

# Socio-behaviour challenges to phase III HIV vaccine trials in Sub-Saharan Africa

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## Abstract

**Background:** A number of countries in sub-Saharan Africa are preparing for HIV vaccine efficacy trials. Social and behavioural factors related to HIV transmission require examination in each setting where these trials are considered. As part of this, several countries have also recently begun preparatory research investigating relevant social and behavioural issues. There is a need for a review of the literature to help focus such research efforts in Sub-Saharan Africa.

**Objective:** To examine key social and behavioural issues that may impact on the conduct of HIV vaccine efficacy trials in sub-Saharan Africa.

**Design:** Literature review

**Methods:** Major databases (PubMed, PsychInfo, EBSCOhost, and AIDSline) were searched for literature that discussed social and behavioural issues related to HIV vaccine trials. Three areas are highlighted as being particularly significant for HIV vaccine research: (1) willingness to participate in future HIV vaccine efficacy trials, (2) retention of participants in studies, and (3) sexual risk reporting during trials. For each of these topics, major findings from both developed and developing countries are described and avenues for further research are discussed.

**Results:** There are few data from Sub-Saharan Africa regarding willingness to participate in HIV vaccine trials. Data on participant retention rates varies widely, and maintaining large cohorts of individuals within Phase III trials presents an important challenge. In addition, the possible impact of trial participation on sexual disinhibition, and response bias on sexual risk-reporting remain as issues for HIV vaccine trials in African contexts.

**Conclusions:** Social and behavioural research forms an important part of preparations for HIV vaccine efficacy trials, and there is a clear need for more research of this type in Sub-Saharan Africa. Innovative approaches are required to address issues such as willingness to participate in vaccine research, participant retention during efficacy trials, and the accurate reporting by participants of sexual risk behaviours.

**Key words:** Africa, HIV, vaccines, clinical trials, preparation, behaviour, review

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## Introduction

More than twenty years after the start of the epidemic, HIV/AIDS remains one of the most important threats to health around the globe.<sup>1</sup> Sub-Saharan Africa is heavily affected by the epidemic with 25 million people currently infected and an estimated 3 million new infections every year.<sup>2</sup> A range of structural and personal level factors have been thought

to contribute to the rapid spread of the epidemic in Africa. Major structural factors include social, economic and healthcare development<sup>3</sup> including reduction of poverty and gender-based violence.<sup>4,5</sup> Individual-level factors include sexual risk behaviours such as transactional sex, age of sexual debut, number of sexual partners, and low condom use.<sup>5-7</sup> Despite moderate successes in decreasing individual-level risk<sup>8</sup>, and international efforts to address structural factors<sup>9,10</sup>, the epidemic continues unabated. In this light, an affordable and effective HIV vaccine remains vitally important to curtailing the population-level spread of infection.

Clinical trials for HIV vaccines include three distinct phases: Phase I trials are conducted on a small number

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of healthy humans at low risk for HIV infection to assess safety. Phase II trials use larger numbers (several hundreds) of low risk individuals to build on this safety data and also assess immunogenicity. A range of scientific<sup>14,15</sup> and ethical issues<sup>16</sup> needs to be considered before moving to phase III trials, which is one of the reasons why few such trials have taken place since the start of HIV vaccine development.<sup>1</sup> Phase III HIV vaccine trials are conducted on large numbers of people (several thousands) at high risk for HIV infection which is currently defined as an HIV incidence rate of 2% or more.<sup>17</sup> These trials usually take a number of years to complete and require participants to return for frequent HIV tests and immunizations.<sup>17</sup>

Despite acknowledging the need for an HIV vaccine, progress has been slow for many resource-poor countries.<sup>1,11</sup> Of the phase I and II HIV vaccine trials that have taken place globally, most have been conducted in the United States (US) and Europe with only four phase I and II trials completed, or currently in progress in sub-Saharan Africa (see also [www.iavi.org](http://www.iavi.org) for list of preventative trials to date).<sup>1</sup> The first phase III HIV vaccine trials have recently been completed in North America and Thailand (AIDSVAX B/B and AIDSVAX B/E, respectively; VaxGen Inc, Brisbane, CA, USA).<sup>12</sup> Thailand has also been the only developing country that has been part of a phase III trial, and has also had more phase I and II trials than any other developing country.<sup>13</sup>

