

COGNITIVE FACTORS AND WILLINGNESS TO PARTICIPATE IN AN HIV VACCINE
TRIAL IN INJECTION DRUG USERS

by

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ABSTRACT

HIV vaccine preparedness studies (VPS) are important precursors of vaccine trials, assessing the feasibility of such trials. This thesis presents a study of HIV vaccine preparedness, with a focus on the investigation of cognitive factors as predictors of willingness to participate (WTP) in preventive and therapeutic HIV vaccine trials. These cognitive factors include HIV treatment optimism, self-efficacy beliefs, and knowledge of HIV vaccine trial concepts. The introductory chapter covers HIV epidemiology, prevention measures including HIV vaccines, background information on HIV VPS and HIV vaccines, and a description of cognitive factors potentially associated with WTP. Chapters 2 and 3 are review articles: one describing retention rates (17 studies) and WTP (22 studies) in the Organization for Economic Co-operation and Development (OECD) countries, and the other in the non-OECD countries (16 studies on retention; 21 studies on WTP). The studies indicated that high-risk factors were positively associated with WTP and that retention and WTP were adequate for conducting HIV vaccine trials.

Chapter 4 consists of a VPS involving HIV-negative injectors in the Vancouver Injection Drug Users' (VIDUS) study. This study found that Aboriginal ethnicity, educational level (\geq high school), and an increase in self-efficacy had statistically significant positive associations with WTP. The majority of participants in this study had relatively high levels of self-efficacy so we are most confident about this relationship at such levels. HIV treatment optimism and knowledge of HIV vaccine trial concepts were unrelated to WTP. Chapter 5, using the AIDS Care Cohort to Evaluate Exposure to Survival Services (ACCESS) study in HIV-positive injectors, demonstrated that self-efficacy again had a statistically significant positive association with WTP. Again, the majority of participants had high levels of self-efficacy. HIV treatment

optimism and knowledge were unrelated to WTP. These studies address a gap in knowledge of cognitive factors regarding relation to WTP in HIV vaccine trials. In conclusion, Chapter 6 discusses 1) a summary of the findings and comparisons between the studies 2) novelty (3) strengths and weaknesses (4) implications and (5) future directions.

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DEDICATION

To my parents

CO-AUTHORSHIP STATEMENT

Chapters 2 and 3 are review articles with myself, Dr. Shayesta Dhalla (S.D.), as the lead author.

Chapter 2 was co-authored by Ryan Woods (R.W.), Dr. Steffanie A. Strathdee (S.A.S.),

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conceptualized and formulated the research question. S.D. interpreted the data, and prepared the

initial draft of the manuscript. R.W. prepared the graphs for the manuscript. The remaining co-

authors provided a critical assessment of the manuscript. The second review article (Chapter 3)

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(G.P.). S.D. and R.S.H. conceptualized and formulated the research question. S.D. interpreted

the data, and prepared the initial draft of the manuscript. K.E.N. added information to the

manuscript, and along with J.S. and G.P., also provided critical feedback on the manuscript.

Chapter 4 was co-authored by Dr. Gary Poole (G.P.), Dr. Joel Singer (J.S.), Dr. David M. Patrick

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Study (VIDUS) and was involved in raising funding for the study, and in the in day to day

management of the cohort during the period that data for the present study were collected. S.D.

conducted the data analysis with some advice from G.P. and Dr. Chris Richardson (C.R.). S.D.

interpreted the data with advice from the other co-authors and Dr. Hubert Wong (H.W.) also

contributed to data interpretation. The initial draft of the manuscript was prepared by S.D.

T.K. contributed to the study design, was involved in the data collection, and along with G.P.,

J.S. and D.P. and E.W. provided critical feedback on the manuscript. All authors approved the

final manuscript.

Chapter 5 was co-authored by G.P., J.S., D.P., and T.K. S.D. and G.P. conceptualized the study. R.S.H. contributed to the topic of the study. E.W. is the principal investigator of the AIDS Care Cohort to Evaluate Exposure to Survival Services Study (ACCESS) and was involved in day to day management of the cohort during the period that data for the present study were collected. S.D. conducted the data analysis, interpreted the data, and drafted the initial version of the manuscript. C.R. provided advice on the analysis. T.K. contributed to the study design, was involved in data collection, and along with G.P., J.S., D.P., E.W., and H.W., assisted in the the interpretation of the data, and provided critical feedback on the manuscript. Dr. Jonathon Angel (J.A.) provided feedback on the introduction of the study. All authors approved the final manuscript.

Chapter 1

Introduction

This thesis presents a study of HIV vaccine preparedness, with a focus on the investigation of cognitive factors as predictors of willingness to participate (WTP) in preventive or therapeutic HIV vaccine trials.

1.1 GLOBAL IMPACT OF HIV

Globally, there were an estimated 33 million (range = 30 million-36 million) people living with HIV in 2007, and overall, 2.0 million (range = 1.8 million-2.3 million) people died from AIDS in 2007 (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2007). Sub-Saharan Africa remains the region most heavily affected by HIV, accounting for 67% of all people living with HIV and for 75% of AIDS deaths in 2007. These figures are derived from recently improved UNAIDS methodology producing more reliable estimates of the scope of the HIV epidemic and its impact, especially in sub-Saharan Africa and Asia.

1.2 HIV EPIDEMIOLOGY

Knowledge about trends and current patterns of HIV infection is essential for planning and evaluating prevention efforts (Hall et al., 2008). Here follows a discussion of HIV epidemiology in Canada and the United States (US):

1.2.1 Canada

In Canada, between 2005 and 2008, the estimated number of people living with HIV infection

increased from 57,000 to an estimated 65,000 (range = 54,000-76,000) (Public Health Agency of Canada, 2008). Of the estimated 65,000 people, 17% were injection drug users (IDU). An estimated total of 3300 (estimated range = 2300-4300) new HIV infections occurred in 2008 (Public Health Agency of Canada, 2008), with an incidence rate (IR) of 10 per 100,000 population per year (denominator = whole Canadian population 2008 (Statistics Canada, 2009). An estimated 600 IDU were newly infected with HIV in 2008, with a rate of approximately 600 per 100,000 population per year (denominator = IDU population, 2008) (Canadian Centre on Substance Abuse, 2009). Aboriginal persons continue to be over-represented in the HIV epidemic in Canada and the HIV incidence rate (IR) for the Aboriginal population was approximately 30 per 100,000 population per year in 2008 (denominator = Aboriginal population, 2006) (Public Health Agency of Canada, 2008). Injection drug use is the main HIV exposure category among Aboriginal persons in Canada.

1.2.2 United States

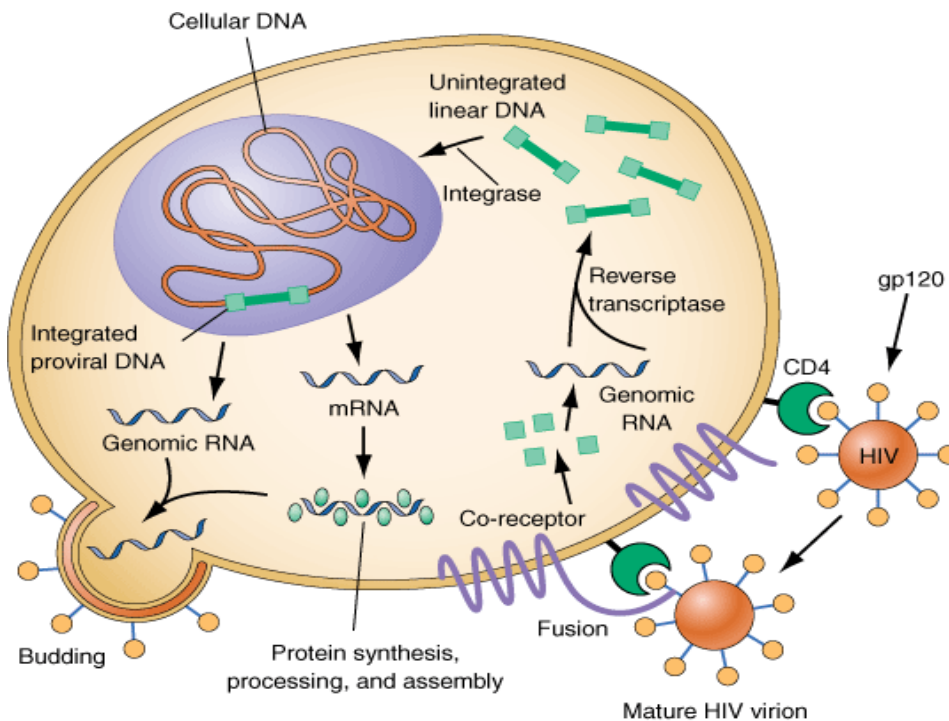
It is estimated that 1.1 million adolescents and adults were living with diagnosed or undiagnosed HIV infection in the US at the end of 2006, and injection drug use (IDU) accounted for 18.5% of total cases (CDC, 2008). A 2008 study examined the HIV IR in the US (Hall et al., 2008). HIV seroincidence was determined using the BED immunoassay, examining 22 states, and was extrapolated to the entire country. New infections of HIV remain concentrated among men who have sex with men (MSM) and among African-Americans. An estimated 56,300 (95% confidence interval [CI] = 48,200-64,500) adolescents and adults were newly infected with HIV in 2006 in the US, with a rate of 23 per 100,000 population per year (95% CI = 19.5-26.1) (denominator = all persons 13 years or older). Seventy-three percent of

infections occurred in males, 45% among African-Americans, and 53% of the infections were attributed to MSM. HIV incidence increased nationally in the late 1990s; however, among those exposed through injection drug use, incidence remained relatively stable throughout the mid and late 1990s and then decreased. Overall, the HIV IR among IDU has decreased approximately 80% in the US since the 1990's. This decrease has been attributed to the availability of needle exchange programs and reduction in needle sharing behavior (Hall et al., 2008).

1.3 HIV DESCRIPTION

HIV is an RNA virus which belongs to the family of human *retroviruses* (Retroviridae) and the subfamily of lentiviruses. The HIV virus has an icosahedral structure containing numerous external spikes formed by the two major envelope proteins, the external gp120 and the transmembrane gp41 (Fauci & Lane, 2008) (Figure 1.1). The replication cycle of HIV begins with the binding of the gp120 protein of HIV to its receptor on the host cell surface, the CD4 molecule (the CD4 molecule is a protein found predominantly on a subset of T lymphocytes that are responsible for helper function in the immune system [T-helper cells]). Once the gp120 binds to CD4, the gp120 undergoes a conformational change that facilitates binding to one of a group of co-receptors: CCR5 and CXCR4. Fusion with the host cell membrane then occurs through the gp41 molecule. The *reverse transcriptase* enzyme in the HIV virus helps the viral RNA to change into DNA. Here it is integrated into the host cell chromosomes with the help of the *integrase* enzyme. This provirus (DNA) may remain transcriptionally inactive (latent) or it may manifest varying levels of gene expression, up to active production of virus.

Figure 1.1 *Life cycle of HIV*¹



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: <http://www.accessmedicine.com>
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1.3.1 HIV clades

The most common cause of HIV disease throughout the world is HIV-1, which comprises several subtypes with different geographic distributions (Fauci & Lane, 2008). Three genetic classes of HIV-1 are present globally: M (major), O (outlying) and N (new) (Wainberg, 2004). The M class is responsible for most cases worldwide. The M class has substantial genetic diversity, and has been classified into nine major clades, including A-D, F-H, J, and K, as well as

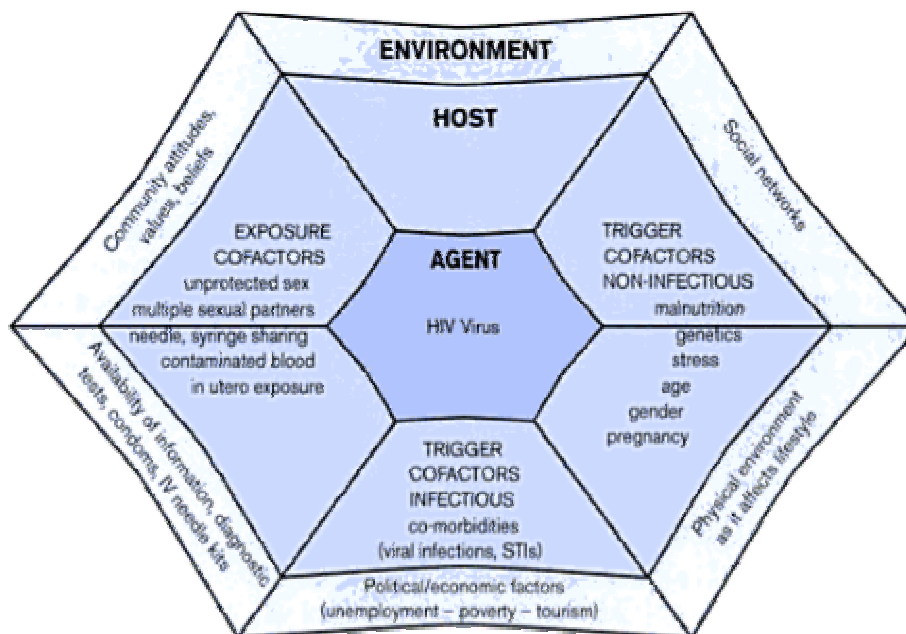
¹ Permission to use obtained, McGraw-Hill Permissions department, December, 2009.

circulating recombinant forms. Injection drug users are known to predominantly have Clade B (Geretti et al., 2009). Viral diversity is greatest in sub-Saharan Africa. The presence of genetic diversity is a consequence of the high error rate of reverse transcriptase, the mutagenicity of the virus, and propensity for recombination (Wainberg, 2004). The widespread genetic diversity of the virus as well as the absence of a known correlate of protection pose substantial scientific hurdles to the development of an HIV vaccine (Buchbinder et al., 2008).

