counseling has been shown to be effective in reducing risk behavior and subsequent sexually transmitted diseases [70].

Areas for further research: Although more extant studies suggest that risk compensation after HIV trials is not observed, more longitudinal studies after HIV trials monitoring changes in self-reported sexual risk behavior or the incidence of pregnancy or sexually transmitted disease among key populations are needed to shed light on this phenomenon. Cohort studies for hypothetical vaccines may offer an invaluable opportunity to confirm or dispel the existence of risk compensation.

Social harm or social impact:

Overview: Although efforts to develop an effective HIV vaccine may have produced ancillary benefits, this section will focus solely on social harms associated with HIV vaccine research. HIV vaccine research includes the potential for physical, emotional, and psychosocial harm to trial participants [90]. Assessing the frequencies of occurrence, the magnitude, and seriousness of the harm is important to protect future participants in HIV vaccine trial. Extant literature suggests that social harms following participation in HIV trials are not a common occurrence and when they do occur, serious harms are rare. P Pitisuttithum, K Choopanya, V Bussaratid, et al. [91], enrolled 2546 injecting drug users (IDU) in a 36-month vaccine trial in Thailand. Volunteers received education and risk reduction counseling at every six-month study visit. Although social harms were not actively solicited, volunteers were encouraged to report any such events during the process of counseling at every six-month visit. Only a few participants (n=37) reported study-related social harms during the course of the trial. Most harm had minimal impact and all could be resolved by the end of the study. Studying the negative social impacts (NSIs) among 5417 volunteers in the North American phase III trial of AIDSVAX B/B vaccine, J Fuchs, M Durham, E McLellan-Lemal, et al. [92], found that a modest proportion of vaccine efficacy trial volunteers (18%) reported problems in interpersonal relationships; serious harms involving insurance and employment were rare. RA Jenkins, D Thapinta, PA Morgan, et al. [93], investigated behavioral and social issues in 363 phase I/II preventive HIV-1 vaccine trial volunteers in Thailand. Data were collected at baseline and at 4, 8, and 12-month follow-up visits respectively. Overtly negative reactions from family or friends were reported by 5.9% of participants. No experiences of discrimination in employment, health care, or insurance were reported.

Findings from North America and Thailand contrast sharply with the results of studies conducted in Africa. L Nyblade, S Singh, K Ashburn, et al. [94], conducted eighteen focus groups with a total of 133 participants and 82 individuals at two centers in Nairobi, Kenya. Respondents included peer leaders, community advisory board members, former and current volunteers in clinical research, study staff, community leaders, and community members. HIV-related stigma and discrimination emerged among all respondent groups as important hypothetical barriers to participation in HIV-vaccine related research. In a descriptive prospective cohort study conducted among 33 out of 60 volunteers of HIVIS03 trial in Dar es Salaam, Tanzania, who received three HIV-1 DNA injections boosted with two HIV-1 MVA doses, E Tarimo, P Munseri, S Aboud, et al. [95], found that participants in the phase I/II HIV vaccine trial were likely to face negative comments from relatives and colleagues after the end of the trial, but those comments decreased over time. Most of the comments were associated with discrimination; stigma, and mistrust towards the HIV vaccine trial. J Stadler, S Delany-Moretlwe, T Palanee and H Rees [96], interviewed 150 participants in the microbicide Development Program (MDP) trial in Johannesburg, South Africa. More than one-third of these 150 women reported intimate partner violence (IPV), of which half the cases were related to involvement in the trial. They reported verbal abuse, abandonment, and in some cases, beatings. Although these studies seems to support findings by C Milford, N Barsdorf, and Z Kafaar [97] who argued that social harms were likely to occur in South African trials, the results from three phase 1 HIV vaccine clinical trials in Kenya, Uganda, Rwanda, Zambia, and South Africa say otherwise.G Mutua, L Mutengu, J Mpendo, et al. [98], studied 383 trial volunteers who received 2-4 injections and followed them for up to 16 months with repeated HIV testing and counseling, plus mucosal sampling at the Kenyan sites. At the final study visit, self-reported data on potential social impact of trial participation were collected using a standardized questionnaire. The results showed that trial volunteers reported largely positive social impacts and few major negative impacts after participation in phase 1 HIV vaccine trials. The majority of the respondents (175/256, 68%) reported as positive impacts, with the most common being 'affecting your feelings on the AIDS epidemic' 58% (101/175), and 'affecting feelings about

yourself' 14% (24/175). The most common negative impacts were 'affecting health' 33% (27/81) and 'affecting relationship with friends' 17% (14/81).

The goal of an HIV vaccine is to induce protective immune responses in the recipients. However, this may cause volunteers to test positive in routine HIV testing despite being HIV uninfected. CJ Cooper, B Metch, J Dragavon, et al. [99], assessed the frequency of vaccine-induced seropositivity/reactivity (VISP) using data combined from all phase 1 HIV-1 vaccine trials conducted by HVTN clinical trial sites located in 9 countries (Botswana, Brazil, Haiti, Jamaica, Peru, South Africa, Thailand, and Trinidad and Tobago, and the United States) between December 14, 2000, and January 15, 2010. Among 2176 participants free of HIV infection who received a vaccine product, 908 (41.7%) had VISP. The occurrence of VISP varied substantially across different HIV vaccine product types. The induction of VISP is common with vaccines containing both the HIV-1 envelope and group-specific core antigen gene proteins. he International AIDS Vaccine Initiative (IAVI) sponsored 7 Phase I and IIA single- and multicenter HIV preventive vaccine clinical trials among healthy HIV-uninfected African adults in East and South African countries [100]. Two different recombinant plasmid DNA vaccines and three vaccines based on viral vectors (Modified vaccinia Ankara [MVA], Adeno-associated virus type 2 [AAV-2], and Adenovirus type 5 [Ad5]) were tested. After completion of vaccine trials conducted between 2001–2007, both vaccine and placebo recipients were offered enrollment into an observational, long-term follow-up study (LTFU) to monitor potential late health effects and persistence of immune responses. At scheduled 6-monthly clinic visits, a health questionnaire was administered; clinical events were recorded and graded for severity. Blood was drawn for HIV testing and cellular immune assays. 287 volunteers were enrolled; total follow-up after last vaccination was 1463 person years (median: 5.2 years). Ninety-three percent (93%) of volunteers reported good health at their last LTFU visit. Infectious diseases and injuries accounted for almost 50% of the 175 reported clinical events, of which over 95% were mild or moderate in severity. There were 36 pregnancies, six incident HIV infections and 14 volunteers reported cases of social harm. HIV vaccines studied in these trials had a low potential of induction of persisting HIV antibodies.

Vaccine-induced seropositivity may last for more than 15 years [101]. The development of vaccine-induced seropositivity/reactivity may lead to difficulties with obtaining employment, medical or disability/life insurance, donating blood or organs, enrolling in the army or with immigration owing to a false-positive HIV test result[102].

Areas for further research: Long-term follow-up studies of future HIV vaccine study participants should be organized to monitor potential benefits and harms associated with participating in HIV vaccine trials and to better understand 'triggers' of social harm and evaluate potential interventions for decreasing instances of social harm.

Community stakeholder engagement:

Importance of community engagement in HIV trials: Community engagement refers to the process of collaborative work with relevant partners who share common goals and interests [103]. Over the past several decades, we have learned vital lessons which showed how a lack of community engagement can threaten the viability of research trials. In 2004 researchers conducted trials in five countries (Cambodia, Cameroon, Ghana, Nigeria, and Thailand) to assess the safety and effectiveness of oral pre–exposure prophylaxis (PrEP) to prevent HIV transmission. Despite the promise of Tenofoviras a potential new method for HIV prevention, trials in four of the five countries—Ghana being the exception—were prematurely closed because of what local communities and civil society perceived as a lack of transparency and communication, and disagreements over certain aspects of trial implementation [104-106].