Phase III HIV vaccine trials to date have largely focused on sub-groups most at risk for HIV infection, such as commercial sex workers (CSW), intravenous drug-users (IDU), and men who have sex with men (MSM). The AIDSVAX B/B trial (North America) recruited mainly MSM and the AIDSVAX B/E study (Thailand) focused on prevention against blood-borne infection in IDU.<sup>12</sup> These trials therefore targeted specific populations known to be at high risk for HIV infection. In contrast, the epidemic in sub-Saharan Africa is most severe in heterosexual men and women<sup>2,18</sup> who may not consider themselves to be at high risk for HIV infection and perceive obvious benefits to volunteering for phase III trials. Sub-Saharan Africa is also characterised by great social, economic and political diversity, with high rates of migration<sup>19</sup>, political unrest<sup>20</sup>, a lack of sustained, stable infrastructure<sup>20,21</sup>, and low literacy levels<sup>22</sup>. In many respects these factors present a challenge to the conduct

of phase III vaccine trials.

Moreover before the first phase III trials commenced a range of issues were discussed in the literature pertaining to both developed<sup>17,23,24</sup> and less-developed countries.<sup>25-28</sup> While the AIDSVAX trials refuted many of these concerns<sup>29,30</sup> they remain important in countries where trials have not taken place. Key issues addressed by these studies include:

- a) whether it will be possible to recruit and retain the large numbers of at-risk individuals over long time-periods as required for phase III trials<sup>31-34</sup>
- b) whether high-risk individuals from the general population be willing to enroll in these trials,<sup>32,33</sup> and
- c) whether trial participation will result in an increase, rather than decrease in sexual behaviour due to a false sense of protection by the vaccine.<sup>35,36</sup>

Researchers working in HIV vaccine trials describe these and related issues using the collective term *social and behavioural issues*. Given the importance of an effective HIV vaccine for addressing the HIV/AIDS epidemic in sub-Saharan Africa, and the growing movement to test experimental HIV vaccines in different parts of the continent, here we review existing evidence regarding the social and behavioural issues involved in HIV vaccine trials. We use this review to help highlight topics that require attention as part of future research to prepare for upcoming HIV vaccine trials.

## Methods

The aims of this review were to (a) report on the key findings of social and behavioural research conducted to date involving HIV vaccine trials; (b) to use these findings to identify the important topics emerging from this literature; (c) to compare major findings from Africa with the rest of the world, and (d) to suggest areas for further research in Africa as part of preparations for Phase III efficacy trials.

## Search strategy

Data for this review were identified by: searches of the electronic databases Medline (PubMed), PsychInfo, EBSCOhost and AIDSline. These databases were chosen because they provide comprehensive coverage of peer-reviewed social and behavioural research involving HIV/AIDS. Search terms used in electronic databases were “HIV/AIDS”, “vaccine”, “vaccine trials”, “risk behaviours”, “reporting” and “trial participation”, with different combinations of these search terms used to identify articles that met the selection requirements. We also identified materials through references from relevant articles and contacting investigators working in this field

throughout sub-Saharan Africa. Numerous articles were identified through searches of the extensive files of the authors. English and French language papers were eligible for the review.

Research findings from HIV vaccine preparedness and clinical trials were then collated for both developed (United States and Europe) and developing countries. One-thousand and fifty-nine articles were found that discussed HIV vaccines and clinical trials; of these 204 articles discussed issues related to behaviour and 208 articles discussed clinical trials in Africa. Only 86 articles discussed HIV clinical trials in African countries.

### **Inclusion Criteria**

As part of an ongoing programme of social and behavioural research under the auspices of the South African AIDS Vaccine Initiative (SAAVI) we identified three key topics that are particularly important for work in sub-Saharan Africa to form the basis for this review:

- a) Willingness to participate in future phase III HIV vaccine trials;
- b) Retention during trials; and,
- c) Sexual risk behaviour and reporting of risk behaviour during trials.

