WILLINGNESS TO PARTICIPATE AMONG HIGH RISK SUBGROUPS IN HIV VACCINE TRIALS

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ABSTRACT

Current preventive measures against Human Immunodeficiency Virus (HIV) infection have to deal with obstacles, such as feasibility and logistics. Therefore a lot of effort is put into the development and clinical testing of possible new HIV vaccines. The development of an potential vaccines is strongly influenced by the effectiveness of the vaccine and the willingness to participate (WTP) of volunteers in clinical studies were the potential vaccine could be tested.
The overall WTP in current literature is around 65%. However, there are differences between high risk subgroups: Men who have sex with men (MSM); injecting drug users (IDU); and women at high risk. The reasons underlying and the correlated factors of WTP differ widely between these subgroups.
For future HIV vaccine trials it will be essential to take into consideration these differences between subgroups and use the knowledge gained from previous trials for more successful recruitment of participant. Contrariwise, critical appraisal of new trials and vaccines is needed to retain the balance between the need to test new vaccines in a trial and the amount of potential new trial participants.

INTRODUCTION

Many measures can be used to prevent transmission of Human Immunodeficiency Virus-1 (HIV-1) infection, for example; screening of blood donors, consistent condom use, male circumcision and monogamy. However, in practice these preventive measures have to deal with a lot of obstacles such as feasibility, logistic and economic difficulties and the resistance to change behavior.(Girard & Plotkin, 2012) Therefore, a highly efficacious vaccine against HIV infection is thought to be an effective tool in the fight against HIV and Acquired Immunodeficiency Syndrome (AIDS). (Flynn et al., 2005; Girard & Plotkin, 2012)

The development of a successful HIV vaccine has been challenging. The basic immunologic knowledge of HIV infection, gained in animals; primates and humans, is hard to translate into a successful vaccine. Reasons for this are the difficult recapturing of the disease process in models and the genetic diversity of the virus. (Buchbinder et al., 2008; Yin et al., 2008) Nevertheless, many attempts to create and test a vaccine have been performed. Over 30 different products have been tested in more than 85 trials. (Duerr, Wasserheit, & Corey, 2006)The vaccines tested can be divided into 8 categories: Recombinant protein (eg. Rgp160-mam (Belshe et al., 1993)), DNA (eg. Six-plasmid HIV-1 DNA vaccine (Catanzaro et al., 2007)), Carnarypox (eg. ALVAC-HIV (vCP1521) – AIDSVAX B/E prime-boost combination (Nitayaphan et al., 2004)), Vaccinia (eg. NYVAC-C (McCormack et al., 2008)), MVA (eg. MVA.HIVA Vaccine (Cebere et al., 2006)), FPV (pHIS-HIV-B prime-rFPV-HIV-B boost vaccine (Mallolas et al., 2006)), Adenovirus serotype 5 (eg. rAd5 vector HIV-1 vaccine (Catanzaro et al., 2006)) and polypeptide (eg. EP-1043 (Jin et al., 2009)). Of these phase I trials, only 3 types of vaccines made it to phase II: Recombinant protein, Canarypox and Adenovirus serotype 5. The Adenovirus serotype 5 vaccine of Merck (MRKAd5 HIV-1 gag/pol/nef vaccine) was one of the most promising vaccines in phase I. (Buchbinder et al., 2008) Furthermore, the vaccine showed control of viraemia in some challenge models in non-human primates. (Buchbinder et al., 2008) However, in the STEP study, a phase IIb trial, the MRKAd5 vaccine did not lower viral loads and the incidence of HIV-1 was higher in vaccine-treated men with pre-existing Ad5 immunity.(Buchbinder et al., 2008; McElrath et al., 2008) The MRKAd5 vaccine therefore did not proceeded into a phase III trial. Lessons that can be learned of the STEP study are discussed later on. On the other hand, both Recombinant protein and Canarypox vaccine types did reach phase III.

During the late nineties, the first phase III trials with HIV-1 vaccines were performed. The bivalent subtype B/B rgp120 vaccine was tested in North America and the Netherlands. The bivalent subtype B/E rgp120 vaccine was evaluated in Thailand. Both vaccines are recombinant protein vaccines based on the gp120 envelope protein and focus on the most prevalent genotypes of the circulating HIV (indicated by the B/B or B/E notation). (Flynn et al., 2005; Pitisuttithum et al., 2003)
The trial in North America and the Netherlands (VAX004) was a double blind, randomized trial in healthy volunteers. The healthy volunteers were either men who have sex with men (MSM) (n=5108) or high-risk women (n=309). Women were defined as high risk if they had sexual intercourse with HIV-1-infected male during the last 30 days, smoked crack cocaine during the last year, had sex for drugs or money in the preceding year or had intercourse with over 5 male partners during the preceding year.
The trial was not able to show a reduction in new HIV-1 infections between the vaccine and the placebo group. Because of the very small number of women enrolled, the study had little power to