1.4 HIV PREVENTION

The Host-Agent-Environment epidemiological web of causation model is shown in Figure 1.2 (McMurray, 2007). The figure describes the inter-relationships between the host,

Figure 1.2 *Web of causation for HIV/AIDS*²



² From McMurray A, *Community Health and Wellness: A Socio-Ecological Approach*, 3rd edition, 2007;pp.64, Copyright Elsevier. Permission to use obtained, Elsevier, January 2010.

agent, and environment. This model can be used to illustrate HIV prevention measures such as HIV vaccines. Biomedical (Padian, Buve, Balkus, Serwadda, & Cates, 2008), structural (Gupta, Parkhurst, Ogden, Aggleton, & Mahal, 2008), and behavioral (Coates, Richter, & Caceres, 2008) approaches for HIV prevention must be integrated.

1.4.1 Biomedical interventions

Male condoms

When male condoms are used consistently, their effectiveness can be as high as 95% (Padian et al., 2008). Condom use is crucial to the containment of concentrated epidemics (affecting vulnerable groups) but has limited impact in generalized epidemics (affecting the general population) (Shelton, 2007). In terms of behavioral and attitudinal issues related to condom usage, many people in regular relationships do not use them, protection is imperfect, use is often irregular, and condoms may foster disinhibition (Shelton, 2007). Male condoms raise important challenges in terms of the need for negotiation of their use. Furthermore, there are specific challenges for women in negotiating with men in this regard (Padian et al., 2008).

Male circumcision

Male circumcision has been shown in randomized controlled trials (RCTs) in sub-Saharan Africa to partially reduce the risk of heterosexual transmission of HIV from females to males (Potts et al., 2008). Three such RCTs were halted early with a summary rate ratio for HIV acquisition of 0.42 (95% CI = 0.31-0.57), identical to the results of observational studies. The World Health Organization (WHO) and UNAIDS (2007) recommended that male circumcision be recognized as an effective intervention for HIV prevention in heterosexual men (Padian et al., 2008;

WHO/UNAIDS, 2009) and should be offered with other risk-reduction strategies. It should be noted that, in the recently failed STEP vaccine trial, the HIV vaccine was associated with enhanced susceptibility to HIV, most significantly in uncircumcised MSM who had pre-existing immunity to the adenovirus (Ad5) vector (Buchbinder et al., 2008).

Antiretroviral treatment

The benefits of triple-drug highly active antiretroviral therapy (HAART) in the management of HIV are well established (Wood et al., 2003). Through the suppression of plasma HIV-1 RNA (viral load), HAART has been shown to improve CD4 cell counts and in turn to decrease morbidity and mortality rates among HIV-infected patients.

Current guidelines for starting HAART support earlier initiation than previous recommendations (Hammer et al., 2008). For this reason, a higher proportion of individuals would be expected to receive HAART today, and this could, in turn, affect willingness to participate (WTP) in a vaccine trial and also vaccine uptake. Antiretroviral therapy can also be used before exposure to HIV (pre-exposure prophylaxis [PrEP]) in order to prevent infection, and can also be used in people once they test positive in order to lower viral load to prevent the spread of HIV from an infected person to his or her sexual partner(s) (treatment as prevention) (Padian et al., 2008). Currently, there is an ongoing US National Institutes of Health (NIH) (2009) sponsored phase 3 PrEP international trial in MSM examining the use of tenofivir/emtricitabine vs. placebo for HIV prevention.

The role of sexually transmitted infections

Preventing and treating sexually transmitted infections (STIs), particularly ulcerative STIs,

decreases the sexual transmission of HIV (WHO, 2007). Longitudinal studies have shown that STIs in HIV-uninfected men and women increase susceptibility to HIV infection, with genital ulcerative diseases (syphilis, chancroid, genital herpes) having larger effects than non-ulcerative infections (gonorrhea, chlamydia, and trichomonas) (Padian et al., 2008). The presence of bacterial vaginosis is also associated with increased acquisition of HIV (Expert working group for the guidelines on sexually transmitted infections, 2008). The Canadian guidelines for the treatment of STIs, including antimicrobial therapy, provide 2006 guidelines that were revised in 2008 (Expert working group for the guidelines on sexually transmitted infections, 2008).

Syndromic management of STIs is based on the identification of a group of symptoms and easily recognized signs associated with infection with well-defined pathogens (WHO, 2007).

Treatment for each syndrome is directed against the main organisms within that geographical setting responsible for the syndrome. Syndromic management is used primarily in resource-poor settings lacking proper laboratory facilities. In developed countries, syndromic therapy is not primarily recommended due to the availability of reliable and affordable diagnostic tests (Sobel, 1999). A comprehensive case management of STIs comprises identification of the syndrome, antimicrobial treatment for the syndrome, education of the patient, condom supply, counseling, and notification and management of sexual partners (WHO, 2003).

There is limited evidence from RCTs for STI control as an effective prevention strategy for HIV at the community-based level (Sangani, Rutherford, & Kennedy, 2009). A review of three RCTs that examined population-based interventions for STI control (Sangani et al., 2009) showed that in Rakai (Uganda), after three rounds of mass antibiotic treatment every 10 months, the adjusted

odds ratio (AOR) of HIV incidence in the intervention versus control was 0.97 (95% CI = 0.81-1.16); in Mwanza (Tanzania), for syndromic management provided through the existing primary health care clinics, the adjusted relative risk (RR) for HIV incidence was 0.58 (95% CI = 0.42-0.70); in Masaka (Uganda), the rate ratio after three rounds of follow-up of treatment versus control was 1.00 (0.63-1.58, $p = 0.98$). Therefore, only one trial demonstrated a decreased HIV IR in a particular environment of an evolving immature epidemic where there was poor STI treatment and STIs were highly prevalent (Sangani et al., 2009).

1.4.2 Structural interventions

Structural approaches aim to change the social, economic, political, or environmental factors that determine HIV risk and vulnerability in specified contexts (Gupta et al., 2008). An example of a structural approach for HIV prevention in IDU involves the creation of a policy and legal environment allowing syringe and needle exchange. These factors commonly require a shift in policy in contexts where the use of certain drugs is illicit (Gupta et al., 2008). The inclusion of IDU in the design of such programs can further increase the programs' effectiveness. Drug control policies that stigmatize and marginalize drug users can act as barriers to medical and social services and foster behaviors such as sharing equipment and sex work.

Harm Reduction

Harm reduction means that reducing the negative consequences of psychoactive drug use is considered even more important than reducing illicit drug consumption (Wodak & McLeod, 2008). Harm reduction measures in IDU consist of education, needle syringe programs, and drug treatment (especially opiate substitution treatment) (Wodak & McLeod, 2008). It also

consists of improving the basic social conditions of IDU, including general health, housing, welfare, and employment. Needle syringe programs and opiate substitution are regarded as the hallmarks of harm reduction.

Needle exchange

Providing access to and encouraging utilization of sterile needles and syringes for IDU is considered a key component of any HIV prevention program (Wodak & Cooney, 2005). Wodak & Cooney (2006) published a review in which the Bradford Hill criteria³ were used to evaluate needle or syringe exchange programs internationally. Needle syringe programs for lowering HIV infection fulfilled six of the nine Bradford Hill criteria including strength of association and temporal sequence, and there was no convincing evidence of any major negative consequences. Earlier reviews by Gibson et al. (2001) and Ksobiech (2003) reached similar conclusions. In sum, it is evident that needle syringe programs reduce HIV incidence and HIV prevalence by reducing risk behavior (Wodak & Cooney, 2006).

Methadone maintenance therapy

The contribution of opioid use to the transmission of HIV is significant, as nearly one-third of new HIV infections outside of sub-Saharan Africa are due to injection drug use (Gowing, Farrell, Bornemann, Sullivan, & Ali, 2009). Methadone is the medication that is most commonly used

³ Wodak & Cooney (2006) suggested nine Bradford Hill criteria: strength of association, replication of findings, specificity of association, temporal sequence, biological plausibility, biological gradient, experimental evidence, reasoning by analogy, and coherence

for substitution therapy of opioid dependence to prevent HIV in IDU (WHO/United Nations Office on Drugs and Crime [UNODC] /UNAIDS, 2004). Other forms of substitution treatment include buprenorphine, morphine, dihydrocodeine, and diacetylmorphine (Oviedo-Joekes et al., 2009). A recent systematic review found that methadone maintenance therapy (MMT) for IDU significantly reduced injection drug use, the frequency of injection, sharing of injection equipment, multiple sexual partners, and commercial sex work, but resulted in little change in unprotected sex (Gowing et al., 2009). Studies in this review demonstrated that MMT has not always been successful at retaining patients in treatment for prolonged periods (Oviedo-Joekes et al., 2009). Lack of adherence may be due to people receiving less than the minimum effective dose of methadone, the development of side effects, and severe withdrawal.

The WHO, UNODC, and UNAIDS have developed a joint position on substitution maintenance therapy for opioid dependence (WHO/UNODC/UNAIDS, 2004). The position paper covers the rationale and recommendations for this treatment modality, with specific considerations regarding its provision for people with HIV/AIDS.

Heroin assisted treatment

Heroin assisted treatment (HAT) has been postulated for addicts who do not benefit sufficiently from MMT or buprenorphine substitution therapy (ie. are treatment resistant). Randomized trials have been conducted in several countries including Switzerland, the Netherlands, Germany, Spain, the United Kingdom, and Canada (Gartry, Oviedo-Joekes, Laliberte, & Schechter, 2009). Heroin assisted treatment is an option for treatment-resistant patients in several European countries (eg. Switzerland, the Netherlands, Germany, United Kingdom, Denmark). One benefit

of HAT that has been shown is that it reduced participants' use of illegal drugs (Gartry et al., 2009).

1.4.3 Behavioral Interventions

Goals for behavioral strategy include counseling to increase knowledge, stigma reduction, access to services, delay of onset of first intercourse, increases in condom use, and decreases in sharing needles and syringes (Coates et al., 2008). Multilevel behavioral approaches can focus on individuals, couples, families, peer groups or networks, institutions, and communities (Coates et al., 2008). Certain behavioral interventions have shown to be effective in reducing risk behaviors. A list of effective behavioral interventions and results through 2009 is provided by the Centers for Disease Control and Prevention (CDC, 2009).

1.5 STAGES OF HIV VACCINE DEVELOPMENT

Animal models are used initially in the first stages of vaccine development. The animal models that have been used for the purpose of HIV vaccine development include non-human primate models such as rhesus macaque challenge models (Puls & Emery, 2006). Subsequently, several HIV vaccines have been examined in phase 1, phase 2 and phase 3 trials since 1987 (Ackers et al., 2003). **Phase 1** trials involve small numbers of low-risk volunteers to primarily test the safety of the product. **Phase 2** trials are used to further test safety as well as the immunogenicity of the product. **Phase 2B** (proof-of-concept) trials involve a smaller number of volunteers than phase 3 trials and can determine a preliminary assessment of efficacy. They can guide future research efforts, but are not enough for licensure of a vaccine (Buchbinder et al., 2008). **Phase 3** trials involve thousands of high-risk individuals to test the effectiveness of HIV

vaccines on HIV incidence in diverse populations. Currently, there are no licensed preventive (in HIV-negative participants) or therapeutic (in HIV-positive participants) HIV vaccines. A standard of licensure for vaccine efficacy-susceptibility is a vaccine efficacy of $\geq 30\%$ in a phase 3 HIV vaccine trial (Follmann et al., 2007).

1.6 HIV VACCINE PREVENTIVE TRIALS

Phase 3 preventive trials have taken place in both the Organization for Economic Co-operation and Development (OECD) countries (eg, US, Canada) (Dhalla, Woods, Strathdee, Patrick, & Hogg, 2007) and the non-OECD countries (eg. Thailand) (Dhalla, Nelson, Singer, & Poole, 2009), including the AIDSVAX B/B (VaxGen) HIV vaccine trial (North America, Europe), and the AIDS VAX B/E (VaxGen) HIV vaccine trial in IDU (Thailand) (Francis et al., 2003). These trials did not demonstrate efficacy of the tested vaccines. The failure of the phase 2B STEP study dealt a blow to HIV vaccine trial development (Buchbinder et al., 2008). This study of 3000 HIV-negative participants, using the Merck adenovirus 5 (MRKAd5) HIV-1 vaccine, was conducted in North America, South America, the Caribbean, and Australia in high-risk populations. This trial, which was halted in 2007, showed that the vaccine was not efficacious and that there was an increased HIV IR in those who received the vaccine and had high pre-existing adenovirus immunity (Buchbinder et al., 2008). The Phambili trial in South Africa, using the same vaccine, was also halted in 2007 due to concerns emanating from the STEP study (HIV Vaccine Trials Network [HVTN] 503). However, a recently completed phase 3 HIV vaccine trial in Thailand consisting of 16,000 community-based volunteers of any risk level that tested the vaccine vCP1521 given as the “prime” vaccine and AIDSVAX B/E vaccine given as the “boost” (US Military [HIV]) Research Program) showed promising results. The results of

this study showed the vaccines to be safe and also 31.2% effective at preventing HIV infection, a modest level of efficacy (Rerks-Ngarm et al., 2009).