### **Exclusion criteria**

The following areas, although considered significant, were excluded or limited in the review of literature and subsequent discussion:

- a) Ethical issues during HIV vaccine trials are discussed only as they pertain to the issues above. The impact of discrimination during trials may be a major concern in African countries where HIV-related stigma have been documented.<sup>37-42</sup> A number of studies have examined the impact of trial-related discrimination,<sup>23;43;44</sup> and the reader is referred to these texts for a full discussion.
- b) Economic (site selection, financial impact, etc), statistical (sample size, trial endpoints) and scientific concerns (level and type of induced immunity, host genetics) were excluded from the review. However the literature in these areas is comprehensive and the interested reader are referred to these reviews.<sup>45-47</sup>
- c) Since HIV transmission in sub-Saharan Africa occurs predominantly in heterosexual populations this review will focus only on sexual behaviours pertaining to this population,<sup>48-50</sup> and exclude other forms of transmissions such as needle-sharing during

intravenous drug-use or sexual practices related to MSM, for example.

## **Results and Discussion**

### **Willingness to participate in future phase III HIV vaccine trials**

For phase III HIV vaccine trials to be feasible, high risk groups must endorse and be willing to participate in such trials.<sup>51;52</sup> However, reported Willingness To Participate (WTP) in phase III HIV vaccine trials have varied greatly between studies. In America, WTP in future efficacy trials ranged from 91% in MSM<sup>53</sup> to 27% in a mixed group of MSM, IDU and high-risk women.<sup>54</sup> Among army conscripts, 25 to 30% were willing to participate in Thailand,<sup>55-57</sup> while 80% endorsed such trials in Uganda.<sup>58</sup>

Reported WTP in hypothetical trials does not necessarily guarantee enrolment into an actual trial. An American study reported that only 29% of those who indicated “definitely willing” and 16% of those who indicated “probably willing” to take part in a HIV vaccine trial during the preparedness study actually enrolled.<sup>59</sup> Similarly, less than 50% of those enrolled in a preparedness cohort, who stated that they would take part in a phase III vaccine trial, eventually enrolled into the North American AIDS VAX trial.<sup>52</sup>

Reasons for non-participation in trials include fears that the vaccine may not be safe for humans;<sup>53;54;56;60</sup> may cause side-effects<sup>44;56-58</sup> or AIDS,<sup>54;55</sup> or that they may be discriminated against.<sup>53-56;60</sup> Reported WTP may also be influenced by negative media reports,<sup>61</sup> and by increased knowledge of vaccine trials with data suggesting that the more participants knew about HIV vaccines and clinical trials, the less likely they were to participate.<sup>59;62-64</sup>

Despite this, many participants remained willing to participate in vaccine trials. Selfless aims such as altruism<sup>56;65;66</sup> and a desire to fight AIDS<sup>53;58;67</sup> have often been cited as motivating factors. Material benefits such as free medical care<sup>58</sup> and monetary compensation have also been reported as important factors, especially in resource-poor settings.<sup>56;57</sup>

Studies also examined the differences between participants who remained positive about participation and those who eventually changed their minds after receiving information about the risks involved. These studies found that those who remained willing reported more risk behaviour<sup>52;54;62;68;69</sup> and were often younger and more depressed compared to those who declined participation.<sup>52</sup> More importantly, WTP has also been associated with low socio-economic status and education,<sup>52;54;62</sup> and with a greater difficulty in understanding vaccine-related con-

cepts.<sup>68</sup> This raises important ethical questions about the inclusion of vulnerable populations in clinical trials.<sup>25,70</sup>

### ***Measuring willingness to participate***

The decision to take part in a HIV vaccine efficacy trial is embedded within a context of personal, emotional and cognitive factors. Cross-sectional studies often strip the answer (willing or not) from these contexts and does not provide insight into how different contexts may influence decision-making.<sup>57,58,71</sup> Another limitation is that it may be less important to know whether someone is willing or not willing at a particular point in time, but what factors influence this decision-making process. For example, it has been suggested that African people may have entirely different ways of making decisions about trial participation since their concept of self is defined in affiliation with the larger group, compared to Westerners whose decision-making may primarily be based on individual terms.<sup>27</sup> While this has been widely contested by others,<sup>72</sup> it has encouraged informed consent procedures to take cultural differences into account.<sup>73,74</sup> Yet, whether and what cultural factors impact on decision-making related to phase III trial participation remains uncertain and requires investigation.