Community engagement in HIV vaccine trial is necessary to improve awareness of the effort and favorably influence attitudes and referent norms [107]. In addition, communities are important advocates to motivate governments to prioritize HIV vaccine development as part of their comprehensive response. Investment in community work helps cultivate a sense of community ownership that builds trust and deepens knowledge of local realities. It can improve the quality of the data collected by ensuring that trial protocols, procedures, and strategies are acceptable to trial participants and build on locally understood languages and customs. It also optimizes the likelihood of eliciting high levels of adherence and accuracy in self–reporting [108].

Community engagement strategies: In the early l980s, determined to expedite the search for treatments to combat HIV/AIDS, AIDS activists who were affluent and well-educated called for their involvement in HIV decision making. Suddenly the biomedical research field was faced with a well–informed, energized community of activists demanding to be involved. In response to their demands, the community advisory boards (CABs) were established. They were composed primarily of non–scientists to advise on research protocols and help to educate communities about the research taking place. While the AIDS activists who first pushed for HIV stakeholder involvement were a relatively homogenous group of people whose goal was to make HIV treatment trials the primary focus of their activism, things changed as the individuals and communities who participated in HIV prevention research trials became more diverse including sex workers, MSM, women, and adolescents. In the 2000s we witnessed a progressive shift from an activist–led movement, where individuals pushed for inclusion to a researcher–led effort, where study staff worked to encourage often marginalized individuals into relationships with Western–educated researchers. Community empowerment required a shift in the role of researchers from that of an expert who enters a community to deliver an intervention toward that of an advocate, collaborator, or mentor who assists community members in developing the resources, skills, and social networks to implement and maintain these programs [109,110]. Community liaison program is another strategy to improve community participation in HIV vaccine research. Kelly et al., (2012) described a 16-month health education pilot program based on diffusion of innovation and social network theories implemented by volunteer community liaisons to increase awareness and support for HIV vaccine research in minority populations. Through training in participatory engagement, volunteers were able to tailor and

adapt an HIV prevention message for their communities. Process evaluation data showed that the acceptance of participatory engagement and HIV vaccine message dissemination far exceeded expectations [111].

Challenges of community engagement in HIV trials: There is an ongoing global debate concerning researchers' obligations to meet the health needs of people participating in HIV prevention trials in resource-poor settings. Whose responsibility is it to care for individuals who seroconvert when participating in HIV trial? What is the correct standard of prevention? What are the obligations, if any, to the larger communities hosting clinical trials?

The ethical issues associated with community engagement in HIV vaccine trials led to the development of international guidelines, such as UNAIDS' good participatory practice (GPP), to ensure that stakeholders are effectively involved in all phases of biomedical HIV prevention trials [112]. These guidelines provide trial funders, sponsors, and implementers with systematic guidance on how to effectively engage with all stakeholders in the design and conduct of biomedical HIV prevention trials. Unfortunately, existing guidelines and best practices provide little insight into the expected outcomes of engagement activities, indicators of success, or useful monitoring and evaluation (M&E) tools for assessing impact on research and communities. To fill this gap, a consortium of organizations (AVAC, International HIV/AIDS Alliance, International AIDS Vaccine Initiative, NIAID, TB Alliance and Well come Trust), developed a user-friendly M&E Toolkit for engagement programs in clinic for engagement programs in clinical research settings in developing countries [113].

Areas for further research: There is a need to monitor and evaluate the impact of various community engagement strategies on the implementation of HIV trials and the uptake of products.

Risk behaviors in key populations and HIV trials:

Overview: Research has the potential to play a decisive role in the efforts to slow the transmission of HIV infection in key populations. However, its ability to do so depends in part on both the success to engage key population groups and learn from and the likelihood for the latter to uptake the research products. The World Health Organization (2014) defined *key populations* as select groups of people who, due to specific higher-risk behaviors, are at increased risk of HIV irrespective of the epidemic type or local context [114]. Also, they often have legal and social issues related to their behaviors that increase their vulnerability to HIV [114]. The four main key population groups include gay men and other men who have sex with men, sex workers and their clients, transgender people, and people who inject drugs. However, based on local epidemiological and social context, many countries especially from sub Saharan Africa consider youth, fishermen around some African lakes, people in the military and long-distance truck drivers as key populations. This review focuses only on female sex workers (FSW) and men who have sex with men (MSM).In spite of an aggregate decline in HIV incidence worldwide, a growing body of epidemiological evidence shows that key populations continue to bear a disproportionately high burden of HIV infection in both low and high-prevalence countries [115]. Female sex workers and their clients have been recognized as a potential epidemiological bridge for HIV transmission to other populations. Evidence shows that HIV prevalence among sex workers is 12 times greater than among the general population globally [116]. Even in very high prevalence countries, HIV prevalence among sex workers is much higher than among the general population. An analysis of 16 countries in sub-Saharan Africa in 2012 showed a pooled prevalence of more than 37% among sex workers [116]. Likewise, high HIV prevalence and incidence burdens have been reported among MSM throughout the world [117]. Epidemics of HIV in MSM continue to expand in most countries [117]. A growing number of studies on African MSM have shown high HIV transmission rates through unprotected anal sex [118-123]. In two South African cities (Johannesburg and Durban), LC Rispel, CA Metcalf, A Cloete, V Reddy, and C Lombard [122] found a prevalence of 49.5% among MSM aged 18 years or older compared to 43.0% in Mombasa, Kenya [119]. A cross-sectional survey of 272 and 239 MSM aged ≥ 18 from Douala and Yaoundé, found a HIV prevalence of 28.6% and 47.3%, respectively [118].

Global efforts to address the AIDS epidemic have brought promising developments, including effective antiretroviral therapy and new prevention technologies. Cohorts of key populations to support research on new prevention technologies and adherence to treatment are critical to improve the quality of HIV trials, ensure the uptake of new prevention technologies, and improve health outcomes. Furthermore, although HIV vaccine remains the ultimate solution to control the HIV pandemic, its availability does not guarantee its uptake. A good understanding of factors that hinder HIV vaccine trials is critical. This section focused more on studies from sub Saharan Africa.

Factors that interfere with HIV trials in key populations: Several studies examined key populations' willingness to participate in HIV trials and their retention rate [17-19,21,22,124].This section examines how key population risk behaviors may interfere with the implementation of HIV trials. The following factors affect key populations' abilities to participate in HIV trials. They include: 1. Structural factors including gender-based expectations, poverty, violence and other human rights violations. Criminalization of sex work and homosexuality, like the kind existing in sub-Saharan Africa, is a huge hindrance to promoting public health. Protective legislation for MSM exists only in South Africa. Recent legal reforms in some East African countries have aimed to strengthen anti-homosexual legislation, rather than make the law more inclusive [125]. Many governments in Africa do not promote the health for key populations. K Makofane, C Gueboguo, D Lyons et al. [126], analyzed Aids National Strategic Plans (NSPs) from 46 African countries to assess (1) the representation of MSM and their HIV risk, (2) inclusion of epidemiologic information on the HIV epidemic amongst MSM, and (3) government-led interventions addressing MSM. Overall, the governments of the countries included in the study exhibited little knowledge of HIV disease dynamics amongst MSM and little knowledge of the social dynamics behind MSM's HIV risk. Hostile legal environments, repressive policies, unfair police practices, absence of funding for research and HIV programs, human rights violations, and stigma and discrimination drive members of key