assess vaccine efficacy in women. However, the study showed a trend toward efficacy in certain subgroups: nonwhites and high risk volunteers. Because of the small sample of women, the subgroup analysis was performed on only MSM, but this did not change the results. (Flynn et al., 2005)
The trial in Thailand was a randomized, double-blind, placebo controlled efficacy trial in injection drug users (IDU). These IDUs were recruited via drug-treatment clinics in Bangkok. All participants injected drugs during the past year and were HIV-1 negative at screening and baseline. The primary endpoint was HIV-1 infection and the secondary endpoints were safety and delayed disease progression. In the end the overall conclusion was that the vaccine did not prevent HIV-1 infection and did not delay disease progression. (Pitisuttithum et al., 2006)
After the disappointing results, regarding efficacy, of the previous two trials a new study was started in 2003 in Thailand where the gp120 vaccine was used in a prime-boost vaccine. (Cohen, 2003)This was a community-based, randomized, multicenter, double-blind, placebo controlled efficacy trial in 16,402 volunteers without HIV infection. Recruiting was not based on risk of infection and both male and females were recruited.
Infection with HIV and infection time after vaccination with the Carnarypox vaccine, ALVAC-HIV (vCP1521) prime – AIDSVAX B/E boost, was evaluated in this study. (Vaccari, Poonam, & Franchini, 2010) Different analyses were used to determine the outcome. The intention-to-treat analysis showed a trend to prevention of infection in the vaccine group. The per-protocol analysis did not shown significant results and the modified intention-to-treat analysis showed a modest significant reduction in HIV infection in the vaccine group. More details on the different analysis can be found elsewhere. (Rerks-Ngarm et al., 2009)Even though this study showed a modest reduction in HIV infections, more work is still needed for the development of a vaccine that will protect the whole population from HIV infection. (Vaccari et al., 2010)

These previous trials demonstrate the need for new trials with other vaccines. The two most important ingredients for future trials are a more effective vaccine and participants. The success of recruitment and follow up is mainly determined by the willingness to participate, which is the sum of many different factors. For instance, in the trial in Thailand 4943 persons were screened of which 2546 were randomized. The main reason for not being enrolled in the trial was HIV infection (70.6%), which is unavoidable. However, the second reason for not being enrolled was unwillingness to participate (7.4%). (Vanichseni et al., 2004) The unwillingness to participate was even higher in the trial in North America and the Netherlands, 18.6 %. (Flynn et al., 2005) Overall, the mean WTP, in current literature, is around 65% (Table1). To increase this factor it is important to create an image of the willingness to participate, the cons and the pros and its implications for future trials.

WILLINGNESS TO PARTICIPATE

The WTP in HIV vaccine trials is very complex and multiple factors are either negatively or positively correlated. Besides the different factors, this chapter will focus on WTP in different subgroups and on the effects of the early termination of the STEP study, on the effectiveness of an Adenovirus serotype 5 vaccine, on future WTP. (Table 1, 2 and 3)

VACCINE ACCEPTABILITY

A systematic review on HIV vaccines showed a mean HIV vaccine acceptability of 65.3 (range 37.2-94.0) on a 100-point scale. (Peter a Newman & Logie, 2010) A fictional vaccine with high efficacy will have a mean acceptability of 73.9 (SD=9.2) and a fictional vaccine with moderate efficacy will have a mean acceptability of 40.4 (SD=20.2). (Peter a Newman & Logie, 2010)

Expected vaccine efficacy and the presumed duration of protection were positively correlated with vaccine acceptability. Other factors that were positively correlated were perceived susceptibility to HIV infection and perceived benefits of the vaccine. (Peter a Newman & Logie, 2010) Expected side effects; safety concerns; fear of needles; pragmatic obstacles; costs; non-risk group membership; fear of vaccines; mistrust of the government and the scientific community; and being African American were negatively correlated with vaccine acceptability. (Peter a Newman & Logie, 2010; Sayles, Macphail, Newman, & Cunningham, 2010)

Vaccine acceptability could be improved through governments, individual community leaders and the media. This could be done by providing more education about the vaccine, influencing social norms, for instance through the head of the church or other influent local persons, and providing incentives for vaccine use. (Sayles et al., 2010)

WTP

The WTP in a North American cohort ranged from 34.8% to 76.2%, depending on different trial designs. (Peter a Newman et al., 2007) Positive correlations were shown between WTP and free HIV medication and shorter trials. (Peter a Newman et al., 2007) On the contrary, fear of vaccine-induced infection, false HIV-positives and trial related discrimination were negatively correlated, in this cohort, with WTP. Monetary reimbursement, number of vaccine doses and minor side effects did not influence the WTP. (Peter a Newman et al., 2007)

A study in the Caribbean, Botswana and South America showed a decrease of WTP over time. The baseline WTP was over 90% in all included centres and slightly decreased at 12 months to around 85% (not all declines were statistically significant).(Djomand et al., 2008) Another study reported similar results, a significant decrease from over 75% at baseline to around 65% after 18 months. (Koblin et al., 1998) The main concerns in this trial were the fear of permanent injury or death due to the vaccine, long term side effects and partners that did not want to use a condom. (Djomand et al., 2008)

These results show that WTP generally is positively related with free medication and shorter trials, while it is negatively correlated with fear of HIV infection and discrimination. Furthermore, WTP

appears to decrease over time. Although these results give an indication of factors that influence WTP, it is more interesting to focus on factors that influence WTP in certain subgroups, since these factors possibly are very different for different subgroups. The most common subgroups in HIV vaccine trials are MSM, IDU and women at high risk of HIV infection, since these subgroups generally display high incidence.