### *Areas for further research*

1. Data on the willingness to participate in future HIV vaccine efficacy trials are required for different African countries..
2. Reported willingness must be compared with actual enrolment into phase I/II trials in the same study population. This will be important to ascertain whether stated willingness corresponds to actual enrolment before commencing to phase III trials.
3. The relationship between knowledge of HIV vaccine trials and WTP has not been examined in countries with low literacy levels.
4. More research needs to focus on the impact of culture and social context on decision-making as well as how individual factors (age, gender, knowing someone with HIV, emotional states) interact with culture and social factors during decision-making.
5. Innovative ways to examine and address issues about participation are required to ensure that participants make informed decisions.

### **Retention and attrition**

The ability to recruit and retain large numbers of participants is a key concern in HIV vaccine efficacy trials.<sup>24</sup> Before the first phase III trials were conducted, longitudinal studies examined recruitment and retention in a range of different sub-groups in America.<sup>34</sup> These studies reported the ability to retain between 70 - 90% of participants between 9 and 18 months after enrollment,<sup>31,75</sup> which suggested that phase III trials would indeed be feasible. Similarly, studies in Thailand reported high retention rates - about 90% in CSW, army conscripts and MSM.<sup>76</sup> The retention rates of the two AIDSVAX trials have not yet been made available, but early reports suggest that retaining participants, while possible, were not without difficulties and required an extensive investment from study staff.<sup>12</sup>

Retention data from other forms of HIV prevention research are highly variable. In studies of HIV prevention in pregnancy in Uganda, for example, very low rates of attrition have been maintained over relatively long periods<sup>77</sup>, while researchers working with CSW in Kenya reported high drop-out rates (up to 33.7% after enrolment) and a very high attrition rate due to seroconversion (37% in the first year).<sup>78</sup>

### *Reasons for retention and/or attrition*

Incarceration, migration and homelessness constituted major problems in finding participants who missed their follow-up visits in longitudinal studies of inner city drug-users in the USA.<sup>79,80</sup> The North American AIDSVAX trial, which also recruited IDU reported similar reasons for attrition.<sup>12</sup> In contrast, in African studies, attrition was associated with higher risk behaviour and fear of knowing your HIV status in heterosexual population in Kenya and Tanzania.<sup>78,81</sup> This suggests that factors related to attrition may differ between population groups, and may require different approaches to retention.

### *Retention strategies*

Sixty recruitment sites were strategically located across a large geographic region during the North American AIDSVAX trial. This prevented loss-to-follow-up due to migration since participants could be transferred to another recruitment site in a neighbouring area.<sup>12</sup> Other studies have formed alliances with social service agencies (governmental and other) to track participants<sup>12,79</sup> or provided counselling, assistance with housing and employment, food parcels, toiletries and small gifts.<sup>79,82</sup> However, a concern is that providing incentives for retention in populations where even basic provisions are limited may have ethical implications.<sup>25</sup> Logistical factors, such as travelling long distances to trial-sites, inadequate roads, a lack of public transport and electricity may also

negatively impact retention in these settings. Retention strategies require a significant investment in human, financial and technological resources, which can be costly and time-consuming. It is therefore imperative to understand attrition in different context, to be able to intervene effectively and in a resource-efficient manner during efficacy trials.

#### *Areas for further research*

1. Diverse retention rates have been noted across studies. Research needs to examine what factors impact on retention.
2. While innovative recruitment and retention strategies are needed, the ethical implications of these on vulnerable populations need to be assessed.
3. It is uncertain what infrastructure, resources and technology are required to optimize retention in African contexts.
4. Creative retention strategies need to be piloted in different settings to determine cost-effective ways of retaining participants.

#### **Sexual risk monitoring**

Apart from the challenge of retaining trial participants, there is also a concern that participants in a vaccine trial may increase their risk-taking behaviour by thinking the vaccine is protective against infection. A range of studies, including phase I and II trials, have reported that participants either increased or stated that they would increase their risk behaviour if part of a vaccine trial.<sup>35;36;65;68;77;83;84</sup> Concerns have been raised that this may lead to a perverse outcome where phase III HIV vaccine trials result in more, rather than less HIV infections.<sup>36</sup> Related to this, condom distribution and promotion for sexual risk reduction is a necessary component of HIV vaccine trials, though there is no evidence to suggest that increasing the availability or accessibility of condoms alters sexual activity itself.<sup>85</sup>

For ethical reasons it is thus essential that HIV risk behaviours are carefully monitored and that effective risk reduction procedures are in place to prevent sexual disinhibition during trials. Apart from the fact that there is little data available on sexual disinhibition during trials, another concern is that the reliability of sexual risk-reporting is constrained by memory biases and a range of demand characteristics<sup>86</sup>, which have been shown to negatively impact on vaccine preparedness research in developed countries<sup>87</sup> and must also be addressed in African contexts.