populations underground and further reduce the chances for their participation in HIV trials. The consequences of homophobic stigma from society, communities, churches, family and friends have direct impacts on an individual's sense of personal worth. In other parts of the world, lack of self-esteem arising from stigma has been shown to reduce a person's motivation to protect themselves or others from high risk behaviors.[127]
2. Alcohol, substance use, and mental health issues are prevalent in key populations. They affect key populations' recruitment, participation, and retention in HIV trials.AM Secor, E Wahome, M Micheni, et al. [128], assessed psychosocial and mental health among 112 MSM participating in two ongoing HIV-positive and HIV-negative cohorts in Mtwapa, Kenya. One-third of participants (16.1%) met criteria for major depressive disorder or other depressive disorder (15.2%). Alcohol abuse was reported by 45% of respondents and other substance abuse by 59.8% of respondents. Alcohol use is associated with adverse physical health, illicit drug use, mental health problems, and sexual violence [129]. High rates of heavy alcohol use among MSM and transgender women (TW) have been linked to increased vulnerability for HIV and poor mental health [130]. Alcohol use is among the most prevalent behaviors associated with HIV and other sexually transmitted infections (STIs) [131,132]. It has been shown to be associated with inconsistent condom use [133,134]. In addition, EJ Sanders, SM Graham, HS Okuku, et al. [119], reported that less than 2% of their cohort injected drugs. Mental health conditions can erode the quality of life and interfere with health-related behaviors such as medication adherence [128]. Alcohol and/or substance use impairs adherence with medical treatment, whether with medications, appointments, or treatment recommendations[135,136], leading to poor response to HIV therapy in general [137].

3. High mobility makes the recruitment of hard-to-reach populations a particularly challenging task. Travelling is an important component of gay lifestyle and identity, as gay men travel to destinations where they can socialize with peers and in some cases avoid the social constraints and intolerance of their home environments [138]. The internet permits the creation of social and sexual networks that facilitate contact and the security of having a sexual encounter [138-140].

Economic and political instability force many women in developing countries to move into neighboring countries in search for work. Many of them often enter sex work out of financial necessity upon arrival. In Benin, 58% of sex workers interviewed had lived there for less than six months [141]. Women from rural areas, in particular, may move in search of a better life in cities, drawn either by friends or family there, or by images of cities as places of opportunity [142]. These women move along busy highways or between mining cities in search for sex work.

Snowball sampling, respondent-driven sampling (RDS), and time-location sampling have been successful in recruiting key populations in previous studies [143-145]. Although research has the potential to be a decisive factor in slowing the HIV/AIDS epidemic, its ability to do so depends on the success with which it engages and learns from people most affected by HIV/AIDS [146]. High mobility has been shown to be associated with low adherence [136].

4. High risk sexual behaviors, lack of knowledge and skills to protect themselves, and lack of access to health services put them at high risk of HIV and consequently reduce the pool of qualified individuals for HIV trials. The proportion of MSM reporting multiple partnerships varied between studies, with some reporting that as high as 86% had more than five partners in the last months [147]. Since homosexuality is not tolerated in many sub-Saharan Africa, MSM often have female sexual partners to conceal their true sexual orientation [148-150]. Bisexuality and close links with heterosexual networks are further supported by viral genetic studies that shows similarities of HIV subtypes from MSM and from heterosexual populations in same geographic areas [151]. Furthermore, several studies from Africa have shown low general knowledge about HIV among MSM. Most MSM live unaware of their HIV status, due in part to ignorance of the risks of their own sexual behaviors and/or a reluctance to use HIV testing services. In a study of 425 MSM in Kenya, S Geibel, S Luchters, N King'ola, E Esu-Williams, A Rinyiru and W Tun [152] found that 35% of respondents did not know that HIV can be transmitted via anal sex and that such behaviors might be actively sought after because of this misconception. Other studies have documented inconsistent use of condoms and high usage of petroleum products, baby oils, and other lotions for lubrication during anal sex [121,153]. In addition, key populations in Africa have a high burden of sexually transmitted infections. Studies done among men in South Africa, Senegal and Kenya found that about 4 of every 10 MSM were infected with a STI, which can be passed between MSM through oral, anal and oral-anal sex. Discriminatory laws and policies, stigma and discrimination, and substance abuse contribute to and reinforce the suboptimal utilization of health services by key populations who remain severely underserved in too many settings. Key affected populations often face significant barriers to access prevention services (condoms, HIV testing and counseling or pre exposure prophylaxis therapy) and treatment.

Strategies to address risk behaviors in key populations: There has been considerable progress over the last decade in developing HIV biomedical and behavioral interventions [154-157], as well as stigma-reduction interventions [156]. However, critical challenges which are impeding the effectiveness of these strategies still exist. The acceptance and uptake of biomedical interventions such as ART and pre-exposure prophylaxis (PrEP) are required to expect good outcome. In addition, increased risk behavior can outweigh the effectiveness of ART in reducing HIV incidence [158]. The outcomes of recent PrEP studies highlight the importance of adherence behavior in obtaining the most impact from PrEP [82]. The development, validation, and consistent use of globally relevant scales of stigma and discrimination are a critical next step for advancing the field of research in this area [156].

In the next section, we describe few promising strategies to assist key populations. In order to increase awareness about the needs and issues important to key populations, improve access, coverage and uptake of effective and acceptable services; and catalyze greater national and global commitment to adequate funding and services, the World Health Organization published a document titled *Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations*

that provides a comprehensive package of evidence-based HIV-related recommendations for all key populations [114]. The comprehension package include (1) essential health sector interventions including comprehensive condom and lubricant programming; harm reduction interventions, behavior intervention, HIV testing and counseling, HIV treatment and care etc. and (2) essential strategies for an enabling environment including supportive legislation, policy and financial commitment; addressing stigma and discrimination, community empowerment and addressing violence. Sensitivity training of front-line African health care workers (HCWs) attending to men who have sex with men (MSM), an eight-modular online training free of charge (available at http://www.marps-africa.org) is actively promoted through national HIV prevention programming in Kenya as an effective strategy to address risk behaviors among MSM [159].

The rates of HIV among gay men and transgender persons are increasing worldwide. Meanwhile, there has been exponential growth in access to communication technology over the last decade. Innovative prevention and care technology (ICT)-based programming can be used to help these populations. Profound changes brought about by ICT on sexual practices can increase the effectiveness of social and biomedical HIV and AIDS research, prevention and care [160].

Another strategy was outlined by Benjamin Eveslage who showed how community-based organizations and nongovernmental organizations delivering sexual health services could possibly improve HIV prevention and care outreach within these subpopulations of gay men and MSM by mimicking how they use social media. Such an approach entails ambitious and undercover methods for leveraging these subpopulations' use of social media networks in order to connect them to localized HIV prevention and care services [161].

Areas for further research: To monitor the trends of the HIV/AIDS epidemic, more longitudinal studies are needed to measure changes in the incidence of the disease in key populations. Male commercial sex workers are a diverse group of people worldwide. Information about their practice is limited. Since intersectional stigmas of same-sex practices, commercial sex, and HIV augment risk for HIV and sexually transmitted infections among male sex workers, more studies are needed to examine the magnitude of this phenomenon and it impact on society. Considering the impact of substance abuse and mental health on adherence behavior, more studies on substance abuse and mental health in key population are needed and new and effective harm reduction interventions are critical.

Limitation

Although efforts were made to present the results of an extensive literature search on socio-behavioral challenges associated with HIV vaccine trials, this study is not certainly an exhaustive review. It was limited mostly to HIV vaccine trials excluding other trials such as PrEP and microbicides. There is a need to expand the search to include non-published documents including conference abstracts and IAS databases to get more information on other possible socio-behavioral concerns related to HIV vaccine trials that were not captured in this review.