WTP AMONG MEN WHO HAVE SEX WITH MEN

In many countries, the most common transmission route of HIV is male-to-male sexual transmission and in some countries transmission has shifted from IDU to sexual, mainly in MSM. (De Cock, Jaffe, & Curran, 2012; Etcheverry et al., 2010) Moreover, MSM remain at high risk for HIV infection (Bartholow et al., 1997; Etcheverry et al., 2010) Therefore, MSM became a highly relevant high risk group for future HIV vaccine trials.

A study on WTP in Chinese MSM was conducted to determine the WTP in this risk group in a Chinese setting, since it is thought that this context might differ from studies done in other countries. (Li et al., 2010) Overall, 71% of the participants in this study stated that they were willing to participate. (Li et al., 2010) This percentage is similar to other WTP measured. (Bartholow et al., 1997; Etcheverry et al., 2010; Périssé et al., 2000; Vieira de Souza, Lowndes, Szwarcwald, Bastos, & Chagas, 2010)However, some studies reported lower WTP of around 60%. (Strathdee et al., 2000) Considerably lower was the WTP in MSM from London, only 23.4 %. (Sherr, Bolding, & Elford, 2004) This could be due to the fact that MSM in London have better access to anti-HIV therapy and therefore may not feel the need for a vaccine.

The primary reasons for WTP are altruistic, such as helping to end the epidemic and the community; and solidarity. (Koblin et al., 1998; Périssé et al., 2000; Vieira de Souza et al., 2010) The second most common reason for WTP was self-protection against HIV infection. (Vieira de Souza et al., 2010) The main reasons for unwillingness to participate were fear of HIV infection due to the study vaccine, possible adverse effects of the vaccine and false positive HIV test results. (Périssé et al., 2000; Vieira de Souza et al., 2010)

The Chinese study showed that WTP was negatively correlated with older age, high monthly income, college education, residential status, participation in male group sex, social risk (eg. discrimination and stigma against perceived HIV infected persons), perception of possible ineffective vaccine, fear of possible health problems caused by the vaccine and fear of false positive HIV tests. (Li et al., 2010) Family support for participation, receiving an incentive for participation, expected protection against HIV infection and high depression scores were positively correlated with WTP in MSM in these studies. (Li et al., 2010; Strathdee et al., 2000) A multivariate logistic regression model identified family support and expected protection against HIV by the vaccine as the only two positive independent predictors. The only negative independent predictor was being worried that people may avoid study participants.(Li et al., 2010)Furthermore, MSM at (perceived) high risk of HIV infection were more likely to be WTP than MSM at low risk. (Li et al., 2010; Strathdee et al., 2000)

Different studies in Brazilian MSM showed in multivariate analysis different positive correlations with WTP than the Chinese study, such as low level of education, infection with condylomata, syphilis infection, risky behaviour under influence of alcohol and sex in exchange for goods. (Périssé et al., 2000; Vieira de Souza et al., 2010) A negative correlation was found with being a student and

reporting sex at first encounter. (Périssé et al., 2000) These differences in predictor variables for WTP indicate that WTP is likely to differ between countries and populations.

The positive correlation between family support and WTP is explained by the important role of family in traditional Chinese culture. (Li et al., 2010)The negative correlation between WTP and social risks is explained by the discrimination and stigma against HIV infected people, which are still present in China. (Li et al., 2010)This variable is mentioned in almost all literature and appears to be an issue in all countries and population.

A study in American MSM showed an association between WTP and the following factors: higher number of male sex partners, unprotected casual sex, group sex, sex in public sex environments, paid sex, poor sexual communication skills, drug or alcohol use (whether or not during sex), frequent gay bar visitor, disliking condoms, being openly gay, number of gay friends. (Hays & Kegeles, 1999)Another factor among MSM which influenced WTP is friends wanting them to be vaccinated. (Kakinami, Newman, Lee, & Duan, 2008)

Similar to studies in mixed cohorts, a study in MSM showed a decrease in WTP over time, but this was due to more information that was provided. The WTP after information about safety and the testing status of the vaccine was 82%. After more extensive information about potential risks of the vaccine, the WTP dropped to 77%. (Bartholow et al., 1997)At the 12 month follow up, the WTP decreased even further to 52%. (Bartholow et al., 1997)

In brief, the main reason for participation in a HIV vaccine trial among MSM was altruism and the main reason not to participate was fear of the risks of the vaccine. Research in Chinese MSM showed a large correlation between family support and higher WTP. However, the results from the Chinese study should be handled with caution and one should take into account that these results could not be applied to other populations.