#### *Measuring sexual risk behaviour*

Since ethical and practical issues prevent measuring sexual behaviour through direct observation, research on sexual behaviour aims to provide conditions that will facilitate reliable and valid reports. The assumption is that honest reports are more accurate and will increase when privacy and anonymity is assured.<sup>88;89</sup> Self-administered questionnaires are thus preferred as they offer more privacy than face-to-face interviews, but requires a high level of literacy and familiarity with questionnaire completion.<sup>88</sup> In cases where this is not possible interviews remain the best method to obtain information of sensitive behaviours. However, this method can introduce response biases which may affect the accuracy of the data.<sup>90;91</sup>

Social desirability is one of the key biases that can influence data based on self-report. It refers to self-presentation, a tendency to present personal information in a way that will enhance one's status in interpersonal situations.<sup>90</sup> In HIV research where safe sexual practices may be considered desirable, participants may thus bias their responses accordingly, especially when negative outcomes are feared.<sup>86;90;92</sup> Social desirability may also be prominent when there is a large discrepancy in race, class or social status between the researcher and respondent, which is often the case when research is conducted in African contexts.<sup>25;93</sup>

Recently computer-assisted self-interviewing (CASI) has been examined as an alternative method of assessment to overcome the limitations inherent in the interviewing process. This involves the use of a computer where questions are either visibly displayed or asked by the computer in an audio-format (called audio-CASI or ACASI).<sup>94</sup> This is useful in low-literacy populations where respondents can listen to the questions on earphones and reply by pressing clearly marked keys on the keyboard or a touch-screen.<sup>94;95</sup> This technology has many advantages compared to paper-and-pencil tests such as increased privacy, fewer problems related to multi-lingual and low literacy contexts, and also ensures a fully standardized data-collection procedure.<sup>94-96</sup> CASI or ACASI has been successfully used in general population surveys,<sup>97</sup> as well as with high-risk groups such as adolescents,<sup>94;98</sup> and IDU.<sup>99</sup> However, there is still debate whether CASI is more reliable than pen-and-paper tests or interviews,<sup>100</sup> and the acceptability of this technology has not been established in sub-Saharan Africa. A study in Zimbabwe suggested that unfamiliarity with technology may be a barrier against effective usage in rural, low literacy populations.<sup>96</sup>

Cultural and religious beliefs against talking about sex may however be less responsive to methodological advancements.<sup>90;101</sup> In societies where strong cultural or religious taboos exist, research on sexual behaviour may

not only be inaccurate, but also considered offensive.<sup>102,103</sup> In addition, urbanization may mediate cultural taboos, resulting in differential levels of sexual self-disclosure between members of the same cultural group,<sup>90</sup> and more variability in the accuracy of sexual risk reporting in these regions.<sup>104</sup> Ways to improve the acceptability of sexual research in these settings are complex but essential for phase III HIV vaccine trial preparations.

#### *Areas for further research*

1. Longitudinal studies need to examine changes in self-reported sexual risk behaviour over time to examine sexual disinhibition and the effectiveness of risk reduction counseling.
2. Culturally-attuned ways to examine sexual risk reporting related to HIV infection are required.
3. More research on CASI, ACASI and other methods are needed in sub-Saharan Africa to establish their appropriateness for use in low literacy populations who may be unfamiliar with technology.
4. Research needs to establish whether and how cultural and religious factors impact on sexual risk disclosure.

## **Conclusion**

Socio-behavioural research is essential in preparing for HIV vaccine efficacy trials and should be strengthened in sub-Saharan Africa. Few data exist on how different cultural, economic and social contexts may influence the decision to enter a trial, the reasons for leaving a trial and the honest reporting of sexual risk behaviour and needs further investigation.

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