1.7 HIV VACCINE THERAPEUTIC TRIALS

Therapeutic vaccine trials have also taken place in various countries using products such as Remune (Salk HIV-immunogen) (Kahn, Cherng, Mayer, Murray, & Lagakos, 2000), rgp160 (Sandstrom & Wahren, 1999), and the canarypox vaccine vCP1452 (Kinloch et al., 2009). A therapeutic vaccine would potentially slow the progression of HIV, but there was no success with Remune in a therapeutic phase 3 HIV vaccine trial (Kahn et al., 2000).

1.8 HIV VACCINE PREPAREDNESS

Many HIV vaccine preparedness studies (VPS) have taken place in various populations in both the OECD (“developed”) (Dhalla et al., 2007) and the non-OECD (“developing”) countries (Dhalla et al., 2009). Vaccine preparedness studies are important as a precursor to actual vaccine trials as they assess the feasibility of vaccine trials (Seage et al., 2001). These studies can provide information with respect to HIV seroincidence; recruitment and enrolment strategies; retention and determinants of retention; willingness to participate (WTP) and determinants of WTP in a trial; and knowledge of vaccine trial concepts. These studies can also address social factors such as motivations (eg. altruism) and barriers (eg. stigma) in relation to WTP in an HIV vaccine trial (Dhalla et al., 2007).

1.9 COGNITIVE FACTORS

Cognitive factors can also be important in the implementation of a vaccine trial. The cognitive

factors examined in this dissertation include HIV treatment optimism, self-efficacy beliefs regarding an HIV vaccine trial, and knowledge of HIV vaccine trial concepts. *Optimism* is defined as the “hopefulness and confidence about the future or the success of something” (Soanes & Stevenson, 2005). *Self-efficacy* is defined as “people’s judgement of their capabilities to organize and execute courses of actions required to attain designated types of performances, and is concerned with what one can do with whatever skills one possesses” (Bandura, 1986). *Knowledge* is defined as the “information and understanding of a specific topic or of the world in general, usually acquired by experience or learning” (VandenBos, 2007). These concepts may be important for enrolment purposes and WTP in a vaccine trial. The assessment of knowledge is important in the process of educating people during an HIV vaccine trial to increase WTP, as well as for obtaining ethically-mandated ongoing informed consent (Koblin, Holte, Lenderking, & Heagerty, 2000). To our knowledge, self-efficacy has not been examined in IDU with respect to WTP in an HIV vaccine trial, and optimism and knowledge have been examined in few studies in other populations and in different settings; therefore, the relationship between these cognitive factors and WTP is worthy of additional study in IDU.

1.10 MOTIVATORS AND BARRIERS

Motivations and barriers with regards to HIV vaccine trials have been examined in several studies using IDU populations, both in the OECD and the non-OECD countries. Peters (2006) suggests that the information derived from examining these factors can be used to improve the way HIV vaccine studies are presented to volunteers and to provide better support through an actual vaccine trial.

1.10.1 Motivators/Incentives

Potential motivators to participation in an HIV vaccine trial include (1) altruism (2) protection against HIV infection (3) free insurance and medical care and (4) monetary incentives (Newman et al., 2006). “Altruism” in this context is defined as how participation in a preventive HIV vaccine trial would help groups beyond the self, such as the community, family, or society at large (Strauss et al., 2001).

Altruism was found to be a primary motivating factor in IDU for participation in an HIV vaccine trial taking place in the OECD countries such as the US (Koblin et al, 1998; Strauss et al., 2001), and in one Italian study that consisted of some IDU participants (Starace et al., 2006). Altruism was also found to be the main motivating factor in the majority of studies in IDU in the non-OECD countries (MacQueen et al., 1999; Suhadev et al., 2006). In a study in Thailand (MacQueen et al., 1999) involving IDU, altruism was ranked highly (78.6% of people) as an important motivation for participation in an HIV vaccine trial (MacQueen et al., 1999). Similarly, in a study that was recently conducted in India and that included IDU as participants (Suhadev et al., 2006), almost all (98%) agreed that their participation in a HIV vaccine trial was important for the common good of India.

Monetary incentives as a self-benefit were also found to be an important factor in relation to participating in an HIV vaccine trial in IDU (Golub et al., 2005).

1.10.2 Barriers

Potential barriers to participation for IDU in an HIV vaccine trial include (1) uncertainty about

vaccine efficacy (2) safety concerns such as side effects and fear of contracting HIV from the vaccine (3) fear or mistrust of the government, researchers, and the research process (4) concerns or misunderstandings about study design (5) discrimination/social risks such as vaccine-induced seropositivity and (6) pragmatic obstacles including problems with travel or immigration or problems with insurance (Mills et al., 2004).

A study by MacQueen and colleagues (1999) among IDU in Thailand found that 31.2% of participants ranked the following barrier as a “major problem”: “There is a slight chance that people who become infected with HIV after receiving the vaccine will develop AIDS more quickly than people who are not vaccinated”. In a study that was recently conducted in India and that included IDU as participants, the most frequently rated barriers regarding future HIV vaccine trials were questions about vaccine efficacy and safety (Suhadev et al., 2006). Another study found that possible problems with health or life insurance and problems with travel to foreign countries in IDU were frequently cited barriers (Koblin et al., 1998). In the latter study, those who mentioned these factors as important were less likely to be WTP than those who did not mention these factors as important.

In the only phase 3 HIV vaccine trial in IDU that took place in Thailand (AIDSVAX B/E vaccine), 37/2545 (1.5%) of trial participants reported a total of 39 social harms, with the majority (84.6%) being disturbances in personal relationships (friends, family, or a partner thinking that the volunteer was HIV-positive) (Pitisuttithum et al., 2007). Any social harms were typically resolved with counseling by trial staff before the end of the trial (Pitisuttithum et al., 2007).

1.11 OBJECTIVES OF THESIS

This dissertation consists of both a preventive and therapeutic HIV VPS and cross-sectionally examines determinants of WTP in a hypothetical HIV vaccine trial in IDU in Vancouver, Canada. The participants were part of the Vancouver Injection Drug Users' Study (VIDUS) (HIV-negative active injectors) and the AIDS Care Cohort to Evaluate Exposure to Survival Services Study (ACCESS) (HIV-positive IDU). For the study, 276 HIV-negative IDU and 85 HIV-positive IDU were recruited. The determinants examined include cognitive factors and risk variables, the former including HIV treatment optimism, self-efficacy beliefs, and knowledge of HIV vaccine trial concepts.

The objectives of this cross-sectional study were: 1) To determine how selected cognitive factors predict WTP in a hypothetical preventive HIV vaccine trial of HIV-negative IDU 2) to determine how WTP is affected by other risk factors, including sociodemographic factors, HIV risk behaviors, experiences in addiction treatment, and psychosocial factors 3) to determine how cognitive and other factors predict WTP in a hypothetical therapeutic vaccine HIV vaccine trial of HIV-positive IDU.

1.12 QUESTIONNAIRE DEVELOPMENT

A questionnaire supplemental to the main questionnaire used in the VIDUS and ACCESS cohorts was developed, assessing the cognitive factors of self-efficacy and knowledge levels of participants and their WTP in an HIV vaccine trial. The two HIV treatment optimism statements were already part of the main questionnaire (which was administered prior to the supplemental questionnaire). These treatment optimism items were measured on a Likert scale from

1 (strongly agree) to 5 (strongly disagree) for each item (Appendix A).

The self-efficacy items consist of five items (Appendix A), which were developed from a previous study in which self-efficacy was measured in the context of discontinuation of HAART in IDU (Kerr et al., 2005). The 10 knowledge items (possible responses: true/false/don't know) measuring HIV vaccine trial concepts were taken from a study by Koblin et al. (2000) who measured knowledge related to WTP in a longitudinal HIV vaccine trial in IDU and MSM (Appendix A). Apart from the Koblin scale, it should be noted that other knowledge scales have been used in other studies to determine the relationship between knowledge and WTP (Smit, Middelkoop, Myer, Seedat, Bekker, & Stein, 2006; Starace et al., 2006).

1.13 THESIS CHAPTERS

Chapters 2 and 3 examine determinants of participation in an HIV vaccine trial in the OECD (Dhalla et al., 2007) and the non-OECD (Dhalla et al., 2009) countries in two separate review articles. The OECD and the non-OECD countries are examined separately for comparability. The chapters provide an in-depth review of populations previously examined in phase 3 vaccine trials. The emphasis in these review articles is put on 1) retention rates 2) WTP in an HIV vaccine trial 3) cognitive factors and their relationship to WTP and 4) motivators and barriers to participation. These studies also examine risk variables and thus provide information about the feasibility of conducting HIV vaccine trials. The chapters also reflect the differences in populations examined in VPS. The non-OECD countries contain different populations of interest compared to the OECD countries; for example, commercial sex workers (CSW), transport workers, military conscripts, and serodiscordant couples have been examined in the

non-OECD countries (Dhalla et al., 2009). These chapters are included to illustrate the range in retention rates and WTP across a variety of settings. Chapters 4 and 5 explore factors that may predict WTP in one particular setting.

In Chapter 4, the cognitive factors of HIV treatment optimism, self-efficacy, knowledge of vaccine trial concepts, and risk behaviors relating to WTP were examined in HIV-negative IDU using the VIDUS study. To our knowledge, self-efficacy has not been previously described in relation to WTP in an HIV vaccine trial, in HIV-negative or HIV-positive IDU. Knowledge has been examined in few studies in HIV-negative IDU, with conflicting results (Halpern, Metzger, Berlin, & Ubel, 2001; Koblin et al., 2000). Knowledge is important to examine, as educating participants on vaccine trial concepts may increase WTP in an HIV vaccine trial.

Comprehension is also an important factor for informed consent.

In Chapter 5, the same factors listed above were examined in relation to WTP in HIV-positive individuals using the ACCESS study. To our knowledge, there have been no previously conducted therapeutic VPS in HIV-positive individuals. We saw value in conducting a therapeutic VPS in order to examine cognitive factors associated with WTP to inform enrolment strategies into a therapeutic HIV vaccine trial.

Chapter 6 is the concluding chapter, addressing the contribution of the VPS to the current literature. The chapter compares findings between Chapters 4 and 5, discusses strengths and weaknesses of the studies, implications, and future directions.

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Chapter 2

HIV vaccine preparedness studies in the organization for economic co-operation and development (OECD) countries

2.1 INTRODUCTION

Since the HIV epidemic began in the early 1980s, there have been an estimated 60 million cases worldwide (Joint United Nations Programme for HIV/AIDS [UNAIDS], 2008). The development of an effective preventive HIV vaccine is, therefore, an urgent public health priority. Many HIV vaccine trials have been sponsored in high and low income countries since 1987 by the National Institute for Allergy and Infectious Diseases (NIAID) in the United States (US) (Ackers et al., 2003). These include preventive and therapeutic HIV vaccine trials. A vaccine preparedness study (VPS) assesses feasibility or practicability of a vaccine trial and should ideally be a precursor of a vaccine study (Seage et al., 2001). Recruitment, retention, and willingness to participate (WTP) can be assessed by a VPS, and can determine whether a vaccine trial can be conducted successfully.

For preventive HIV vaccine trials, it is essential to attract high-risk candidates who can be retained (Koblin, Taylor, Avrett, & Stevens, 1996). If the HIV incidence rate (IR) is too low, a phase 3 preventive trial would be uninformative because the sample size required would be too large for an effect to be shown. Typically, an HIV seroincidence below 2% is considered

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too low to detect an appreciable effect size in most studies (Rida, Fast, Hoff, & Fleming, 1997). In a population with an HIV seroincidence of 2% per year, a phase 3 clinical trial would require approximately 3000 participants per arm recruited over a one-year period and observed for an additional period of two-and-a-half years (Rida et al., 1997; Seage et al., 2001). The bias introduced from competing risks presents another problem (Seage et al., 2001). If mortality rates from other causes are too high, HIV seroconversion will be lower than expected. Participants must also remain at sufficiently high risk despite other risk-reduction interventions (Koblin et al., 1996), such as ethically mandated HIV pre- and post-test counseling. HIV seroincidence rates may also be influenced by introducing highly active antiretroviral therapy (HAART) or through other interventions such as needle exchange programs (Seage et al., 2001). A cohort effect, in which there would be a saturation of HIV infection of those at the highest risk, could also affect HIV seroincidence (Seage et al., 2001). In summary, conducting a trial when the HIV seroincidence is low would make it impossible to detect a real difference between the vaccine and placebo.

A number of HIV VPS have been conducted to examine recruitment, retention, (Table 2.1) and WTP (Table 2.2) in HIV vaccine trials. The majority of these have been in HIV-negative individuals. Participants included injection drug users (IDU), men who have sex with men (MSM), and women at heterosexual risk (WAHR).