WTP AMONG INJECTING DRUG USERS (IDU)

The second subgroup discussed are IDU. This population also portraits high incidence.

The phase III HIV vaccine trial in Thailand showed that social harm in IDU appeared to occur in about 1.5 % of the participants and occurred mainly in personal relationships. The main reason for social harm was suspicion of the participant being HIV infected. Participants indicated the impact of the social harm as minimal. (Pitisuttithum et al., 2007)

The WTP among IDU ranges widely in current literature. Among HIV-negative IDU the reported WTP was around 50% which is much lower than the reported WTP in MSM (~75%). (Dhalla et al., 2010; Meyers, Metzger, Navaline, Woody, & McLellan, 1994; Serpelloni, Vlahov, Mazzi, & Rezza, 1995) On the contrary, a study in Canadian IDU reported a WTP of 83%. However, this study did not provide excessive information about HIV vaccines, which may influence WTP since others reported that about one third of the IDU did not know what a vaccine was and WTP actually decreased when more information was given. (Meyers et al., 1994; Serpelloni et al., 1995; Strathdee et al., 2000) These results are affirmed by a study in American IDU, which showed a WTP of 83%-86%. (Golub et al., 2005)The WTP among HIV positive IDU was slightly lower than among HIV negative IDU (54% vs. 56%). (Dhalla, Poole, Singer, Patrick, & Kerr, 2012)

Factors that were positively correlated with WTP among HIV-negative IDU were self-efficacy; aboriginal ethnicity; and education level(Dhalla et al., 2010)motivation by monetary incentives; motivation by non-monetary incentives; female sex (Golub et al., 2005); first drug use at young age; frequent needle exchange programme (NEP) visitor and perceived high risk of HIV infection. (Strathdee et al., 2000) Self-efficacy also had a positive correlation with WTP in HIV-positive IDU. (Dhalla et al., 2012)Participants without health insurance and participants who stated no incentive could motivate them to participate were less likely to be WTP. (Golub et al., 2005)

The relation between aboriginal ethnicity and WTP is not explained yet and thus further research was suggested. (Dhalla et al., 2010)Optimism about HIV treatment and prior knowledge about HIV, vaccines and trials was not correlated with WTP. (Dhalla et al., 2010, 2012)

A study about WTP in Chinese IDU showed, in line with a similar study in Chinese MSM, that perceived family support was positively correlated with WTP. Other positive correlations were between WTP and having had sex with a drug use partner, sharing of needles within the last 3 months with a new partner and perceived protection against HIV infection by the vaccine. The only negative association to WTP was perceived risk of stigma and isolation. Overall, almost 75% of the participants were WTP. (Yin et al., 2008)

Overall, the WTP among IDU appears to be lower than in MSM. Positive correlations were found between WTP and self-efficacy and frequent NEP visitor. On the other hand, sharing needles is also positively correlated to WTP. The main negative correlation can be found between WTP and the risk of stigma and isolation.

WTP AMONG WOMEN

Women account for about half of all new HIV infections worldwide and are therefore a potential source for participants of HIV trials. (Rudy et al., 2005) Moreover, an efficacious vaccine would be very valuable for women to protect themselves against HIV infection, without depending on their sexual partner. (Rudy et al., 2005) A lot of trials included only a very small sample of women, which led to too little power to draw conclusions. Furthermore, there does not appear to be a big difference in the WTP between women and men. (Kakinami et al., 2008) An Indian study showed a slightly higher WTP in women (98% vs. 90%) with as main reason for WTP: protection against HIV infection via their husbands. (Suhadev et al., 2006)

Just as in other cohorts, women expressed the fear that the vaccine could lead to HIV infection. (Rudy et al., 2005) Concerns about a HIV vaccine which are of particular interest in women are the concerns about reproductive side effects, effects on the foetus, breast feeding and long term fertility. (Mills et al., 2006; Rudy et al., 2005) Until these concerns are proven to be unfounded, these concerns might have a great effect on the WTP of women. Another factor which negatively influenced WTP among women was gender dynamics. Women stated that it is difficult to communicate with their partner about getting vaccinated against HIV, since this might make their husbands or partners mistrust them. Furthermore, women stated that their sexual partners would not inform them of being at potential risk of HIV infection. Therefore, women might underestimate the risk of getting infected with HIV. (Rudy et al., 2005) Besides this, women were reluctant to admit misbehaviour of their partner and were in denial of their own risk. (Rudy et al., 2005) Furthermore, many black Canadian women believed they were not at all at risk of HIV infection and thought it was

mainly a problem in other parts of the world, such as Africa. (Williams, Newman, Sakamoto, & Massaquoi, 2009) Women also were concerned that a vaccine might induce sexual promiscuity and decrease the willingness among men to use condoms. (Sayles et al., 2010; Williams et al., 2009) These concerns seem to be legit, since men reported an advantage of the vaccine to be not having to use condoms. (Sayles et al., 2010)