CONCLUSION

This review was undertaken to examine the social and behavioral factors associated with HIV trials. Despite moderate successes in decreasing individual-level risk and addressing structural HIV risk factors, HIV epidemic remains a public health threat worldwide. The last ten years have witnessed an expansion in new HIV prevention technologies to protect people against HIV/AIDS since an effective HIV vaccine remains elusive. As the efforts to develop a vaccine continue, the research community is showing increasing interest in understanding a myriad of social, behavioral, and ethical challenges that efficacy trials will likely encounter. Several conceptual frameworks and models integrating these factors have been developed to assist social scientists in addressing key gaps in understanding factors important to trial success, including trial participation and eventual vaccine uptake.

Many of these studies dealing with behavioral and structural factors once conducted in North America or Asia among MSM or injecting drug users are now taking place in Africa, the epicenter of HIV infection. There is a need for a sustained investment of resources in Africa to integrate promising effective biomedical, behavioral, and structural interventions targeting HIV key populations including fisherman, motorcycle drivers, commercial sex workers, and youth to curtail the spread of HIV/AIDS. Briefly, this review showed that the ability to recruit/enroll and retain people at risk in a trial is critical. Although not substantiated in the review, risk compensation during HIV-trials remains an issue, especially among key populations. Except in sub-Saharan Africa, social harms following HIV trial is rare. Community engagement is paramount for a successful conduct of a HIV trial.

ACKNOWLEDGEMENT

The authors are immensely grateful to Fran Priddy, Pat Fast, Prince Bahati and Beryl Koblin for their insightful and thorough review of this manuscript. We also thank Jennifer Rundels, the librarian from Central Michigan University, for assisting the authors in the database search.

REFERENCES

1. UNAIDS: Global AIDS Update 2016. In. GENEVA; 2016.
2. Mascola JR, Montefiori DC. The role of antibodies in HIV vaccines. Annu Rev Immunol. 2010; 28: 413-444.
3. Plotkin SA. Vaccines: correlates of vaccine-induced immunity. Clin Infect Dis. 2008; 47: 401-409.
4. Koff WC, Burton DR, Johnson PR, Walker BD, King CR, Nabel GJ, et al. Accelerating next-generation vaccine development for global disease prevention. Science. 2013; 340: 1232910.
5. Newman PA. Integrating social and biomedical science in HIV vaccine research: obstacles, opportunities and ways forward. Expert Rev Vaccines. 2012; 11: 1-3.
6. Koblin BA, Andrasik M, Austin J. Preparing for the unexpected: the pivotal role of social and behavioral sciences in trials of biomedical HIV prevention interventions. J Acquir Immune Defic Syndr. 2013; 63: 183-186.
7. Lau CY, Stansbury JP, Gust DA, Kafaar Z. Social and behavioral science in HIV vaccine trials: a gap assessment of the literature. Expert Rev Vaccines. 2009; 8: 179-190.

8. Lau CY, Swann EM, Singh S, Kafaar Z, Meissner HI, Stansbury JP. Conceptual framework for behavioral and social science in HIV vaccine clinical research. Vaccine. 2011; 29: 7794-7800.

9. Smit J, Middelkoop K, Myer L, Lindegger G, Swartz L, Seedat S, et al. Socio-behaviour challenges to phase III HIV vaccine trials in Sub-Saharan Africa. Afr Health Sci. 2005; 5: 198-206.

10. Frew PM, Archibald M, Martinez N, Carlos del Rio, Mulligan MJ. Promoting HIV vaccine research in African American communities: does the theory of reasoned action explain potential outcomes of involvement? Challenge (Atlanta, Ga). 2007; 13: 61.

11. Frew PM, Archibald M, Hixson B, del Rio C. Socioecological influences on community involvement in HIV vaccine research. Vaccine. 2011; 29: 6136-6143.

12. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009; 6: e1000097.

13. Thomas B, Ciliska D, Dobbins M, Micucci S. A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions. Worldviews Evid Based Nurs. 2004; 1: 176-184.

14. Etcheverry MF, de Lazzari E, Fuchs JD, Merono M, Sierra E, Del Romero J, et al. Pilot study assessing HIV vaccine trial readiness among female sex workers, injection and non-injection drug users, and men who have sex with men in Spain. AIDS Behav. 2010, 14: 607-617.

15. Fisher CB. Enhancing HIV vaccine trial consent preparedness among street drug users. J Empir Res Hum Res Ethics. 2010; 5: 65-80.

16. Koniak-Griffin D, Nyamathi A, Tallen L, Gonzalez-Figueroa E, Dominick E. Breaking the silence: what homeless 18- to 24-year-olds say about HIV vaccine trials. J Health Care Poor Underserved. 2007; 18: 687-698.

17. Li Q, Luo F, Zhou Z, Li S, Liu Y, Li D, et al. Willingness to participate in HIV vaccine clinical trials among Chinese men who have sex with men. Vaccine. 2010; 28: 4638-4643.

18. Chu Z, Xu J, Reilly KH, Lu C, Hu Q, Ma N, et al. HIV related high risk behaviors and willingness to participate in HIV vaccine trials among China MSM by computer assisted self-interviewing survey. Biomed Res Int. 2013; 2013: 493128.

19. Newman PA, Roungprakhon S, Tepjan S, Yim S. Preventive HIV vaccine acceptability and behavioral risk compensation among high-risk men who have sex with men and transgenders in Thailand. Vaccine. 2010; 28: 958-964.

20. Barroso PF, de Souza MB, do Lago RF, Pedrosa J, Yoshida CB, Faulhaber JC, et al. Barriers to recruit female commercial sex workers for HIV vaccine trials: the Rio de Janeiro experience. J Acquir Immune Defic Syndr. 2009; 50: 116-117.

21. Deschamps MM, Zorrilla CD, Morgan CA, Donastorg Y, Metch B, Madenwald T, et al. Recruitment of Caribbean female commercial sex workers at high risk of HIV infection. Rev Panam Salud Publica. 2013; 34: 92-98.

22. Young AM, Di Clemente RJ, Halgin DS, Sterk CE, Havens JR. HIV vaccine acceptability among high-risk drug users in Appalachia: a cross-sectional study. BMC public health. 2014; 14: 537.

23. Jaspan HB, Berwick JR, Myer L, Mathews C, Flisher AJ, Wood R, et al. Adolescent HIV prevalence, sexual risk, and willingness to participate in HIV vaccine trials. J Adolesc Health. 2006; 39: 642-648.

24. Mbunda T, Bakari M, Tarimo EA, Sandstrom E, Kulane A. Factors that influence the willingness of young adults in Dar es Salaam, Tanzania, to participate in phase I/II HIV vaccine trials. Glob Health Action. 2014; 7: 22853.

25. Farquhar C, John-Stewart GC, John FN, Kabura MN, Kiarie JN. Pediatric HIV type 1 vaccine trial acceptability among mothers in Kenya. AIDS Res Hum Retroviruses. 2006; 22: 491-495.

26. Asiki G, Abaasa A, Ruzagira E, Kibengo F, Bahemuka U, Mulondo J, et al. Willingness to participate in HIV vaccine efficacy trials among high risk men and women from fishing communities along Lake Victoria in Uganda. Vaccine. 2013; 31: 5055-5061.

27. Newman PA, Woodford MR, Logie C. HIV vaccine acceptability and culturally appropriate dissemination among sexually diverse Aboriginal peoples in Canada. Glob Public Health. 2012; 7: 87-100.

28. Frew PM, Mulligan MJ, Hou SI, Chan K, del Rio C: Time will tell: community acceptability of HIV vaccine research before and after the "Step Study" vaccine discontinuation. Open Access J Clin Trials. 2010; 2010: 149-156.