There is one completed HIV phase 3 vaccine trial that was carried out in the US, Canada, and Puerto Rico, ending in 2003 (Francis et al., 2003). This clinical trial of the HIV vaccine rgp120, called the AIDSVAX B/B (VaxGen 004) study, involved MSM [n=5100] and WAHR [n=300]

at centers in these three countries. The population used in this study, however, is ineligible for future studies. A phase 2B preventive HIV vaccine multi-centre study that is currently in progress in high-risk participants is the phase 2B Merck / HIV Vaccine Trials Network (HTVN) collaboration in the US, Canada, Australia, the Dominican Republic, Haiti, and Peru (STEP study, 2007). This is testing a replication defective adenovirus vaccine with an HIV gene insert.

The objective of this paper was to provide a systematic review of HIV VPS to identify factors important for HIV vaccine development in IDU, MSM, and WAHR from the generally high-income nations of the Organization for Economic Co-operation and Development (OECD). We attempt to summarize a wide body of information on HIV VPS, and also discuss current vaccine trials, as both may be useful for those requiring an in-depth summary of this research.

2.2 METHODS

In 2006, two people independently searched the Cochrane Database for Systematic Reviews, Medline (1966 to 2006), Pubmed, and Embase (1980 to 2006) using the search terms: 'HIV' and 'vaccine preparedness', and 'HIV vaccines'. These terms were also searched with respect to the individual 30 Organization for Economic Co-operation and Development (OECD) countries. Thirty-eight abstracts were retrieved from Medline, 104 from Pubmed, and 188 from Embase. Additional articles were retrieved from bibliographic references. Articles were included if they were: 1) published in a peer-reviewed journal; 2) took place in the OECD areas.

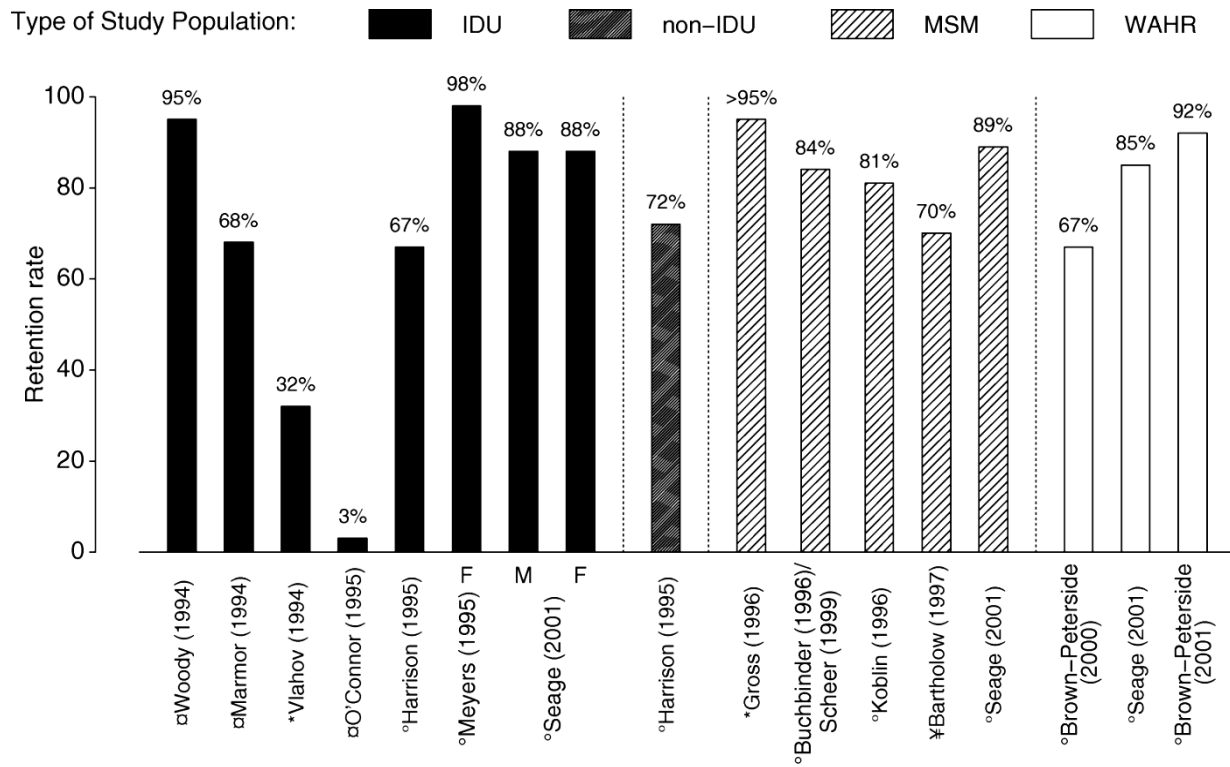
Information on the study population, location, and sample size was extracted from the text and tables of the articles, and then tabulated in our review to describe retention and WTP of VPS participants. Retention rates and WTP reported from the reviewed studies, and any predictors found to be associated with WTP, were included in the appropriate table. The subject information collected varied from study to study, and thus the models used to determine factors associated with subject retention and WTP differed between studies. We have presented a summary measure of association (e.g. adjusted odds ratios [AOR]) for any variables found to be associated with WTP. Willingness to participate and retention rates were also plotted by the study population (IDU, MSM, WAHR) using barplots.

2.3 RESULTS

There were no systematic reviews on the Cochrane database. A total of 27 studies assessed recruitment, retention, or WTP, and were included in this review. For retention rates, eight studies involved IDU, six involved MSM, and three involved WAHR (Table 2.1, Figure 2.1). The mean sample size was 423 for IDU, 1700 for MSM, and 254 for WAHR. For the WTP studies, eight studies involved IDU, 11 involved MSM, and only one involved WAHR (Table 2.2, Figure 2.2). The mean sample size was 434 for IDU, 1017 for MSM, and 509 in the one study of WAHR. The study by Starace et al. (2006) on WTP in Italy was not used for calculations, as data regarding the breakdown of IDU, MSM, and WAHR were not available. Only at-risk or non at-risk data were recorded in their database.

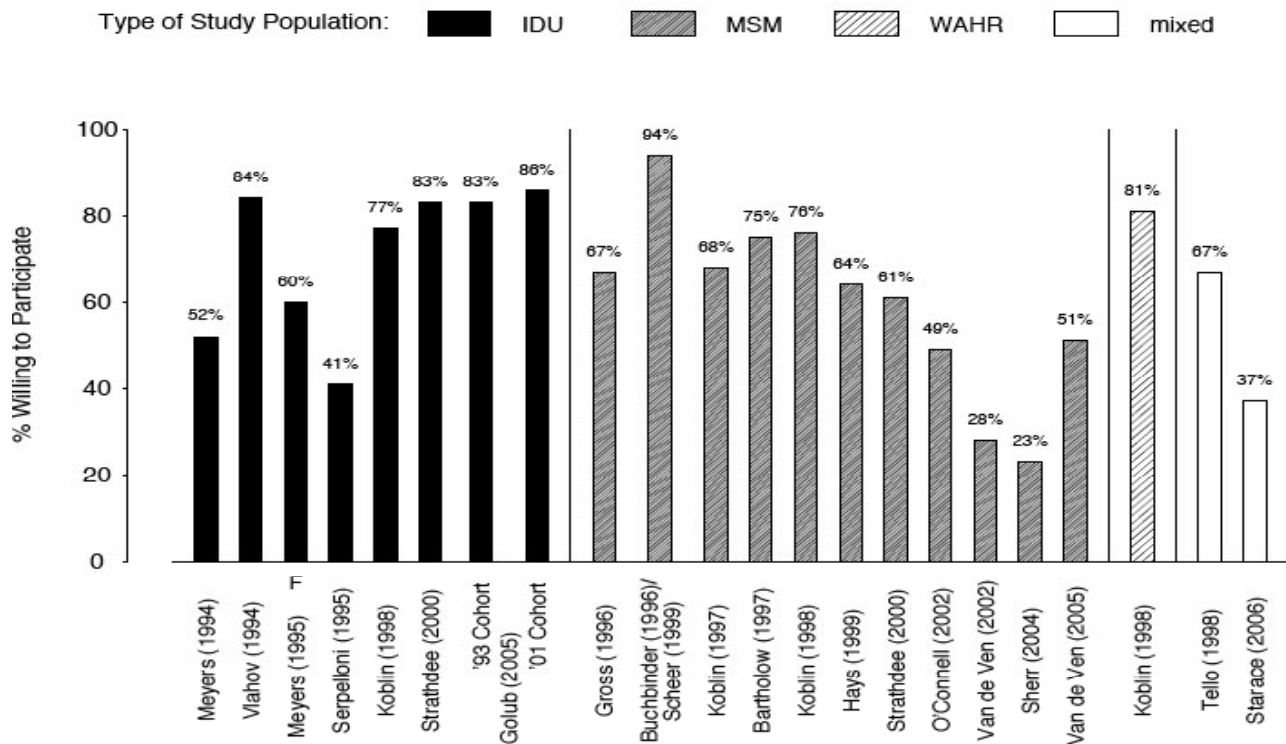
Many VPS have taken place in the OECD countries, dating back to 1992 (Tables 2.1 and 2.2; Figures 2.1 and 2.2). The majority of the studies have taken place in the US, with others in Canada, European countries, and Australia. These VPS have been carried out in cities with high HIV seroincidence rates such as Baltimore, New York, San Francisco, and Vancouver.

Figure 2.1 *Barchart of published retention rates from reviewed vaccine preparedness studies.*



*, α, °, ¥ represent 6, 9, 12 and 18-month retention rates respectively

Figure 2.2 *Barchart of published willingness to participate rates from reviewed vaccine preparedness studies.*



2.3.1 Retention

Retention rates are shown in Table 2.1 and Figure 2.1. Retention refers to completion of study visits in an HIV VPS for follow-up interviews, counseling, and HIV antibody testing. Studies on retention in the OECD countries have only taken place in the US. For retention at 12 months, IDU overall were found to be retained at a range of 67-98%, MSM at 84-89%, and WAHR at 67-92% (Figure 2.1, Table 2.1). Some of the reviewed studies did not provide a 12-month retention rate and thus Figure 2.1 presents retention at either 6, 9, or 18 months for the studies for which a 12-month rate was not provided. In most studies, IDU including both male and female IDU, MSM, and WAHR appeared to be well retained. However, in one study in Baltimore by Vlahov et al. (1994), the 6-month retention rate was only 32%. In addition, in another study in New

Haven, Connecticut by O'Connor et al. (1995), the 9-month retention rate was only 3% in IDU, an outlier with respect to the other studies. Possible reasons included a combination of unstable housing of the participants and the fact that the project had to change sites 4 months into the study. Other possible reasons included the sex (70% male) and the race/ethnicity (50% non-Caucasian) of the participants. For IDU and MSM, it was apparent that males (IDU), younger subjects, those with non-white race/ethnicity, and those who were less educated, were most likely to be lost to follow-up (Bartholow et al., 1997; Brown-Peterside, Chiasson, Ren, & Koblin, 2000; Brown-Peterside et al., 2001; Buchbinder et al., 2004; Harrison, Vlahov, Jones, Charron, & Clements, 1995; Koblin et al., 1996; Marmor et al., 1994; O'Connor et al., 1995; Scheer et al., 1999; Seage et al., 2001; Woody, Metzger, & Mulvaney, 1994).

Seage et al. (2001) found in the HIVNET VPS that there was no significant difference between MSM, and male and female IDU in loss to follow-up. Women at heterosexual risk were more likely to be retained (AOR = 0.64, 95% CI = 0.43-0.94) than MSM (AOR = 1.00), when adjusting for confounding of site, frequency of moving, and unstable housing. This was an interesting finding because the raw retention for WAHR (15% lost, crude OR=1.42) was less than that for MSM. It was only after adjusting for these variables that we see WAHR were better retained than MSM (Seage et al., 2001). With respect to WAHR, Brown-Peterside et al. found better retention rates in their 2001 study than in their 2000 study involving WAHR located in South Bronx, New York City. In the 2001 study, retention was made a larger priority. For example, contact information regarding each participant's physician and case manager was collected, and appointment times were made flexible.

2.3.2 Willingness to participate

Table 2.2 shows self-reported WTP for a hypothetical HIV vaccine trial for IDU, MSM, and WAHR groups as well as determinants of their participation. The different studies allowed the participants to indicate their WTP to various degrees (e.g. 'very interested in participating', 'somewhat interested in participating', etc.). We have grouped together all responses indicating some WTP into our overall WTP for a given study. In general, a large number of participants demonstrated interest in being included in HIV vaccine trials. Overall, WTP ranged in IDU at 41-86%, MSM at 23-94%, and WTP in the one study involving WAHR was at 81% (Figure 2.2, Table 2.2). Willingness to participate was less in non-North American studies (UK, Italy, and Australia) compared to studies in the US and Canada (Table 2.2, Figure 2.2). The majority of studies that assessed WTP were in HIV-negative individuals. Exceptions were in the studies by Hays & Kegeles (1999), Serpelloni et al. (1995) (untested), Tello et al. (1998) (untested), (HIV-negative /untested), and Van de Ven et al. (2002) (HIV-negative/untested).