Women appeared to have more concerns about the reaction of their families, sexual partners and churches about being vaccinated against HIV. They thought their families and churches would label them promiscuous. (Kakinami et al., 2008; Sayles et al., 2010; Williams et al., 2009) These concerns were also described among men, but men did not relate them to family or church. (Sayles et al., 2010) Other concerns related to stigmatization and discrimination were related to discrimination in health care and difficulties getting health insurance. (Kakinami et al., 2008) These concerns mainly affected WTP in women, especially in women who previously experienced discrimination in health care settings. (Kakinami et al., 2008) Black women were especially concerned that the vaccine might increase discrimination against the black community by the general population and they did not trust the health care system, researchers, pharmaceutical companies and the government. (Williams et al., 2009) This lack of trust in these institutions was fuelled by the Tuskegee syphilis trial. (Williams et al., 2009)

On the contrary to before mentioned concerns about the relation between the vaccine and fertility, women also indicated raising children or starting a family with a HIV infected partner as reasons to get the vaccine. (Kakinami et al., 2008; Sayles et al., 2010)

Barriers for WTP in women are mainly related to their personal/intimate relationships and health care associated discrimination. On the contrary, barriers in men, both homo- and heterosexual, are mainly related to the fear of the effects of the vaccine on their health. (Kakinami et al., 2008) These differences suggest the need for a targeted, gender-specific approach in future HIV vaccine trials. (Kakinami et al., 2008)

Concisely, women are concerned about the effects of a potential vaccine on their fertility and unborn children. Additionally, they fear the prejudices from their community. On the contrary, women recognize their lack of self-protection against HIV infection nowadays and endorse the beneficial effects of getting vaccinated against HIV infection. These factors are the main contributors to WTP among women.

LESSONS LEARNED

The STEP study was terminated after the first interim analysis, because then it became clear the trial would not be able reach its efficacy endpoints. (Buchbinder et al., 2008; P a Newman et al., 2011) This trial created an unique opportunity to explore the effects of early termination of a trial and unexpected risk on the WTP. [Newman, 2011] A study on the perspective and experiences of trial participants compared WTP and related questions given before and after the trial. (P a Newman et al., 2011)

Before the start of the STEP study the participants indicated they were willing to participate because of altruistic reasons. Other reasons for participation were being at high risk of HIV infection and to

get extra protection against HIV. (P a Newman et al., 2011) After the trial was ended, these reasons for participation were still the same.

The participants had complete trust in the informed consent process. However, after the trial ended some participants questioned the clarity and transparency of the informed consent process. Most of these participants claimed they were not accurately informed about the possibility of early termination of the trial and participants suspected that this information was withheld to ensure enough participants. On the contrary, there were still participants who had complete trust in the informed consent process after the trial; they reasoned that the unforeseen outcomes could occur. (P a Newman et al., 2011)

The participants reported a great sense of collaboration and companionship during the trial with trial staff, investigators and other participants. The importance of these feelings was underlined by trial staff. (P a Newman et al., 2011)

After the study was terminated, it was unblinded and participants were informed about the termination of the study and whether they were allocated to vaccine or placebo. Most participants expressed negative reactions to learning about the early termination of the study and the increased susceptibility in the vaccine group. However, a small proportion (7%) of participants was aware of the possibility of this outcome and realised it could happen, even though they were disappointed that it did. (P a Newman et al., 2011)

Information about study termination and unblinding was given to participants around two months after terminating the study. To the study staff and investigators this seemed reasonable. Nevertheless, participants thought the communication was slow and sporadic. Some participants even heard about the early termination through the media. Participants who dropped out early of the study were not informed at all by the study staff. The process of unblinding also lead to insecurity with the participants, some were worried they were not told correctly which group they were allocated to and some participants thought the time till unblinding was too long. (P a Newman et al., 2011) The key obstacle here was communication with participants and the fact that participants may have had other expectations about communication than what was thought reasonable by staff and investigators.

Another point brought forward was counselling, participants had fears before the trial about reactions and discrimination regarding volunteering in a HIV vaccine trial. Many participants believed the STEP trial lacked in counselling after the trial and it is emphasized that both participants in the vaccine and placebo group should receive counselling about the emotional impact of participating and the results. (P a Newman et al., 2011)

Overall, WTP in future trials was affected in some participants, mainly because they were discouraged by the unexpected risks. Some participants would still participate in clinical trials, but are no longer willing to participate specifically in vaccine trials. In men who have sex with men (MSM) and transgender (TG) participants the intentions for enrolment did not change in light of the results of the STEP study. (Frew, Mulligan, Hou, Chan, & del Rio, 2010) The main reasons for unchanged WTP were on-going altruism, the memory of a friend who died of AIDS and the desire for new HIV preventive measures. (P a Newman et al., 2011) Participants from the STEP study suggested some implications for future trials. The first implication was on communication: it was suggested

that communication to and between trial volunteers, trial investigators and trial sponsors should be improved and clarified. The second implication covered camaderie: the advice was to train, support and reward staff for collaborative engagement with trial volunteers. Other implications focused on post-trial information and psychological support. The main implication states that resources should be allocated to providing post-trial information to volunteers, local communities, high-risk groups, the general public and the media; and to provide post-trial debriefing and psychosocial support. (P a Newman et al., 2011)

The main lesson learned from the STEP study in communication. Most negative associations with the trial are a result of poor communication, for instance about the communication during the informed consent process about the possible early termination of trials. Decrease in WTP was mainly due to the unexpected risks. Nonetheless, some participants indicate that their WTP did not change taking into account the course of the STEP study. The main reason for unchanged WTP was on-going altruism.