29. Otwombe KN, Sikkema KJ, Dietrich J, de Bruyn G, van der Watt M, Gray GE: Willingness to participate in biomedical HIV prevention studies after the HVTN 503/Phambili trial: a survey conducted among adolescents in Soweto, South Africa. J Acquir Immune Defic Syndr. 2011; 58: 211-218.

30. Dhalla S, Poole G. Socioeconomic status and HIV vaccine preparedness studies in North America. Vaccine. 2015; 33: 2536-2545.

31. Priddy FH, Cheng AC, Salazar LF, Frew PM. Racial and ethnic differences in knowledge and willingness to participate in HIV vaccine trials in an urban population in the Southeastern US. Int J STD AIDS. 2006; 17: 99-102.

32. Giocos G, Kagee A, Swartz L. Predicting hypothetical willingness to participate (WTP) in a future phase III HIV vaccine trial among high-risk adolescents. AIDS Behav. 2008; 12: 842-851.

33. Kiwanuka N, Ssetaala A, Mpendo J, Wambuzi M, Nanvubya A, Sigirenda S, et al. High HIV-1 prevalence, risk behaviours, and willingness to participate in HIV vaccine trials in fishing communities on Lake Victoria, Uganda. J Int AIDS Soc. 2013; 16: 18621.

34. Meque I, Dube K, Bierhuizen L, Zango A, Veldhuijzen N, Cumbe F, et al. Willingness to participate in future HIV prevention trials in Beira, Mozambique. Afr J AIDS Res. 2014; 13: 393-398.

35. Kiwanuka N, Mpendo J, Nalutaaya A, Wambuzi M, Nanvubya A, Kitandwe PK, et al. An assessment of fishing communities around Lake Victoria, Uganda, as potential populations for future HIV vaccine efficacy studies: an observational cohort study. BMC public health. 2014; 14: 986.

36. Kaewkungwal J, Pitisuttithum P, Rerks-Ngarm S, Nitayaphan S, Khamboonruang C, Kunasol P, et al. Issues in women's participation in a phase III community HIV vaccine trial in Thailand. AIDS Res Hum Retroviruses. 2013; 29: 1524-1534.

37. Buchbinder SP, Metch B, Holte SE, Scheer S, Coletti A, Vittinghoff E. Determinants of enrollment in a preventive HIV vaccine trial: hypothetical versus actual willingness and barriers to participation. J Acquir Immune Defic Syndr. 2004; 36: 604-612.

38. Brooks RA, Newman PA, Duan N, Ortiz DJ. HIV vaccine trial preparedness among Spanish-speaking Latinos in the US. AIDS care. 2007; 19: 52-58.

39. Dhalla S, Poole G. Barriers of enrolment in HIV vaccine trials: a review of HIV vaccine preparedness studies. Vaccine. 2011; 29: 5850-5859.

40. Olin J, Kokolamami J, Lepira FB, Mwandagalirwa K, Mupenda B, Ndongala ML, et al. Community preparedness for HIV vaccine trials in the Democratic Republic of Congo. Cult Health Sex. 2006; 8: 529-544.

41. Andrasik MP, Yoon R, Mooney J, Broder G, Bolton M, Votto T, et al. Exploring barriers and facilitators to participation of male-to-female

transgender persons in preventive HIV vaccine clinical trials. Prev Sci. 2014; 15: 268-276.

42. Chakrapani V, Newman PA, Singhal N, Jerajani J, Shunmugam M. Willingness to participate in HIV vaccine trials among men who have sex with men in Chennai and Mumbai, India: a social ecological approach. PloS one. 2012; 7: e51080.

43. Tarimo EA, Thorson A, Kohi TW, Bakari M, Mhalu F, Kulane A. Reasons for declining to enroll in a phase I and II HIV vaccine trial after randomization among eligible volunteers in Dar es Salaam, Tanzania. PloS one. 2011; 6: e14619.

44. Toledo L, McLellan-Lemal E, Arreola S, Campbell C, Sutton M. African-American and Hispanic perceptions of HIV vaccine clinical research: a qualitative study. Am J Health Promot. 2014; 29: e82-90.

45. Voytek CD, Jones KT, Metzger DS. Selectively willing and conditionally able: HIV vaccine trial participation among women at "high risk" of HIV infection. Vaccine. 2011; 29: 6130-6135.

46. Fincham D, Kagee A, Swartz L. Inhibitors and facilitators of willingness to participate (WTP) in an HIV vaccine trial: construction and initial validation of the Inhibitors and Facilitators of Willingness to Participate Scale (WPS) among women at risk for HIV infection. AIDS Care. 2010; 22: 452-461.

47. Ruzagira E, Wandiembe S, Bufumbo L, Levin J, Price MA, Grosskurth H, et al. Willingness to participate in preventive HIV vaccine trials in a community-based cohort in south western Uganda. Trop Med Int Health. 2009; 14: 196-203.

48. Loutfy MR, V LK, Mohammed S, Wu W, Muchenje M, Masinde K, et al. Recruitment of HIV-Positive Women in Research: Discussing Barriers, Facilitators, and Research Personnel's Knowledge. Open AIDS J. 2014; 8: 58-65.

49. Lee SJ, Newman PA, Duan N, Cunningham WE. Development of an HIV vaccine attitudes scale to predict HIV vaccine acceptability among vulnerable populations: L.A. VOICES. Vaccine. 2014; 32: 5013-5018.

50. Suhadev M, Nyamathi AM, Swaminathan S, Venkatesan P, Raja Sakthivel M, Shenbagavalli R, et al. A pilot study on willingness to participate in future preventive HIV vaccine trials. Indian J Med Res. 2006; 124: 631-640.

51. Gray K, Legg K, Sharp A, Mackie N, Olarinde F, De Souza C, et al. Participation in two phase II prophylactic HIV vaccine trials in the UK. Vaccine. 2008; 26: 2919-2924.

52. Fuchs JD, Sobieszczyk ME, Madenwald T, Grove D, Karuna ST, Andrasik M, et al. Intentions to use pre-exposure prophylaxis among current phase 2B preventive HIV-1 vaccine efficacy trial participants. J Acquir Immune Defic Syndr. 2013; 63: 259-262.

53. Feldblum PJ, Halpern V, Lie CC, Obunge O, Ogunsola F, Ampofo W, et al. What predicts non-retention in microbicide trials? Contemp Clin Trials. 2011; 32: 512-516.

54. Bakari M, Munseri P, Francis J, Aris E, Moshiro C, Siyame D, et al. Experiences on recruitment and retention of volunteers in the first HIV vaccine trial in Dar es Salam, Tanzania - the phase I/II HIVIS 03 trial. BMC Public Health. 2013; 13: 1149.

55. Kintu K, Andrew P, Musoke P, Richardson P, Asiimwe-Kateera B, Nakyanzi T, et al. Feasibility and safety of ALVAC-HIV vCP1521 vaccine in HIV-exposed infants in Uganda: results from the first HIV vaccine trial in infants in Africa. J Acquir Immune Defic Syndr. 2013; 63: 1-8.

56. Jaspan HB, Flisher AJ, Myer L, Mathews C, Middelkoop K, Mark D, et al. Sexual health, HIV risk, and retention in an adolescent HIV-prevention trial preparatory cohort. J Adolesc Health. 2011; 49: 42-46.

57. Ruzagira E, Wandiembe S, Abaasa A, Levin J, Bwanika A, Bahemuka U, et al. Prevalence and incidence of HIV in a rural community-based HIV vaccine preparedness cohort in Masaka, Uganda. PLoS One. 2011; 6: e20684.

58. Mbabazi E, Abaasa A, Asiki G, Bahemuka U, Ruzagira E, Nambooze M, et al. Determinants of Informed Consent Comprehension among Fisher Folk Cohort in HIV Vaccine Preparatory Studies in SW Uganda. AIDS research and human retroviruses. 2014; 30: A123-A123.