In some studies, high-risk behaviours such as sharing needles (Meyers et al., 1995; Meyers, Metzger, Navaline, Woody, & McLellan, 1994), frequent injections (Vlahov et al., 1994), attendance of needle exchange programs (Strathdee et al., 2000), and commercial sex work (Koblin, Avrett, Taylor, & Stevens, 1997; Meyers et al., 1995) were found to be related to a greater WTP (Table 2.1). Similarly, other high-risk behaviours, such as sex with an HIV-positive partner (Koblin et al., 1998) or with a casual partner (O'Connell et al., 2002), unprotected anal intercourse (Hays & Kegeles, 1999; Koblin et al., 1998; Sherr, Bolding, & Elford, 2004; Van de Ven et al., 2005), and perceived exposure to HIV (Bartholow et al., 1997; Strathdee et al., 2000; Van de Ven et al., 2005) were also related to increased WTP. Importantly,

in one study, monetary incentives were positively associated with WTP (Golub et al., 2005). In addition, two studies showed that there are people who are optimistic regarding HIV treatment (IDU) (Golub et al., 2005) and HIV vaccines/vaccine trials (gay men) (Van De Ven et al., 2002), and that these people are willing to participate in HIV vaccine trials. Another study consisting of gay men who were part of an older age group, found that those who were optimistic about HIV vaccine development, measured by the number of years the respondent felt it would take for a vaccine to be available for public use, were more willing to participate in an HIV vaccine trial than those who were not optimistic (Gross et al., 1996).

Other studies have examined changes in WTP. A study by Koblin et al. (2000) examined this in IDU, MSM, and WAHR, and found that WTP was significantly lower at the follow-up visits of 6, 12, and 18 months, compared to baseline WTP. The change in WTP was not significantly different between the study groups. In Baltimore, Golub et al. (2005) reported that 189 Wave 1 IDU participants in 1993-1994 went on to participate in Wave 2 in 2001-2002. Among these participants, 16.1% went from willing to participate in Wave 1 to not willing to participate in Wave 2, while 83.9% were willing at both waves. Those IDU who completed Wave 2 were less likely to have injected ($p<0.001$), shared needles ($p<0.001$), had a sexually transmitted disease (STD) ($p=0.012$), or had multiple sex partners in the past six months ($p<0.001$), than those who did not (Golub et al., 2005). However, the limitation of this study was that it could only examine factors associated with WTP for those who were followed up.

One VPS conducted in New York City assessed WTP in a site which was enrolling patients in an ongoing HIV vaccine trial. Koblin et al. (1997) conducted a study in MSM at this site, during

which time the NIAID recommended not proceeding with HIV vaccine efficacy trials of the rgp120 vaccine. Willingness to participate in a vaccine trial using the rgp120 vaccine was assessed before, during, and after the NIAID recommendation was issued. Compared to the baseline group who were enrolled during the NIAID recommendation, those enrolled before the recommendation had an AOR of 2.1 (95% CI = 1.3-3.4) for WTP in an HIV vaccine efficacy trial, while those enrolled after had an AOR of 1.7 (95% CI = 1.1-2.7) (Koblin et al., 1997). This indicates a higher WTP in these two periods compared to the baseline group.

In Vancouver, the later 2001 VPS in gay and bisexual men was also done in the context of an ongoing international AIDSVAX B/B (VaxGen) phase 3 preventive trial, although these participants were excluded from the analysis (O'Connell et al., 2002). There were 100 rollover MSM participants who completed questionnaires both in 1997 and 2001 (O'Connell et al., 2002; Strathdee et al., 2000). Comparing WTP in 2001 with that in 1997, 24% who had previously been willing to participate were now not willing to participate. For 73% of participants, WTP responses remained the same. Self-reported willingness to enrol among MSM in 1997 did not translate into actual enrolment into the AIDSVAX B/B trial as measured in 2001 (O'Connell et al., 2002).

In 2004, Buchbinder et al. also compared hypothetical vs. actual willingness and barriers to participation in a preventive HIV vaccine trial. From May 1997 through January 1998, 233 participants consisting of IDU, MSM, and WAHR, were recruited from the HIVNET VPS into a National Institutes of Health (NIH) sponsored phase 2 randomized controlled trial (RCT) of ALVAC-vCP205 +/- HIV-1 SF2 rgp120. Twenty-nine per cent of those who had previously

stated they would be definitely willing to participate in a future phase 2 trial refused enrolment in this phase 2 trial. However, results from the recent AIDSVAX B/B phase 3 HIV clinical trial suggest that MSM are willing to participate, and can be recruited and enrolled in an actual vaccine trial (Francis et al., 2003).

Importantly, it was found in one study that IDU, MSM, and WAHR who were definitely willing to participate in a future vaccine trial had the highest HIV seroincidence rate at 1.96/100 p-yrs (Seage et al., 2001). This was in comparison to those who were either probably willing to participate or not willing.

2.4 DISCUSSION

In our review, we report 17 studies examining retention and 22 studies examining WTP in IDU, MSM, and WAHR. Our review shows that, in all populations, high-risk people were more willing to participate in HIV vaccine trials than lower-risk people, with the exception of the study by Golub et al. (2005). This is important in a preventive trial, as high-risk people are more likely to seroconvert; otherwise, the sample size required for an HIV vaccine study would be too large or follow-up would be required for too long. Of concern, WTP has decreased in the last few years in studies done in England, Italy, and Australia (Serpelloni, Vlahov, Mazzi, & Rezza, 1995; Sherr et al., 2004; Starace et al., 2006; Van De Ven et al., 2002; Van de Ven et al., 2005), and this must be taken into consideration prior to carrying out HIV vaccine trials. The decrease in the above areas may be confounded by the fact the studies took place at later dates.

We report only one study of WTP in WAHR (Koblin et al., 1998), and more of these studies are required. This is a group that must continue to be enrolled in future studies to obtain estimates of vaccine efficacy in women. For recruitment, the sample sizes in the various studies were adequate for a VPS, but larger sample sizes would be required for phase 3 clinical trials.

Retention should also be made a priority in clinical trials in all three risk groups. The VPS we have reported have the longest follow-up of 18 months (Bartholow et al., 1997; Brown-Peterside et al., 2000; Buchbinder et al., 1996; Harrison et al., 1995; Scheer et al., 1999; Seage et al., 2001), and phase 3 clinical trials would require even longer follow-up of patients. As well, other VPS should be conducted in HIV-positive people as a preparation for therapeutic vaccine studies, to determine predictors of participation in this group of people.

In studies that examined motivators for enrolment, altruism was overall the biggest motivator to participate (Buchbinder et al., 2004; Koblin et al., 1998), although this may be more a reflection of social desirability (Starace et al., 2006). Altruism was assessed by the use of open-ended answers (Koblin et al., 1997), the use of a four-point scale (Koblin et al., 1998), or picking from a selection of eight answers (Buchbinder et al., 2004). In one study, it was defined as “helping the community” (Koblin et al., 1997), while in the other two studies, it was commonly expressed as “helping to find a vaccine that works” (Buchbinder et al., 2004; Koblin et al., 1998). With respect to other motivators, only 5% listed compensation as a motivator to participate in the study by Hays & Kegeles (1999), although in the study by Golub et al. (2005), monetary incentives for participation were important.

Disincentives have included vaccine safety, negative side-effects, vaccine-induced seropositivity, and fear of contracting HIV or AIDS from the vaccine (Mills et al., 2004). In a first published systematic review of 26 studies examining barriers to WTP, it was found that vaccine safety was the most important concern among those who would participate in preventive HIV vaccine trials (Mills et al., 2004). In the AIDSVAX study, disturbances in personal relationships were cited as the most important social impact, often resulting from negative comments from family and friends, or misperception that the volunteer might be HIV infected (Jermano, 2000). As another point, breakthrough infections have been interpreted by participants to mean that vaccine caused infections (Bartholow et al., 1997). This also underlines the necessity of education and testing of knowledge of basic trial concepts before enrolment. Increased knowledge may be associated with an increased WTP (Meyers et al., 1995). It is also important as part of an informed consent process among these marginalized and vulnerable populations.

There are some limitations of the studies included in this review. First, differences in WTP may be because surveys are self-administered versus interview-administered (Strathdee et al., 2000). Interview-administered questionnaires may result in more socially desirable reporting. The differences in instruments utilized to assess WTP may have influenced the answers of participants. Second, because of self-selection, results may not be generalizable to other similar populations (Bartholow et al., 1997; O'Connell et al., 2002). As well, those who participate in a VPS may be those who have been involved in other HIV research, and may, therefore, be more willing to participate in a vaccine study than those who have not been involved in such research (Golub et al., 2005; Hays & Kegeles, 1999). Third, participants may be recruited by different methods, which may impact their WTP. For example, in one study, one-third of participants were recruited from previous VPS (Koblin et al., 1998). Finally, due to the large number of VPS in both developed and developing countries, it was not possible to review all studies, and we have, therefore, limited our review to the OECD countries.

In summary, we examined recruitment, retention, and WTP in HIV VPS in the mainly high-income 30 OECD countries. A number of such studies have been conducted, although more studies of WTP would be helpful in WAHR. Educational programs to improve knowledge of vaccine trial concepts may increase WTP in actual trials. Overall, however, in the OECD countries we examined, the factors of recruitment, retention, and WTP have been sufficiently high for phase 3 preventive vaccine trials to be carried out. Such VPS also need to be conducted in HIV-positive individuals, in preparation for therapeutic HIV vaccine trials.

2.5 ACKNOWLEDGEMENTS

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Table 2.1 Retention rates for IDU, MSM, and WAHR populations

Source	Location	Study Population	Sample size	Time Period (Time Interval)	Retention
Woody, 1994	Philadelphia, PA	IDU	467	1992-1993 (9 months)	95%
Marmor, 1994	New York City, NY	IDU	577	1993-1994 (3, 6, 9 months)	69% 75% 68%
Vlahov, 1994	Baltimore, MD	IDU	375	1993-1994 (6 months)	32%
O'Connor, 1995	New Haven, CT Yale	IDU	265	1992-1993 (3, 6, 9 months)	26% 17% 3%
Harrison, 1995	Baltimore, MD Johns Hopkins	IDU (39) Non-IDU (32)	71	0 months 1 month 6 months 12 months or 18 months	100% 100% IDU, 97% non-IDU 97% IDU, 100% non-IDU 67% IDU, 72% non-IDU
Meyers, 1995	Philadelphia, PA	Female IDU	121	1991-1993 (3, 6, 9, 12 months)	97% behavioral*, 96% serological* 98%, 96% 98%, 98% 98%, 95%
Gross, 1996	Boston, MA	Gay and bisexual men (40 +/- 7.4 years)	626	August 1993 – June 1994 (6 months)	>95%
Buchbinder, 1996	Chicago, IL Denver, CO San Francisco, CA	MSM ≥18 years	2189	January 1993 – July 1994 (6, 12, 18 months)	90% 84% 78%
Koblin, 1996	New York City, NY	Gay and bisexual men ≥18 years	622	October 1993-July 1995 (3, 6, 9, 12 months)	88% 83% 81% 81%
Bartholow, 1997	Chicago, IL Denver, CO, San Francisco, CA	MSM ≥18 years	1802	January 1993 – July 1994 (18 months)	70%

Table 2.1, cont'd. **Retention rates for IDU, MSM, and WAHR populations**

Source	Location	Study Population	Sample size	Time Period (Time Interval)	Retention
Scheer, 1999	Chicago, IL Denver, CO San Francisco, CA	Gay and bisexual men ≥18 years	2189	January 1993 – July 1994 (6, 12, 18 months)	Younger men <25 years** 83% 71% 64% Older men ≥25 years** 92% 87% 81%
Brown-Peterside, 2000	South Bronx, New York City, NY	WAHR (18-60 years)	89	1995-1996 (12, 18 months)	67% 62%
Seage, 2001	8 U.S. Cities‡ (HIVNET VPS)	MSM 66.6% Male IDU 15.7% WAHR 10.4% Female IDU 7.2%	4892	1995 - 1996 (6, 12, 18 months)	Overall 88% (18 mos) § Male IDU 88% (18 mos) Female IDU 88% (18 mos) MSM 89% (18 mos) WAHR 85% (18 mos)
Brown-Peterside, 2001	South Bronx, New York City, NY	WAHR (18-60 years)	164	1998 – 1999 (3, 6, 9, 12 months)	98% 96% 96% 92%

*Collection of behavioral data and serological specimens.

**Older men higher retention than younger men (p=0.001).

‡ Boston, MA; Providence, RI; Chicago, IL; Denver, CO; New York City, NY; Philadelphia, PA; San Francisco, CA; Seattle, WA.

§Enrollment criteria, gender, study site, frequency of moving, age, education, race/ethnicity, unstable housing significantly associated with loss to follow-up on multivariate analysis.