FUTURE TRIALS

The above mentioned articles on WTP show a lot of correlations between WTP and characteristics of possible participants, both positive and negative. But which lessons can be learned from these studies? And to which extend can these lessons be generalized to other populations? First, we will look at the pros and cons of high risk group vaccination, such as minor ethnic populations, MSM and IDU. Afterwards, factors that are frequently correlated to WTP in the literature, such as education level and family support, are discussed. Next, indications for performing vaccine trials in IDU are discussed. Finally, the consequences of failed HIV vaccine trials are displayed.

Most phase III studies until now were performed in high risk groups: MSM; IDU; women at high risk of heterosexual HIV transmission; and men at high risk of heterosexual HIV transmission. For future HIV vaccination, these high risk groups would be the most interesting target, since there is a high incidence of HIV infection in these populations. Therefore, it would be most appropriate and efficient to perform future HIV vaccine trials in these high risk populations.
However, it should be explored whether vaccinating high risk populations would be sufficient. Especially women might underestimate their actual risk of HIV infection. Therefore, women might not appoint themselves as high risk, even though they might be at high risk. By eliminating the low risk population from a future HIV vaccination, important sources of further HIV transmission might be missed. The balance between effective HIV vaccination trials (thus using high risk populations) and the possible need of vaccinating low risk groups should be explored.

There are some factors that are frequently reported to be correlated to WTP. One of these factors is ethnicity. Latin American, Han, Aboriginal and African American ethnicity are all related with higher WTP, compared to Caucasians, and therefore these minorities could be interesting populations for future HIV vaccine trials, depending on the overall incidence in these populations. It will be likely that recruiting for future trials in these populations will yield a lot of participants. However, results from these trials might be hard to generalize to other high risk populations, such as MSM, since there might be underlying differences in the effectiveness of future HIV vaccines between different ethnicities, cultures and exposure routes.

Another factor that is positively correlated to WTP is homo- or bisexuality. However, the results about this correlation are conflicting in current literature. Assuming that homo- and bisexuality are correlated to WTP, this would be positive for recruitment for future trials. MSM are currently one of the leading sources of HIV transmission and therefore a vaccine that works in MSM would be a great step forward in the prevention of HIV transmission. If a HIV vaccine was developed that is effective in MSM, the next question is whether the vaccine would be accepted in the MSM population. The acceptability of a future HIV vaccine was estimated around 60 % among MSM in Thailand. (Peter a Newman, Roungprakhon, Tepjan, & Yim, 2010) This indicated that even if a vaccine would be developed, the coverage probably might not reach high levels. One of the questions is whether coverage around 60-70% would be enough to create a sufficient barrier for the spreading of HIV in the community.
The correlation between risky sexual behavior in MSM and a WTP in a future HIV vaccine trial is contradicting in different studies. (Etcheverry et al., 2010; Li et al., 2010; Vieira de Souza et al., 2010; Yin et al., 2008) Some studies report a positive correlation between risky sexual behavior and WTP. MSM who perform risky sexual behavior put themselves at higher risk of HIV infection. Therefore,

they might see a greater need and advantage for the development of a new HIV vaccine and are more willing to participate in a trial which ultimately may lead to such a vaccine. However, an article in Chinese MSM indicated that the correlation between risky sexual behavior and WTP is negatively correlated. (Li et al., 2010) This difference in correlation also supports the recommendation that future HIV vaccine trials should take in account the ethnicity of their study population and should adjust recruitment tactics to this.

Both non-injecting drug use and sharing needles was positively correlated to WTP. Furthermore, the WTP among IDU was high. These results show that drug users, both non-injecting and injecting, might be a good source for future HIV vaccine trials, depending on the incidence in this population. The incidence among IDU ranges from 9% in the USA to around 25% in Russia. (Niccolai et al., 2011; Prejean et al., 2011) These results show that it might be depending on the country whether IDU would be a sufficient population for effective HIV vaccination trials. Another issue might be the compliance in this population. Especially IDU often do not have a permanent address and could be more prone to missing appointments, which could negatively affect follow up. However, it was shown that frequent attending of needle exchange programs (NEP) was the strongest predictor of positive WTP among IDU in Canada (Strathdee et al., 2000). This might indicate that this subpopulation among IDU are more concerned about their health and that the regular interaction with NEP staff increases trust in other health care authorities, facilitating higher WTP among IDU in vaccine trials.(Strathdee et al., 2000) Future trials should take these factors into account and for example use shelter homes, needle exchange programs or methadone clinics as their research sites.