59. Ssetaala A, Nakiyingi-Miiro J, Asiimwe S, Nanvubya A, Mpendo J, Asiki G, et al. Recruitment and retention of women in fishing communities in HIV prevention research. Pan Afr Med J. 2015; 21:104.

60. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. New England Journal of Medicine. 2015; 372: 509-518.

61. Treweek S, Lockhart P, Pitkethly M, Cook JA, Kjeldstrøm M, Johansen M, et al. Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. BMJ Open. 2013; 3: e002360.

62. Nystuen P, Hagen KB. Telephone reminders are effective in recruiting nonresponding patients to randomized controlled trials. J Clin Epidemiol. 2004; 57: 773-776.

63. Trevena L, Irwig L, Barratt A. Impact of privacy legislation on the number and characteristics of people who are recruited for research: a randomised controlled trial. J Med Ethics. 2006; 32: 473-477.

64. Free C, Hoile E, Robertson S, Knight R. Three controlled trials of interventions to increase recruitment to a randomized controlled trial of mobile phone based smoking cessation support. Clin Trials. 2010; 7: 265-273.

65. Hemminki E, Hovi S-L, Veerus P, Sevón T, Tuimala R, Rahu M, et al. Blinding decreased recruitment in a prevention trial of postmenopausal hormone therapy. J Clin Epidemiol. 2004; 57: 1237-1243.

66. Omosa-Manyonyi GS, Jaoko W, Anzala O, Ogutu H, Wakasiaka S, Malogo R, et al. Reasons for ineligibility in phase 1 and 2A HIV vaccine clinical trials at Kenya AIDS vaccine initiative (KAVI), Kenya. PLoS One. 2011; 6: e14580.

67. Karim QA, Kharsany AB, Frohlich JA, Baxter C, Yende N, Mansoor LE, et al. Recruitment of high risk women for HIV prevention trials: baseline HIV prevalence and sexual behavior in the CAPRISA 004 tenofovir gel trial. Trials. 2011; 12: 67.

68. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012; 367: 399-410.

69. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011; 365: 493-505.

70. Eaton LA, Kalichman S. Risk compensation in HIV prevention: implications for vaccines, microbicides, and other biomedical HIV prevention technologies. Curr HIV/AIDS Rep. 2007; 4: 165-172.

71. Underhill K. Study designs for identifying risk compensation behavior among users of biomedical HIV prevention technologies: balancing methodological rigor and research ethics. Soc Sci Med. 2013; 94: 115-123.

72. Heffelfinger JD, Swint EB, Berman SM, Weinstock HS. Trends in primary and secondary syphilis among men who have sex with men in the United States. Am J Public Health. 2007; 97: 1076-1083.

73. Gray GE, Metch B, Churchyard G, Mlisana K, Nchabeleng M, Allen M, et al. Does participation in an HIV vaccine efficacy trial affect risk

behaviour in South Africa? Vaccine. 2013; 31: 2089-2096.

74. Marcus JL, Glidden DV, Mayer KH, Liu AY, Buchbinder SP, Amico KR, et al. No evidence of sexual risk compensation in the iPrEx trial of daily oral HIV preexposure prophylaxis. PLoS One. 2013; 8: e81997.

75. Novak RM, Metch B, Buchbinder S, Cabello R, Donastorg Y, Figoroa JP, et al. Risk behavior among women enrolled in a randomized controlled efficacy trial of an adenoviral vector vaccine to prevent HIV acquisition. AIDS. 2013; 27: 1763-1770.

76. Macphail CL, Sayles JN, Cunningham W, Newman PA. Perceptions of sexual risk compensation following posttrial HIV vaccine uptake among young South Africans. Qual Health Res. 2012; 22: 668-678.

77. Barrington C, Moreno L, Kerrigan D. Perceived influence of an HIV vaccine on sexual-risk behaviour in the Dominican Republic. Cult Health Sex. 2008; 10: 391-401.

78. Tripathi A, Whiteside YO, Duffus WA. Perceptions and attitudes about preexposure prophylaxis among seronegative partners and the potential of sexual disinhibition. South Med J. 2013; 106: 558-564.

79. Brooks RA, Landovitz RJ, Kaplan RL, Lieber E, Lee SJ, Barkley TW. Sexual risk behaviors and acceptability of HIV pre-exposure prophylaxis among HIV-negative gay and bisexual men in serodiscordant relationships: a mixed methods study. AIDS Patient Care STDS. 2012; 26: 87-94.

80. Venkatesh KK, Flanigan TP, Mayer KH. Is expanded HIV treatment preventing new infections? Impact of antiretroviral therapy on sexual risk behaviors in the developing world. AIDS. 2011; 25: 1939-1949.

81. Eisele TP, Mathews C, Chopra M, Lurie MN, Brown L, Dewing S, et al. Changes in risk behavior among HIV-positive patients during their first year of antiretroviral therapy in Cape Town South Africa. AIDS and behavior. 2009; 13: 1097-1105.

82. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010; 363: 2587-2599.

83. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012; 367: 399-410.

84. Mugwanya KK, Donnell D, Celum C, Thomas KK, Ndase P, Mugo N, et al. Sexual behaviour of heterosexual men and women receiving antiretroviral pre-exposure prophylaxis for HIV prevention: a longitudinal analysis. The Lancet infectious diseases. 2013; 13: 1021-1028.

85. Wilde GJ. Risk homeostasis theory: an overview. Inj Prev. 1998; 4: 89-91.

86. Blumenthal J, Haubrich RH. Will risk compensation accompany pre-exposure prophylaxis for HIV? Virtual Mentor. 2014; 16: 909-915.

87. Secura GM, Adams T, Buckel CM, Zhao Q, Peipert JF. Change in sexual behavior with provision of no-cost contraception. Obstet Gynecol. 2014; 123: 771-776.

88. Hansen BT, Kjaer SK, Arnheim-Dahlstrom L, Liaw KL, Jensen KE, Thomsen LT, et al. Human papillomavirus (HPV) vaccination and subsequent sexual behaviour: evidence from a large survey of Nordic women. Vaccine. 2014; 32: 4945-4953.

89. Koblin BA, Bonner S, Hoover DR, Xu G, Lucy D, Fortin P, et al. A randomized trial of enhanced HIV risk-reduction and vaccine trial education interventions among HIV-negative, high-risk women who use noninjection drugs: the UNITY study. J Acquir Immune Defic Syndr. 2010; 53: 378-387.

90. Milford C, Barsdorf N, Kafaar Z. What should South African HIV vaccine trials do about social harms? AIDS Care. 2007; 19: 1110-1117.

91. Pitisuttithum P, Choopanya K, Bussaratid V, Vanichseni S, van Griensven F, Phonrat B, et al. Social harms in injecting drug users participating in the first phase III HIV vaccine trial in Thailand. J Med Assoc Thai. 2007; 90: 2442-2448.

92. Fuchs J, Durham M, McLellan-Lemal E, Vittinghoff E, Colfax G, Gurwith M, et al. Negative social impacts among volunteers in an HIV vaccine efficacy trial. J Acquir Immune Defic Syndr. 2007; 46: 362-368.

93. Jenkins RA, Thapinta D, Morgan PA, Wongkamhaeng S, Sornsathapornkul P, Bussaratid V, et al. Behavioral and social issues among volunteers in a preventive HIV vaccine trial in Thailand. J Acquir Immune Defic Syndr. 2005; 40: 592-599.

94. Nyblade L, Singh S, Ashburn K, Brady L, Olenja J. "Once I begin to participate, people will run away from me": understanding stigma as a barrier to HIV vaccine research participation in Kenya. Vaccine. 2011; 29: 8924-8928.