Table 2.2 Willingness to participate and determinants of participation for a hypothetical HIV vaccine study

Source	City (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
Meyers, 1994	Philadelphia, PA	In-treatment IDU	240	52%	Shared needles/works Trust government to ensure vaccine safety	2.1 (1.2-3.7) 2.0 (1.1-3.7)
Vlahov, 1994	Baltimore, MD (1992-93)	IDU	375 118 (6 mos)	85 % (baseline) phase1 80% phase2 84% phase 3 84% 86%	Injected at least once/day Injected less than daily HIV seropositivity	87% 78% 47%
Meyers, 1995	Philadelphia, PA (1991-93)	Female IDU	121	60%	Sharing needles Commercial sex Not in treatment program Belief vaccine prevents disease	12.8 (2.3-73.3) 6.6 (1.1-40.2) 3.5 (1.1-11.5) 3.0 (1.1-8.7)
Gross, 1996	Boston, MA (1993-1994)	Gay and bisexual men	626	17% very likely 50% somewhat	(Older men 40+/-7.4 years) WTP by peers Optimism re: vaccine development (Younger men 23+/-3.0 years) WTP by peers Attracted through outreach vs. college campuses	1.07 (1.03-1.11) 0.78 (0.65-0.94) 1.05 (1.04-1.07) 2.48 (1.04-5.9)

Table 2.2, cont'd. **Willingness to participate and determinants of participation for a hypothetical vaccine study**

Source	City (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
Buchbinder, 1996	Chicago, IL Denver, CO San Francisco, CA (1993-1994)	MSM	2189	37% definitely 57% probably or might be		
Koblin, 1997	New York City, NY (1993-96)	Gay and bisexual men ≥ 18 yrs	698	30% definitely 38% probably	Older age (>30) Previous HIV-1 antibody testing Commercial sex work Enrolled before media event*† (October 1993-May 1994) Enrolled after media event*† (September 1994+)	1.5 (1.1-2.1) 1.6 (1.0-2.5) 2.0 (1.0-4.0) 2.1 (1.3-3.4) 1.7 (1.1-2.7)
Bartholow, 1997	Chicago, IL Denver, CO San Francisco, CA (1993-1994)	MSM	1267	Baseline 37% definitely 38% probably 6 mos 29% definitely 31% probably 12 mos 21% definitely 31% probably 18 mos 21% definitely 30% probably	↓ WTP: Chicago MSM ↑ WTP: Unprotected receptive anal sex Perceived exposure to HIV	p<0.001 p<0.004 p<0.02
Tello, 1998	Birmingham, UK	Heterosexuals (STD clinic)	167	67% WTP	Female gender Previous testing for HIV	p=0.05 p=0.03

Table 2.2, cont'd. **Willingness to participate and determinants of participation for a hypothetical vaccine study**

Source	City (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
Koblin, 1998	8 U.S. cities‡ (HIVNET VPS)	66.6% MSM 15.7% male IDU 10.4% WAHR 7.2% female (IDU)	4892	27% definitely 50% probably IDU= 77% WAHR=81% MSM=76%	High school graduation College graduate Previous VPS Uninsured Public insurance HIV+ve partner Unprotected receptive anal sex Altruism HIV seropositivity	0.7 (0.5-0.9) 0.6 (0.5-0.9) 0.7 (0.6-0.8) 1.4 (1.2-1.8) 1.6 (1.2-2.1) 1.5 (1.2-1.8) 1.3 (1.1-1.5) 7.9 (6.2-10.0) 0.5 (0.4-0.5)
Hays, 1999	Eugene, OR Santa Cruz, CA Santa Barbara, CA (1994)	Gay and bisexual men (18-29 yrs)	390	22% extremely 20% very likely 22% somewhat	Number of male sex partners Poor sexual communication skills Being out of the closet	p<0.01 p<0.05 p<0.05
Scheer, 1999	Chicago, IL Denver, CO San Francisco, CA (1993-1994)	Gay and bisexual men ≥18 years	2189	Young men <25** 69% definitely or probably Older men ≥25** 74% definitely or probably		
Strathdee, 2000	Vancouver, Canada (1997)	IDU MSM	435 330	83% 34% definitely 27% probably	Frequent NEP attendance High perceived HIV threat High depression scores	2.16 (1.28-3.64) 2.92 (1.10-7.97) 1.74 (1.09-2.80)
O'Connell, 2002	Vancouver, Canada (2001)	Gay and bisexual men (15-30 yrs)	440	49%	Regular sex partner High perceived HIV threat	0.48 (0.25-0.92) 5.35 (1.57-18.25)

Table 2.2, cont'd. **Willingness to participate and determinants of participation for a hypothetical vaccine study**

Source	City (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
Golub, 2005	Baltimore, MD (1993-94)	IDU	440	83%	Monetary incentives No incentive No health insurance	↑WTP ↓ WTP ↓ WTP
	(2001-02)	IDU	582	86%	Female sex Non-monetary incentives	2.39 (1.03-5.57) 2.78 (0.97-7.97)
Sherr, 2004	London, UK (2002)	Gay men	506	3% very likely 20% quite likely	Non-concordant UAI	p<0.001
Van de Ven, 2002	Sydney, Australia (2001)	Gay men	585	28% likely/very likely	Confidence in HIV vaccines/vaccine trials Comfort with participation in HIV vaccine trials	↑ WTP ↑ WTP
Van de Ven, 2005	Sydney, Australia (2001-2002)	Gay men	894	51%	Lack of tertiary education UAI-C or NCR Higher self-rated likelihood of HIV infection Comfort with participation in HIV vaccine trials	p<0.001 p<0.001 p<0.01 p<0.001
Serpelloni, 1995	Italy (no dates given)	IDU	156	41% interested (13% very interested)		
Starace, 2006	Italy (2001-2002)	Gay men IDU WAHR	924	37% willing	Employed At risk for HIV Sufficient knowledge	1.4 (1.1-1.8) 1.4 (1.0-2.0) 1.6 (1.2-2.1)

*NIAID decision not to proceed with a phase 3 efficacy trial of rgp120 HIV vaccine.

†Report of breakthrough infections reported among vaccine recipients in phase I and II trials.

‡Boston, Providence, Chicago, Denver, New York City, Philadelphia, San Francisco, Seattle.

**p=0.07

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Chapter 3

HIV vaccine preparedness studies in the non-organization for economic co-operation and development (non-OECD) countries

3.1 INTRODUCTION

Development of an HIV vaccine remains an urgent priority, particularly in developing countries where HIV prevalence and incidence remain relatively high, but treatment resources are low (Kiwanuka et al., 2004). An HIV preventive vaccine trial requires highly retainable and willing populations, at high-risk for acquiring HIV (Schechter, 2002). Vaccine preparedness studies (VPS) to assess feasibility are an important precursor to HIV vaccine trials.

Several VPS have been conducted in in the non-Organization for Economic Co-operation and Development (non-OECD) countries. The Organization for Economic Co-operation and Development (OECD) is an international organization of 30 countries that accept the principles of representative democracy and a free market economy. Given OECD work in the area of biotechnology, member countries may have more stringent protocols for HIV vaccine research than the non-OECD countries. The non-OECD countries are generally lower-income countries, often with a higher prevalence and incidence of HIV than the OECD countries. Willingness to participate (WTP) might be different in the non-OECD countries because of differences in access to acute HIV therapy, HIV risk, or educational background.

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This paper summarizes the research on retention rates (Table 3.1) and WTP (Table 3.2) in the non-OECD countries. These countries included Brazil, the Democratic Republic of Congo, Haiti, India, Kenya, Russia, South Africa, Tanzania, Thailand, and Uganda (Currently, Brazil, Kenya, and South Africa are entering OECD discussions and could be considered for membership). The types of cohorts examined in these countries were diverse, even within individual countries. HIV vaccine preparedness studies have focused on the groups at highest risk when the studies were conducted.

3.1.1 HIV epidemiology in the non-OECD countries

As a non-OECD country, Brazil has more than one-third of the total number of people living with HIV in Latin America (Joint United Nations programme on HIV/AIDS [UNAIDS], 2007a). In the late 1990s, 86% of the reported AIDS cases in Brazil were among men, and more than two-thirds of these men reported sex with other men as their main risk factor (Périsse et al., 2000). Since 2000, the epidemic has become largely heterosexual (Schechter et al., 2002; Schechter, 2000). Vaccine preparedness studies have therefore followed in this risk pattern.

In India, diverse populations were surveyed in their VPS (Tables 3.1 and 3.2). Recently, India revised its estimates among commercial sex workers (CSW) and males attending sexually transmitted infection (STI) clinics (Mehendale et al., 2007), showing a decline of HIV acquisition in these populations. Surveillance data from India also suggest that in 2006, HIV incidence rates (IR) in injection drug users (IDU) and men who have sex with men (MSM) are increasing, especially in urban centers (Kresge, 2007b).

A recent study on feasibility of HIV vaccine trials in Russia found that IDU exposure remains a primary driver of the Russian HIV epidemic, with approximately 70% to 90% of HIV infections due to injection drug use (Beyrer et al., 2007). Important challenges to the feasibility of conducting trials include methadone prohibition and lack of access to drug treatment services.

In Thailand, populations examined were also diverse (Tables 3.1 and 3.2). In addition, at a peak in December 1994, direct (brothel-based) CSW were found to have an HIV prevalence of 32.7%, while indirect (non-brothel-based) CSW were found to have a prevalence of 9.8% (Hsieh, 2002). In 2006, the prevalence in direct CSW fell to approximately 4.6%, and to 2.3% in indirect CSW (“Thai Ministry”, 2007). Prevalence today among IDU remains high, ranging between 30% to 50%, and there is a growing HIV prevalence among MSM and female spouses (UNAIDS, 2007a).

The results in IDU in Thailand led, in 1999, to the initiation of the first phase 3 preventive trial (the VaxGen 003 study) to evaluate the AIDSVAX B/E vaccine, the first phase 3 study completed in IDU (Francis et al., 2003; Pitisuttithum et al., 2006). The population involved mainly heroin addicts (93.8%) in Bangkok. The study found that the vaccine was ineffective (Pitisuttithum et al., 2006). A phase 3 trial that involved sites in Puerto Rico testing the AIDSVAX B/B vaccine also found a similar result (Bull, 2003). A second phase 3 study was launched in Thailand in 2003 by the US military in 16,000 community-based Thai adults. This study was of a prime-boost regimen consisting of AIDSVAX B/E and a canarypox candidate ALVAC vCP 1521. The trial remains ongoing in this large population cohort (US National Institutes of Health [NIH], 2007).

Vaccine preparedness studies were also conducted in sub-Saharan Africa. A recent VPS conducted among youth 11-19 years of age near Cape Town showed that the average HIV prevalence among 15-year-old adolescents in South Africa was 11% (Jaspan et al., 2006). It is estimated that by 2010 in South Africa, 50% of all infections in women will have occurred before the age of 20 (McClure, Gray, Rybczyk, & Wright, 2004). A recent Merck/HIV vaccine trials network (HVTN) phase 2B sponsored adenovirus trial in South Africa, called the “Phambili” trial in 3000 participants was halted in September 2007, as preliminary analysis found that the vaccine was ineffective (STEP study, 2007). A similar phase 2B clinical trial (STEP study, 2007), also sponsored by Merck/HVTN, which had sites in Brazil, the Dominican Republic, Haiti, Jamaica, Peru, and Puerto Rico, along with sites in Australia, Canada and the US, was also stopped in September 2007, for similar reasons.

3.2 METHODS

In 2007, two people independently searched the Cochrane Database for Systematic Reviews, Medline (1966-2007), Pubmed, and Embase (1980-2007). Two authors (S. Dhalla and G. Poole) used the same search strategy, and obtained the same number of articles. The relevant articles were picked by S.D. The search terms used were “HIV”, “vaccine preparedness”, “HIV vaccines”, “developing country”, “non-OECD”, and the developing countries identified as current HVTN sites.

The sites included were Brazil, the Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, South Africa, and Thailand (HVTN, 2007). Those countries deemed suitable by the World Health Organization (WHO) in 1992 as target sites for testing HIV vaccines in phase 3 trials (Brazil, Rwanda, Thailand, and Uganda) (Excler & Beyrer, 2000) were also checked. Botswana (Kresge & Fernandez-Larsson, 2005), Cuba, China, India, and Trinidad and Tobago (Esparza et al., 2002) were included, as they have been testing sites for HIV vaccines. Also examined were Tanzania, Cote d'Ivoire, Ethiopia, Senegal, Zambia, Nigeria, Zimbabwe, Malawi, Cameroon, Burkina Faso, and The Gambia, all reported to be at varied levels of trial preparedness (Milford, Wassenaar, & Slack, 2006). Russia was included, as the Russian government has supported the plan for an HIV vaccine trial among IDU (Beyrer et al., 2007). Studies examining retention, and those studies examining WTP in phase 3 HIV vaccine trials were included in this review. One prominent January 2008 article on retention in discordant couples in Zambia was also included (Kempf et al., 2008).

Two hundred and thirty-two abstracts were retrieved from Medline (1950-2007), 212 from Pubmed, and 201 from Embase (1980-2007). Additional articles were retrieved from bibliographic references. Articles were included if they were published in a peer-reviewed journal, took place in non-OECD areas, and were in English. International AIDS Vaccine Initiative (IAVI) Reports were also searched for relevant information.

Information on location, study population, and sample size was extracted from the text and tables of the articles, and then tabulated in our review to describe retention rates and WTP. These, as well as predictors found to be associated with WTP, were included in the appropriate table. The subject information collected varied from study to study, and thus the models used to determine factors associated with subject retention and WTP differed among studies. We have presented a summary measure of association (e.g. adjusted odds ratios [AOR]) for any variables found to be associated with WTP.