The data on the correlation between higher education level and WTP are also contradicting among studies. Studies in MSM support a negative correlation between WTP and higher education level, while a study in IDU shows a positive correlation. (Dhalla et al., 2010; Li et al., 2010; Vieira de Souza et al., 2010) This positive correlation might be due to confounders, such as vaccine awareness. It could be recommended to take a closer look to the exact influence of education level on WTP. However, for the generalizability of future trials it would be best to not focus recruitment on participants with either a higher or a lower education level. If this focus is present, education level could be a confounder in the results of the trial and higher education level also might be associated with other underlying factors, such as healthier lifestyle, that could influence the effectiveness of the vaccine. Furthermore, once a vaccine is developed, education level will not be taken into account during the distribution of the vaccine.

Another factor that should be taken into account for future recruitment is family support. Especially in China this is of great influence on the WTP. Therefore, it might be best to provide education on HIV, HIV vaccine and HIV vaccine trials nationwide. This way, both possible future participant and their families will be properly educated which may create more support and thus WTP. Even though this factor seems especially of importance in the Chinese population, it will also be important in population with similar structures of family bounds and hierarchy. Furthermore, nationwide education on HIV vaccines, HIV and HIV vaccine trials could also have a beneficial effect on the WTP in countries where family support is not related to WTP. In most countries perceived stigmatization and discrimination of HIV vaccine trial participants is one of the most important concerns of participation in a HIV vaccine trial. Higher levels of nationwide education might resolve a part of the stigmatization and discrimination. It could make the general population aware of the fact that people who do participate are not infected with HIV or AIDS and that they do not necessarily portrait

high risk behavior. Even though nationwide education could decrease the stigmatization and discrimination, these two factors would probably remain problems in recruiting participants. It would be very difficult to decrease these factors in this population, since they are most of the time rooted in the population due to religion or politics. Therefore, it might be easier and better to protect the participants against discrimination and stigmatization. This could be done through high levels of discretion and secrecy. A big concern regarding discrimination and stigmatization was discrimination in health care and insurance. Since it will be necessary to reveal the participation of a person to health care workers in case of hospitalization or something like this, it will be hard to overcome this problem. It might be a possibility to create study sites in medical centers and education of all personnel. This could decrease the fear among health care workers for dealing with participants.

Only one study reported a beneficial effect of incentives on WTP. This could be due to the fact that most possible participants reported altruism as the main reason to participate. Furthermore, possible participants reported that they would be WTP because of possible protection against HIV after participating. Therefore, future trials would not necessarily need to provide incentives for participants. The money which will be saved due to not providing incentives could be used for providing ancillary care or for nationwide education programs.

Another issue that should be taken into account in future trials is the fact that many potential participants reported that they would display equally as much or more high risk behavior if they would be vaccinated. This should be taken into account in the analysis, when people think they are protected they will put them self at a higher risk of getting infected. The effects of different risks and incidences can be explored with the help of sensitivity analysis. Through this analysis, the effect of variation in certain parameters on the effectiveness of the vaccine and the required vaccination rate can be established.

Overall, a future HIV vaccine trial should take in account the differences between populations and ethnical minorities and adjust its recruitment lay out to the specific population.

A more general concern, related to WTP, which has been expressed, is with regard to reducing the pool of participants in future trials. (Flynn et al., 2005) Every HIV vaccine trial that is conducted uses vaccine negative participants, mainly at high risk for HIV infection. Since trials need a lot of participants for a solid outcome, it is necessary that a phase III trial has a good chance of being successful. Of the potential participants recruited for a trial, only a certain amount of participants will actually be enrolled, this is due to both their eligibility and their WTP. The WTP is, overall, around 65%. Thus study staff should recruit almost twice the amount of participants that should be enrolled. Furthermore, participants from a previous trial reported that they would not enroll in another HIV vaccine trial, which also decreases the pool of potential participants. [Johnston, 2003] More failed trials lead to a loss of public confidence in future vaccines. Future participants may believe the trial is doomed to fail on forehand or even might harm their health. Failed trials thus may mean less potential participants for future trials.(“Trial and failure.,” 2007) Therefore, it might be better if potential HIV vaccine were tested in a Phase IIb trial, before proceeding to phase III trials. Phase IIb trials are used to test efficacy, but have, in general, a smaller sample size and lower costs. By using Phase IIb trials as a design, a smaller number of participants is used and a quite precise indication about the efficacy of the vaccine in phase III trials can be determined. This way, HIV

vaccines that will be effective and promising can be tested in phase III trials in adequate study populations. Furthermore it is suggested, and widely supported by researchers, to develop cross-community forums, with input from all different disciplines within the HIV prevention research. This way, experiences on common problems and the roll out of HIV preventive research can be discussed interdisciplinary. (“Trial and failure.,” 2007)