95. Tarimo EA, Munseri P, Aboud S, Bakari M, Mhalu F, Sandstrom E. E Experiences of social harm and changes in sexual practices among volunteers who had completed a phase I/II HIV vaccine trial employing HIV-1 DNA priming and HIV-1 MVA boosting in Dar es Salaam, Tanzania. PLoS One. 2014; 9: e 90938.

96. Stadler J, Delany-Moretlwe S, Palanee T, Rees H. Hidden harms: women's narratives of intimate partner violence in a microbicide trial, South Africa. Social science & medicine. 2014; 110: 49-55.

97. Milford C, Barsdorf N, Kafaar Z. What should South African HIV vaccine trials do about social harms? AIDS Care. 2007; 19: 1110-1117.

98. Mutua G, Mutengu L, Mpendo J, Kilembe W, Omosa-Manyonyi G, Ruzagira E, et al. Major Negative Social Impacts Are Rare in Phase 1 HIV Vaccine Trials in Africa. AIDS research and human retroviruses. 2014; 30: A190-A191.

99. Cooper CJ, Metch B, Dragavon J, Coombs RW, Baden LR. NIAID HIV Vaccine Trials Network (HVTN) Vaccine-Induced Seropositivity (VISP) Task Force. Vaccine-induced HIV seropositivity/reactivity in noninfected HIV vaccine recipients. JAMA. 2010; 304: 275-283.

100. Schmidt C, Jaoko W, Omosa-Manyonyi G, Kaleebu P, Mpendo J, Nanvubya A, et al. Long-term follow-up of study participants from prophylactic HIV vaccine clinical trials in Africa. Hum Vaccin Immunother. 2014; 10: 714-723.

101. Cooper CJ, Metch B, Dragavon J, Coombs RW, Baden LR; NIAID HIV Vaccine Trials Network (HVTN) Vaccine-Induced Seropositivity (VISP) Task Force. Vaccine-induced HIV seropositivity/reactivity in noninfected HIV vaccine recipients. JAMA. 2010; 304: 275-283.

102. VISR Working Group of Global HIV Vaccine Enterprise, Voronin Y, Zinszner H, Karg C, Brooks K, Coombs R, et al. HIV vaccine-induced sero-reactivity: a challenge for trial participants, researchers, and physicians. Vaccine. 2015; 33: 1243-1249.

103. Nakibinge S, Maher D, Katende J, Kamali A, Grosskurth H, Seeley J. Community engagement in health research: two decades of experience from a research project on HIV in rural Uganda. Trop Med Int Health. 2009; 14: 190-195.

104. Cohen J. AIDS research. Cambodian leader throws novel prevention trial into limbo. Science. 2004; 305: 1092.

105. Singh JA, Mills EJ. The abandoned trials of pre-exposure prophylaxis for HIV: what went wrong? PLoS Med. 2005; 2: e234.

106. McGrory E, Irvin A, Heise L: Research Rashomon: Lessons from the Cameroon pre exposure prophylaxis trial site. Washington, DC: Global Campaign for Microbicides at PATH. 2009.

107. Frew PM, Archibald M, Martinez N, del Rio C, Mulligan MJ. Promoting HIV Vaccine Research in African American Communities. Does

the Theory of Reasoned Action Explain Potential Outcomes of Involvement? Challenge (Atlanta Ga). 2007; 13: 61-97.

108. Slevin KW, Ukpong M, Heise L. Community engagement in HIV prevention trials: evolution of the field and opportunities for growth. In: Aids2031 Working Paper. 2008.

109. Sahay S, Kumar M, Srikrishnan AK, Ramanathan V, Mehendale S. Experiences in recruiting volunteers through community based initiatives in phase-1 vaccine trials in India. Hum Vaccin Immunother. 2014; 10: 485-491.

110. Beeker C, Guenther-Grey C, Raj A. Community empowerment paradigm drift and the primary prevention of HIV/AIDS. Soc Sci Med. 1998; 46: 831-842.

111. Kelley RT, Hannans A, Kreps GL, Johnson K. The Community Liaison Program: a health education pilot program to increase minority awareness of HIV and acceptance of HIV vaccine trials. Health Educ Res. 2012; 27: 746-754.

112. Newman PA, Rubincam C. Advancing community stakeholder engagement in biomedical HIV prevention trials: principles, practices and evidence. Expert Rev Vaccines. 2014; 13: 1553-1562.

113. Bahati P, Hannah S, Seidel S, Aggett S, Siskind R, Campbell R, et al. New tools to measure community and stakeholder engagement and its impact on outcomes of clinical research. Retrovirology. 2012; 9: O24.

114. Organization WH: Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations: World Health Organization; 2014.

115. Morocco K. Tackling HIV/AIDS Among Key Populations: Essential to Achieving an AIDS-Free Generation. 2013.

116. HIV/AIDS JUNPo: The gap report 2014. Retrieved on August 2014; 10:2014.

117. Beyrer C, Baral SD, van Griensven F, Goodreau SM, Chariyalertsak S, Wirtz AL, et al. Global epidemiology of HIV infection in men who have sex with men. Lancet. 2012; 380: 367-377.

118. Park JN, Papworth E, Kassegne S, Moukam L, Billong SC, Macauley I, et al. HIV prevalence and factors associated with HIV infection among men who have sex with men in Cameroon. J Int AIDS Soc. 2013; 16: 18752.

119. Sanders EJ, Graham SM, Okuku HS, van der Elst EM, Muhaari A, Davies A, et al. HIV-1 infection in high risk men who have sex with men in Mombasa, Kenya. AIDS. 2007; 21: 2513-2520.

120. Wade AS, Kane CT, Diallo PA, Diop AK, Gueye K, Mboup S, et al. HIV infection and sexually transmitted infections among men who have sex with men in Senegal. AIDS. 2005; 19: 2133-2140.

121. Baral S, Trapence G, Motimedi F, Umar E, Iipinge S, Dausab F, et al. HIV prevalence, risks for HIV infection, and human rights among men who have sex with men (MSM) in Malawi, Namibia, and Botswana. PLoS One. 2009; 4: e4997.

122. Rispel LC, Metcalf CA, Cloete A, Reddy V, Lombard C. HIV prevalence and risk practices among men who have sex with men in two South African cities. J Acquir Immune Defic Syndr. 2011; 57: 69-76.

123. Price MA, Rida W, Mwangome M, Mutua G, Middelkoop K, Roux S, et al. Identifying at-risk populations in Kenya and South Africa: HIV incidence in cohorts of men who report sex with men, sex workers, and youth. J Acquir Immune Defic Syndr. 2012; 59:185-193.

124. Barroso PF, de Souza MB, do Lago RF, Pedrosa J, Yoshida CB, Faulhaber JC, et al. Barriers to recruit female commercial sex workers for HIV vaccine trials: the Rio de Janeiro experience. Acquir Immune Defic Syndr. 2009; 50: 116-117.

125. KAOMA KJ. Colonizing African Values. 2012.

126. Makofane K, Gueboguo C, Lyons D, Sandfort T. Men who have sex with men inadequately addressed in African AIDS National Strategic Plans. Glob Public Health. 2013; 8: 129-143.

127. Smart Richman L, Leary MR. Reactions to discrimination, stigmatization, ostracism, and other forms of interpersonal rejection: a multimotive model. Psychol Rev. 2009; 116: 365-383.

128. Secor AM, Wahome E, Micheni M, Rao D, Simoni JM, Sanders EJ, et al. Depression, substance abuse and stigma among men who have sex with men in coastal Kenya. AIDS. 2015; 29: S251-259.

129. Li Q, Li X, Stanton B. Alcohol use and sexual risk behaviors and outcomes in China: a literature review. AIDS Behav. 2010; 14: 1227-1236.