3.3 RESULTS

3.3.1 Retention

We report 16 studies of retention (Table 3.1). Retention was tested in mostly HIV-negative individuals, except in the studies by Deschamps et al. (1994) (discordant couples), Kempf et al. (2008) (discordant couples), Kiwanuka et al. (2004) (individuals who were HIV-negative or positive) (Kiwanuka, personal communication, August 2007), Mugusi et al. (2002) (HIV-negative or positive), and Natapratana et al. (1996) (HIV-negative or positive). In the reported VPS, the 12-month retention ranged from 77% to 85% (Table 3.1). In some studies, retention data were only available for 6, 9, or 18 months. Other studies provided a 3-year retention rate, a more appropriate follow-up time (Mehendale et al., 2007). This ranged from 42% in MSM (Sutmöller et al., 2002) to 62% in CSW (Baeten et al., 2000).

One study in Russia examined HIV retention among IDU who used psychostimulants (Kozlov et al., 2006) (Table 3.1). This study did not specifically refer to HIV vaccine trials, but rather to a step in facilitating the development of longitudinal HIV prevention programs. Retention in this population was 80% at 12 months. Of those who were lost to follow-up, 42/520 (8.1%) were jailed or dead, and 58/520 (11.2%) were lost to follow-up without knowledge of their whereabouts (Kozlov et al., 2006). One large study in 2008 examined retention rates in discordant couples in Zambia (Kempf et al., 2008) (Table 3.1). Retention was discussed with respect to a general clinical trial that would prevent transmission from an HIV-positive partner to an HIV-negative partner, rather than with respect to a specific HIV vaccine study.

In one study, retention in a Hepatitis B immunization 0-1-6 month schedule was examined as an

incentive to retention in HIV vaccine trials (Beyrer et al., 1996). For female CSW, retention for those receiving the Hepatitis B vaccine (HBV) was higher (99%) compared to those who were ineligible (declined vaccination, or were positive for the antigen or antibody or both) (44%, $p < 0.001$). This was not observed for male sexually transmitted disease (STD) patients (marginally significant, $p = 0.058$) or discharged Royal Thai Army (RTA) conscripts ($p = 0.715$). This difference in retention between the immunized and non-immunized CSW, and similarly to the male STD patients, disappeared at the 12-month visit. There was no post-immunization visit scheduled for the discharged RTA conscripts.

3.3.2 Willingness to participate (WTP)

We report 21 studies of WTP and their determinants of participation (Table 3.2). The studies allowed the participants to indicate their WTP to various degrees (e.g. “definitely”, “probably”, etc.). We have grouped together all responses indicating some WTP into our overall WTP for a given study. The majority of the studies on WTP were in HIV-negative individuals, other than the studies by Olin et al. (2006) (HIV-negative/untested in university students), Suhadev et al., (2006) (not known, although most HIV-negative) (Suhadev, personal communication, August 2007), Jaspan et al. (2006) (individuals who were HIV-negative or positive), and Kiwanuka et al. (2004) (HIV-negative or positive) (Kiwanuka, personal communication, August 2007). Many participants showed WTP in HIV vaccine trials. Overall, participants showed high WTP in HIV vaccine trials. The lowest WTP was 23% in community residents in Cape Town, South Africa (Smit et al., 2006a), while the highest was 100% in women in Tamil Nadu, India (Suhadev et al., 2006) and in female CSW in Mombasa, Kenya (Jackson et al., 1995) (Table 3.2).

High-risk factors were generally linked to high WTP in HIV vaccine trials. For example, in Brazil, MSM having STDs such as condylomas (Périssé et al., 2000) or a positive serology for syphilis (de Souza, Lowndes, Szwarcwald, Suttmöller, & Bastos, 2003) were found to be associated with an increased WTP. Knowledge was also examined and in the studies by Sahay et al. (2005) in India and Smit et al. (2006b) in Cape Town, higher knowledge of HIV vaccines was related to an increased WTP. In Thailand, conscripts and ex-conscripts who had a higher awareness of vaccines were more WTP in HIV vaccine trials than those who did not (Celentano et al., 1995). Interestingly, in the study of adolescents aged 11-19 years in South Africa, increasing age was found to be related to an increased WTP (Jaspan et al., 2006). This was in contrast to a study in South Africa in an older cohort aged 16-40 years, which found that, compared to a local community sample, individuals who volunteered for an HIV VPS were younger (Smit et al., 2006b).

A 2001 survey evaluated WTP of medical doctors working at a tertiary care hospital in the Western Cape, South Africa (Moodley, Barnes, van Rensburg, & Myer, 2002) (Table 3.2). Willingness of physicians who were at low risk for HIV to be recruited into a phase 1 vaccine trial was associated with willingness to recruit patients into phase 3 trials (Moodley et al., 2002).

3.3.3 Willingness to participate (WTP): Motivations and barriers

In the study by De Souza et al. (2003) in MSM in Brazil, humanitarian concerns were the chief motivation for WTP (60.8% citing this reason). This same association was reported by Périssé et al. (2000) in another study of MSM (96.0%). In the former study, barriers included lack of information about vaccines (34.6%) and concerns regarding possible side effects (33.8%). Fear

of becoming HIV-infected from a vaccine (77%) and fear of a vaccine-induced HIV-positive test were reported by 61% of individuals in the latter study.

In Thailand, altruism was ranked as a major motivation for participation by IDU (78.6%) in a study by MacQueen et al. (1999), by RTA conscripts (43.2%) in a study by Jenkins et al. (2000), and in the AIDSVAX B/E trial in Thailand (96% of participants wanted to do something to stop the spread of HIV) (Vanichseni et al., 2004). A major barrier was the fear that people who became infected with HIV after receiving the vaccine would develop AIDS more quickly than people who were not vaccinated (31.2%) (MacQueen et al., 1999). Side effects were also cited as major barriers (Celentano et al., 1995).

In adolescents in South Africa, the most common motivation was altruism (33%), expressed as “to help find a vaccine against HIV to protect their loved ones and the rest of the world” (Jaspan et al., 2006). The major barrier was fear of unknown side effects. Similar motivations and barriers were reported by Smit et al. (2001a) in a peri-urban South African community, although testing HIV-positive secondary to vaccination was cited as most important in the latter study (39%). Similar barriers were found in the study by McGrath et al. (2001a) in Uganda.

3.4 DISCUSSION

In the current paper, we report 16 studies of retention and 21 studies of WTP. In general, high-risk people were willing to participate in advanced phase studies. In settings where there is a high IR and a large population at risk, the WTP can be lower and still allow a trial to proceed. The retention issue is more critical to the internal validity of the trial, because higher rate of loss to follow-up could affect the results if it were differential or due to unblinding. HIV vaccine trials, particularly early phase trials, also need to be done in low-risk cohorts. With the current state of vaccine science, we expect to see a shift toward early phase trials.

Comparing the OECD countries with the non-OECD countries, the overall numbers of studies, as well as retention rates and WTP were relatively similar, but the populations in the latter countries were more diverse. In the OECD countries, the populations consisted mainly of IDU, MSM, and women at heterosexual risk (WAHR) (Dhalla, Woods, Strathdee, Patrick, & Hogg, 2007).

However, in the non-OECD countries, some populations were not examined; for example, IDU were not examined in Africa, although injection drug use, in particular heroin use, is an emerging problem in this part of the world (Beckerleg, Telfer, & Hundt, 2005; Parry, Pluddemann, & Myers, 2005).

The study by Jaspan examined adolescents 11-19 years of age in South Africa. Adolescents would be ideal recipients of HIV vaccines, as vaccination would occur before the onset of behavioral risks (McClure et al., 2004). Studies in South Africa showed that adolescents commence sexual activity at a young age, and that adolescent girls in developing countries more commonly experience rape, violence, and assault (McClure et al., 2004). Studies may need to be

conducted to examine willingness of parents and guardians to let their adolescent minors, including girls, participate in HIV vaccine trials (Jaspan et al., 2006).

Until relatively recently, women were under-represented as participants in HIV vaccine trials (UNAIDS, 2007b). For example, in the phase 3 AIDSVAX B/E trial of IDU in Thailand, 93.4% were men (Francis et al., 2003). This improved in the STEP study, where approximately 62% of study participants were men and 38% were women (STEP study, 2007).

A major possible barrier to vaccine trial participation, which has been identified recently in the results of the STEP study (STEP study, 2007), is that vaccine exposure might increase the risk of HIV on subsequent exposure in a subset of participants. In this study, 49 (5.36%) of 914 male recipients compared to 33 (3.58%) of 922 male placebo recipients developed incident HIV infections (Kresge, 2007a). Analysis of the data according to the level of Ad5 antibodies at baseline showed the same HIV incidence in vaccine and placebo recipients who were antibody-negative prior to vaccination, but an increasing ratio of HIV infections among vaccinees compared to placebo with increasing levels of Ad5 antibody levels. Whereas no studies have been published or presented on the effect of the STEP trial on WTP in future vaccine trials, this issue needs to be evaluated.

There were several limitations in the studies included in this review. Some studies had small sample sizes (Lindegger et al., 2007; Olin et al., 2006; Sahay et al., 2005; Suhadev et al., 2006). Although most questionnaires were interviewer-administered, there were some that were self-administered, particularly in Thailand - in Thai RTA conscripts (Jenkins et al., 2000), in IDU in

Thailand (MacQueen et al., 1999), and in Thai factory workers (Natpratan et al., 1996). Similarly, in a study in South Africa, data were collected using a self-administered paper-based questionnaire, or direct data entry using Palm Pilot hand-held devices (Jaspan et al., 2006). These answers may have been affected by educational level (Natpratan et al., 1996). The interview-administered questionnaires, on the other hand, may lead to more socially desirable reporting. In addition, in many studies, the questionnaires were often translated into local language, and then back-translated into English. Some phrases were difficult to translate and did not have a specific local term or equivalent concept (McGrath et al., 2001b); therefore, an educational program using locally appropriate analogies was developed (McGrath et al., 2001b). Another limitation may be the lack of generalizability of answers of certain populations to similar populations in other countries, and the fact that cohorts used in certain studies cannot be considered representative of the general population (Sahay et al., 2005). Selective WTP in vaccine trials by subpopulations might impact the ability to implement a preventive vaccine strategy.

3.5 CONCLUSIONS

While finding a safe and effective vaccine is a major challenge, evaluation in appropriate populations is also a challenge. In many non-OECD countries, HIV VPS have taken place using diverse cohorts. In general, in these VPS, retention, and WTP have been adequate to carry out HIV vaccine trials. In addition, high-risk behaviors, knowledge, and altruism were found to be significant contributors to WTP. Educational programs may help improve WTP in HIV vaccine trials in the non-OECD countries.

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Table 3.1 **Retention rates in HIV vaccine preparedness studies**

Source	Location	Study Population	Sample Size	Time Period (Time Interval)	Retention
Carneiro†, 2000	Belo Horizonte, Brazil Project Horizonte	Homosexual or bisexual men (18-59 years)	470	1994-1999 (0, 6, 12, 18 months, etc., every 6 months for 4 yrs)	0 months 100% 6 months 87% 12 months 77% No losses after >3 yrs follow-up
Sutmöller, 2002	Rio de Janeiro, Brazil Projecto Rio	MSM (18-50 years)	647	1994-1998 (12, 24, 36 months)	85% 61% 42%
Deschamps, 1994	Haiti	HIV discordant couples	475	1991-1992 (2, 5 years)	93% 85%
Baeten, 2000	Mombasa, Kenya PAVE study	Female CSW (16-48 years)	953	1993-1996 (3 years)	62%
Kozlov, 2006	St. Petersburg, Russia	IDU (17-42 years)	520	2002-2003 (12 months)	80%
Mugusi, 2002	Dar es Salaam, Tanzania	Police officers (18-55 years)	2894	(1995-1998) (2 years)	72.1%
Carr†, 1994	Bangkok and northern Thailand	Male RTA enlistees (21 years)	17,615	1992-1993 Cohort #1 (9, 15 months) Cohort #2 (9 months)	72% 41% 51%
Nelson†, 1994	northern Thailand PAVE study	Female CSW * Male STD © clinic patients Male RTA conscripts Discharged Conscripts	395 175 “direct” 220 “indirect” 264 679 380	1993 (6 months) (3, 6 months) (6 months) (3 months)	“direct”* 58.5% “indirect”* 85.2% 98.1% 94.3% 90% 94%

Table 3.1, cont'd. **Retention rates in HIV vaccine preparedness studies**

Source	Location	Study Population	Sample Size	Time Period (Time Interval)	Retention
Natpratan, 1996	Lamphum Province, northern Thailand HIV-ve 15/499 HIV+ve	Factory workers (15-50 years)	499	1994 (6 months)	84% 73/106- 69% men 347/393- 88% women
Renzullo‡, 1999	northern Thailand (1993)	Discharged conscripts	551	1993 (4 months)	69% following discharge
Markowitz‡, 1999	Bangkok, Chonburi, Lampang, Thailand	STD clinic attendees (18-45 years)	514	1994-1997 (4, 8, 12 months)	78% 75% 78%
Vanichseni‡, 2001	Bangkok, Thailand Preparatory cohort study	IDU attending methadone clinics (18-50 years)	1209	1995-1998 (12, 24, 36 months)	81.9% 62.2% 47.6%
Hom‡, 1997	Kampala, Uganda PAVE initiative	Ugandan military men (19-22 years)	249	1993-1995 (3, 6, 12, 18 months)	98% 97% 77% 79%
McGrath, 2001a/ 2001b	Kampala, Uganda PAVE initiative	Ugandan military men (18-30 years)	1182	1995-1998 (24 months)	46% (follow-up affected by deployment)
Kiwanuka, 2004	Rakai, Uganda CHER study	Rural population cohort (15-49 years)	14,177	1999-2002 (10 months)	73%†
Kempf, Zambia	Lusaka, Zambia	Discordant couples	675 M+ F- 656 F+ M+	1994-1998 (15 months)	75.1% M+ F- (HIV-positive men) 69.5% F+ M- (HIV-positive women)

MSM, men who have sex with men; IDU, injection drug users; STD, sexually disease chronic disease clinic patients;

CSW, commercial sex workers; RTA, Royal Thai Army conscripts.