Study	N	WTP	Study Population	Location
Djomond, 2008	898 (FSW: 252; HRHW: 234; HRHM: 212; MSM: 200)	93.2	MSM; heterosexual men and women; FSW	Africa; Caribbean; South America
Koblin, 1998	4892 (MSM: 3257; MIDU: 770; WAHR-IDU: 354; WAHR: 511)	77.0	Homosexual men; male and female IDU;	USA
Bartolow, 1997	1267	37.0	MSM	USA
Etcheverry, 2010	844 (number of participants per subgroup not specified)	82.0	MSM; FSW; IDU; NIDU	Spain
Li, 2010	550	70.9	MSM	China
Perisse, 2000	815	69.8	MSM	Brazil
Vieira de Souza, 2003	627 (NCSW: 333; CSW: 294)	57.0	MSM	Brazil
Strathdee, 1999	765 (IDU: 435; MSM: 330)	73.0	IDU; MSM	Canada
Sherr, 2004	506	23.4	MSM	UK (London)
Hays, 1999	390	64.0	MSM	USA
Serpelloni, 1995	156	41.0	IDU	Italy
Meyers, 1994	240	52.0	IDU	USA
Dhalla, 2010	243	56.0	IDU	Canada
Vlakov, 1994	375	85.0	IDU	USA
Golub, 2005	1022 (Wave 1 1994: 440; Wave 2 2001: 582)	83.4	IDU	USA
Dhalla, 2012	75	54.0	IDU	Canada
Yin, 2008	401	92.0	IDU	China
Overall		65.3		
MSM		53.7		
IDU		66.2		

Table 1. Mean WTP per study. Studies were conducted in different high-risk population in different countries.

MSM: Men having sex with men; FSW: Female Sex Workers; HRHW: High Risk Heterosexual Women; HRHM: High Risk Heterosexual Men; IDU: Injecting Drug User; NIDU: Non-Injecting Drug Users; NCSW: Non-Commercial Sex Workers; CSW: Commercial Sex Workers; WAHR-IDU: Women At High Risk-Injecting Drug Users; UK: United Kingdom; USA: United States of America.

		Study population	**References**
Reason for WTP	Altruism	Homosexual men; male and female IDU/ MSM	Koblin, 1998/ Perisse, 2000/ Hays, 1999
	Assurance of confidentiality	IDU	Vlakov, 1994
	Full information about the study	IDU	Vlakov, 1994
	(Monetary) Incentives	IDU	Vlakov, 1994/ Golub, 2005
Reason for concern	False HIV positive test	Homosexual men; male and female IDU;	Koblin, 1998/ Serpelloni, 1995/ Vlakov, 1994

	Personal inconvenience (e.g. problems with health insurance, travel)	Homosexual men; male and female IDU;	Koblin, 1998
	Social risks (avoidance, discrimination)	Homosexual men; male and female IDU/ MSM	Koblin, 1998/ Li, 2010/ Yin, 2008
	Health problems due to the vaccine	Homosexual men; male and female IDU/ MSM	Koblin, 1998/ Li, 2010/ Hays, 1999

Table 2. Main reason for and against participation in future HIV trials.
HIV: Human Immunodeficiency Virus; WTP: Willingness to participate; IDU: Injecting Drug Users; MSM: Men who have Sex with Men.

Correlations to WTP	Positive or Negative	Study population	Reference
Age	+	MSM; FSW; IDU; NIDU	Etcheverry, 2010
Ethnicity			
Latin American	+	MSM; FSW; IDU; NIDU	Etcheverry, 2010
Han	+	MSM	Li, 2010
Aboriginal	+	IDU	Dhalla, 2010
African American	+	Mixed Cohort	Newman, 2010
Homo- or bisexuality	+	MSM; FSW; IDU; NIDU	Etcheverry, 2010
Risky sexual behaviour	+	MSM; FSW; IDU; NIDU	Etcheverry, 2010/ Vieira de Souza, 2003/ Yin, 2008
	-	MSM	Li, 2010
Non-injecting drug use	+	MSM; FSW; IDU; NIDU	Etcheverry, 2010
Low monthly income	+	MSM	Li, 2010
Higher education level	-	MSM	Li, 2010, Vieira de Souza, 2003
	+	IDU	Dhalla, 2010
Family support	+	MSM; IDU	Li, 2010/ Yin, 2008
Incentive	+	MSM	Li, 2010
Protection against HIV	+	MSM; IDU	Li, 2010/ Yin, 2008
Positive serology syphilis	+	MSM	Vieira de Souza, 2003
High perceived HIV threat	+	MSM	Strathdee, 1999; Sherr, 2004; Hays, 1999
Frequent needle exchange programs attenders	+	IDU	Strathdee, 1999
Depression	+	MSM	Strathdee, 1999
Needle sharing	+	IDU	Meyers, 1994/ Yin, 2008
Self-efficacy	+	IDU	Dhalla, 2010/ Dhalla, 2012

Table 3. Correlations to WTP in different high-risk population

WTP: Willingness to Participate; IDU: Injecting Drug Users; MSM: Men who have Sex with Men; FSW: Female Sex Workers; NIDU: Non-Injecting Drug Users.

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