130. Peacock E, Andrinopoulos K, Hembling J. Binge Drinking among Men Who Have Sex with Men and Transgender Women in San Salvador: Correlates and Sexual Health Implications. J Urban Health. 2015; 92: 1-16.

131. Simbayi LC, Kalichman SC, Cain D, Cherry C, Jooste S, Mathiti V: Alcohol and risks for HIV/AIDS among sexually transmitted infection clinic patients in Cape Town, South Africa. Subst Abus. 2007; 27: 37-43.

132. Hendershot CS, George WH. Alcohol and sexuality research in the AIDS era: trends in publication activity, target populations and research design. AIDS Behav. 2007; 11: 217-226.

133. Lane T, Shade SB, McIntyre J, Morin SF. Alcohol and sexual risk behavior among men who have sex with men in South african township communities. AIDS Behav. 2008; 12: S78-85.

134. Luchters S, Geibel S, Syengo M, Lango D, King'ola N, Temmerman M, et al. Use of AUDIT, and measures of drinking frequency and patterns to detect associations between alcohol and sexual behaviour in male sex workers in Kenya. BMC Public Health. 2011; 11: 384.

135. Sansone RA, Sansone LA. Alcohol/Substance misuse and treatment nonadherence: fatal attraction. Psychiatry (Edgmont). 2008; 5: 43-46.

136. Van der Elst EM, Mbogua J, Operario D, Mutua G, Kuo C, Mugo P, et al. High acceptability of HIV pre-exposure prophylaxis but challenges in adherence and use: qualitative insights from a phase I trial of intermittent and daily PrEP in at-risk populations in Kenya. AIDS Behav. 2013; 17: 2162-2172.

137. Braithwaite RS, Bryant KJ. Influence of alcohol consumption on adherence to and toxicity of antiretroviral therapy and survival. Alcohol Res Health. 2010; 33: 280-287.

138. Vanden Berghe W, Nöstlinger C, Hospers H, Laga M. International mobility, sexual behaviour and HIV-related characteristics of men who have sex with men residing in Belgium. BMC Public Health. 2013; 13: 968.

139. Nuno Nodin, Alex Carballo-Diéguez, Isabel MP Leal. Sexual use of the internet: Perceived impact on MSM's views of self and others. New Media & Society. 2014; 16: 719-736.

140. Benotsch EG, Martin AM, Espil FM, Nettles CD, Seal DW, Pinkerton SD. Internet use, recreational travel, and HIV risk behaviors in men who have sex with men. J Community Health. 2011; 36: 398-405.

141. Béhanzin L, Diabaté S, Minani I, Boily MC, Labbé AC, Ahoussinou C, et al. Decline in the prevalence of HIV and sexually transmitted infections among female sex workers in Benin over 15 years of targeted interventions. J Acquir Immune Defic Syndr. 2013; 63: 126.

142. Organization WHO. Preventing HIV among sex workers in sub-Saharan Africa: a literature review. 2011.

143. Magnani R, Sabin K, Saidel T, Heckathorn D. Review of sampling hard-to-reach and hidden populations for HIV surveillance. AIDS. 2005; 19: S67-72.

144. Salganik MJ. Variance estimation, design effects, and sample size calculations for respondent-driven sampling. J Urban Health. 2006; 83: i98-112.

145. Kajubi P, Kamya MR, Raymond HF, Chen S, Rutherford GW, Mandel JS, et al. Gay and bisexual men in Kampala, Uganda. AIDS Behav. 2008; 12: 492-504.

146. Magnus M, Franks J, Griffith MS, Arnold MP, Goodman MK, Wheeler DP: Engaging, recruiting, and retaining black men who have sex with men in research studies: don't underestimate the importance of staffing--lessons learned from HPTN 061, the BROTHERS study. J Public Health Manag Pract. 2014; 20: E1-9.

147. Muraguri N, Temmerman M, Geibel S. A decade of research involving men who have sex with men in sub-Saharan Africa: current knowledge and future directions. SAHARA J. 2012; 9: 137-147.

148. Smith AD, Muhaari AD, Agwanda C, Kowuor D, van der Elst E, Davies A, et al. Heterosexual behaviours among men who sell sex to men in coastal Kenya. AIDS. 2015; 29: S201-210.

149. Mannava P, Geibel S, King'ola N, Temmerman M, Luchters S. Male sex workers who sell sex to men also engage in anal intercourse with women: evidence from Mombasa, Kenya. PLoS One. 2013; 8: e52547.

150. Beyrer C, Trapence G, Motimedi F, Umar E, Iipinge S, Dausab F, et al. Bisexual concurrency, bisexual partnerships, and HIV among Southern African men who have sex with men (MSM). Sex Transm Infect. 2010; 86: 323-327.

151. Tovanabutra S, Sanders EJ, Graham SM, Mwangome M, Peshu N, McClelland RS, et al. Evaluation of HIV type 1 strains in men having sex with men and in female sex workers in Mombasa, Kenya. AIDS Res Hum Retroviruses. 2010; 26: 123-131.

152. Geibel S, Luchters S, King'Ola N, Esu-Williams E, Rinyiru A, Tun W. Factors associated with self-reported unprotected anal sex among male sex workers in Mombasa, Kenya. Sex Transm Dis. 2008; 35: 746-752.

153. Chapman J, Koleros A, Delmont Y, Pegurri E, Gahire R, Binagwaho A. High HIV risk behavior among men who have sex with men in Kigali, Rwanda: making the case for supportive prevention policy. AIDS Care. 2011; 23: 449-455.

154. Higa DH, Crepaz N, Marshall KJ, Kay L, Vosburgh HW, Spikes P, et al. A systematic review to identify challenges of demonstrating efficacy of HIV behavioral interventions for gay, bisexual, and other men who have sex with men (MSM). AIDS Behav. 2013; 17: 1231-1244.

155. Bekker LG, Beyrer C, Quinn TC. Behavioral and biomedical combination strategies for HIV prevention. Cold Spring Harb Perspect Med. 2012; 2: pii: a007435.

156. Stangl AL, Lloyd JK, Brady LM, Holland CE, Baral S. A systematic review of interventions to reduce HIV-related stigma and discrimination from 2002 to 2013: how far have we come? J Int AIDS Soc. 2013; 16: 18734.

157. Stromdahl S, Hickson F, Pharris A, Sabido M, Baral S, Thorson A. A systematic review of evidence to inform HIV prevention interventions among men who have sex with men in Europe. Euro Surveill. 2015; 20: 21096.

158. Mei S, Quax R, van de Vijver D, Zhu Y, Sloot PM. Increasing risk behaviour can outweigh the benefits of antiretroviral drug treatment on the HIV incidence among men-having-sex-with-men in Amsterdam. BMC Infect Dis. 2011; 11: 118.

159. Dijkstra M, van der Elst EM, Micheni M, Gichuru E, Musyoki H, Duby Z, et al. Emerging themes for sensitivity training modules of African healthcare workers attending to men who have sex with men: a systematic review. Intl health. 2015; 7: 151-162.

160. Adams D, Klindera K, Walsh CS, Wolf RC. Innovative programmatic approaches to HIV prevention and care services for gay men, other men who have sex with men (MSM) and transgender persons using information and communication technology (ICT). Digital Culture & Education. 2014.

161. Green K, Girault P, Wambugu S, Clement NF, Adams B. Reaching men who have sex with men in ghana though social media: a pilot intervention. Digital Culture & Education. 2014.

Cite this article

Inungu JN, Bender B, Gieber L (2017) Socio-Behavioral Challenges to HIV Vaccine Trials: Literature Review. Clin Res HIV/AIDS 4(1): 1034.