PAVE study, Preparation for AIDS vaccine evaluation study; CHER study, Community HIV epidemiological research study.

*“direct”, brothel-based, “indirect”, non brothel-based.

†Patients enrolled and visited at home.

‡References not cited in text.

Table 3.2 **Willingness to participate (WTP) and determinants of participation for a hypothetical vaccine study**

Source	City (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
Harrison‡, 1999	Rio de Janeiro, Brazil (1995 – 1997)	MSM (18-50 yrs)	749	715 = 69% (no seroconversion) 34 = 85% (sero-conversion)		
Schechter, 2000	Rio de Janeiro, Brazil (1998) (those attending an HIV testing site)	Heterosexuals	442 men 505 women	53.9% yes 22.6% maybe 54.5% yes 21.4% maybe		
Carneiro‡, 2000	Belo Horizonte, Brazil (1994 – 1999) Projeto Horizonte	Homosexual or bisexual men (18-59 yrs)	470	At enrollment = 50% yes 30% might 59 = only 1 visit 40% yes 27% maybe (6 month visits) 411 = > 1 visit 49% yes 30% maybe		
Périssé, 2000	Rio de Janeiro, Brazil (1995 – 1998) Projeto Praca Onze	MSM (18-50 yrs)	815	Baseline 69.8% 18 mos 68.9%	Incomplete high school / less Student Sex at first encounter Condyloma (last 6 months) Sex to obtain housing/food/ clothing	1.6 (1.1-2.2) 0.7 (0.4-1.0) 0.7 (0.5-1.0) 3.1 (0.9-13.3) 6.1 (1.4-37.8)

Table 3.2, cont'd. **Willingness to participate (WTP) and determinants of participation for a hypothetical vaccine study**

Source	City (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
Sutmöller, 2002	Rio de Janeiro, Brazil	MSM (18-50 yrs)	647	54%	Humanitarian reasons	
	(1994-1998) Projeto Rio	General Public (1995)	505	53%		
De Souza, 2003	Rio de Janeiro, Brazil (1994) Projeto Rio	MSM (18-50 yrs)	675	57% CSW= 62.6% NCSW=51.4%	Positive serology for syphilis* Risky sexual behavior with alcohol* Lower educational level** Positive serology for syphilis** Risky sexual behavior with alcohol**	1.52 (1.04-2.22) 1.83 (1.05-3.20) 1.47 (1.03-2.11) 1.48 (1.01-2.16) 1.85 (1.06-3.23)
Olin, 2006	Democratic Republic of Congo (2003-2004)	High-risk † including 8 female CSW (19-44 years)	15	Not given	Assurances of vaccine safety Animal testing of vaccine Family compensated if die in trial Fears of being injured, infected, or killed by HIV vaccine Receiving a vaccine that was untested on humans First to receive vaccine	↑ WTP ↑ WTP ↑ WTP ↓ WTP ↓ WTP ↓ WTP
		University students	20	many WTP (no numbers given)		

Table 3.2, cont'd. **Willingness to participate (WTP) and determinants of participation for a hypothetical vaccine study**

Source	City (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
Sahay, 2005	Pune City, Maharashtra, India (2002-2003)	Attendees of STI clinics§ Women at RTI clinics +	286 63	48% definitely 16% very likely men=46% women=52%	High risk women No knowledge of current efforts for HIV vaccine Somewhat importance of vaccine for self Not important of vaccine for self Refusal by partner for sex (don't know) Serious adverse events Altruism	2.6 (1.1-6.6) 0.4 (0.2-0.7) 0.1 (0.1-0.3) 0.2 (0.1-0.4) 0.4 (0.2-0.9) 0.3 (0.1-0.7) 3.9 (1.8-8.1)
Suhadev, 2006	Tamil Nadu, India (2004-2005)	Transport workers STD diagnosis IDU MSM CSW Married women >15 yrs	112	Willingness due to common good of India men 97% women 100%		
Jackson, 1995	Mombasa, Kenya PAVE study (1993-1994)	Male trucking company employees (17-52 years) Female CSW (17-46 years)	201 206	67% definitely 18% perhaps 91% definitely 9% perhaps		
Moodley, 2002	Western Cape, South Africa, (2001)	Medical doctors in a tertiary care hospitals	289	37% willing to recruit patients into phase 3 trial		

Table 3.2, cont'd. **Willingness to participate (WTP) and determinants of participation for a hypothetical vaccine study**

Source	City (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
Smit, 2006	Cape Town, South Africa (2003)	Residents in community (16–40 yrs)	198	23%	Knowledge of vaccines (1 unit increase in knowledge score) Knowledge of HIV vaccine (1 unit increase in score)	1.91 (1.25-2.92) 10.72 (4.40-26.12)
Smit, 2006	South Africa (2003) (volunteered for vaccine preparedness cohort)	Observational cohort vs. community sample (16-40 yrs)	140	Not given	(observational cohort vs. community sample) Age (26-40 vs. 16-25) Had been treated for an STD Condom use Sex while drinking alcohol/drugs	 0.48 (0.28-0.82) 1.75 (1.03-2.99) 0.51 (0.30-0.86) 0.15 (0.04-0.53)
Jaspan, 2006	South Africa (2004-2005)	Adolescents (11-19 yrs)	259	79% definitely/ probably	Increasing age Years in community	1.19 (1.01-1.40) 1.14 (1.03-1.26)
Lindegger, 2007	Kwazulu-Natal, South Africa (dates not given)	Members of semirural community	41	40% definitely 37% unsure/ would if certain conditions met ¥		

Table 3.2, cont'd. **Willingness to participate (WTP) and determinants of participation for a hypothetical vaccine study**

Source	City (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
Celentano, 1995	northern Thailand (1994) PAVE study	Female CSW Male STD clients Male RTA conscripts Ex- conscripts	215 219 1453 293	24.7% definitely 24.2% definitely 24.7% definitely 29.0% definitely	Female CSW: Perceived personal importance Impact on income Brothel worker (vs. other) Male STD cohort: Medical encounters Education (≤ 6 yrs) Military conscripts: Perceived personal importance Long-term side effects Sexual side effects Aware of vaccines Insurance incentive CSW visit past 6 months Condoms ineffective Former conscripts: Perceived importance Long-term side effects Blood donor Aware of vaccines Insurance incentive	3.13 (1.45-6.79) 3.32 (1.37-8.09) 4.61 (1.76-12.1) 2.04 (1.01-4.09) 2.25 (1.09-4.65) 1.77 (1.37-2.29) 0.54 (0.39-0.73) 0.68 (0.49-0.93) 1.30 (0.99-1.71) 0.59 (0.46-0.76) 1.44 (1.11-1.86) 3.93 (2.36-6.55) 2.21 (1.18-4.11) 0.21 (0.09-0.47) 2.68 (1.21-5.93) 2.25 (1.11-4.58) 0.51 (0.27-0.96)
Kitayaporn†, 1998	Bangkok, Thailand (1995) Preparatory cohort study	IDU attending methadone clinics	822	82.5% WTP in a prospective cohort study		

Table 3.2, cont'd. **Willingness to participate (WTP) and determinants of participation for a hypothetical vaccine study**

Source	City (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
MacQueen, 1999	Bangkok, Thailand (1996)	IDU attending methadone clinics (20-50 years)	193	Baseline 51% definitely 47% probably / might Follow-up (1 week) 54% definitely 43% probably / might	Observers present at education session Frequency of incarceration Altruism	2.29 (1.08-4.86) 0.78 (0.62-0.99) 1.99 (1.25-3.19)
Jenkins, 2000	Thailand (1994-1997)	Male RTA conscripts	2661	32% definitely 12.9% very likely 45.0 % might	Education (primary school or less) Region (northeast vs. elsewhere Partner-girlfriend (past 6 mos) Errors in transmission knowledge of HIV Endorsement of casual contact as a source of HIV exposure Would use condoms less in a vaccine trial Perceived risk of HIV infection Altruism	1.24 (1.00-1.53) 1.38 (1.14-1.66) 0.69 (0.55-0.86) 1.49 (1.08-2.05) 1.22 (1.02-1.46) 1.28 (1.04-1.57) 1.84 (1.49-2.27) 1.72 (1.38-2.14)

Table 3.2, cont'd. **Willingness to participate (WTP) and determinants of participation for a hypothetical vaccine study**

Source	City (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
McGrath, 2001a / 2001b	Uganda PAVE study (1995-1998)	Ugandan military men 18-30 yrs	1182	Baseline 79%	Baseline Number of sex partners Perceived likelihood of getting AIDS for oneself Perceived likelihood of one's partner getting AIDS 6 months Number of new women partners in last 6 months 12, 18, 24 months No variables associated	Bivariate p=0.039 p=0.013 p=0.007 p=0.001
Kiwanuka, 2004	Rakai, Uganda (1999-2002) CHER study	Rural population cohort 15-49 yrs	14,177	Follow-up (10 mos) 77%	Self-perception of HIV risk Receipt of education on vaccines	1.12 (1.10-1.15) 1.03 (1.01-1.06)

AOR, adjusted odds ratio; CI, confidence interval; MSM, men who have sex with men; CSW, commercial sex workers; STD (STI), sexually transmitted disease (infection) clinics; RTI, reproductive tract infections clinics; IDU, injection drug users; RTA, Royal Thai Army conscripts.

PAVE study, Preparation for AIDS vaccine evaluation study; CHER, Community HIV epidemiological research study.

*Controlled for CSW.

**Not controlled for CSW.

† 1 unemployed, 2 civil servants, 1 taxi helper, 1 airport worker, 2 not recorded.

§ STI patients, sex workers, spouses of STI patients, persons with high-risk behavior.

+ reproductive tract infections clinic.

¥ requests for more information, a guarantee that involvement would incur no significant risks, requests that participants' dependents be cared for if the trial went awry, or simply unsure.

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Chapter 4

Cognitive factors and willingness to participate in an HIV vaccine trial among HIV-negative injection drug users

4.1 INTRODUCTION

While considerable progress has been made towards identifying the factors that predict willingness to participate (WTP) in preventive HIV vaccine trials (Dhalla, Nelson, Singer, & Poole, 2009; Dhalla, Woods, Strathdee, Patrick, & Hogg, 2007), little is known about the relationship between cognitive factors and WTP. Therefore, in the present VPS, we sought to examine cognitive and high-risk factors (for seroconversion) in relation to WTP in a preventive HIV vaccine trial. The cognitive factors examined included HIV treatment optimism, self-efficacy regarding participation in an HIV vaccine trial, and knowledge of HIV vaccine trial concepts. To our knowledge, there is currently no self-efficacy scale pertaining to WTP in an HIV vaccine trial in injection drug users (IDU).

4.1.1 Optimism

Optimism has been defined as the “hopefulness and confidence about the future or the success of something” (Soanes & Stevenson, 2005). Two previous studies, one in men who have sex with men (MSM) and the other in IDU, showed that people who were optimistic about HIV

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vaccines/vaccine trials (Van De Ven et al., 2002) and HIV treatment (Golub et al., 2005), were more willing to participate. However, there have been concerns that optimism may result in an increase in high-risk behavior (Crosby & Holtgrave, 2006) or that high-risk behavior may precede optimism (Huebner, Rebchook, & Kegeles, 2004).

4.1.2 Self-efficacy

Self-efficacy is “people’s judgement of their capabilities to organize and execute courses of action required to attain designated types of performances”. It is concerned with what one can do with whatever skills one possesses (Bandura, 1986). This is important for HIV vaccine trials because adherence is necessary in a multi-dose regimen vaccine trial. In order to comply, participants must believe they can, and that is what self-efficacy measures. A recent study in South Africa examined this variable in relationship to WTP in adolescents, and found that self-efficacy (Giocos called it perceived behavioral control) did not predict WTP in a hypothetical HIV vaccine trial (Giocos, Kagee, & Swartz, 2008).

4.1.3 Knowledge

Knowledge is the “information and understanding of a specific topic or of the world in general, usually acquired by experience or by learning” (VandenBos, 2007). Knowledge is ethically necessary for informed consent (Lindegger et al., 2006) and may increase with discussion with study staff (Koblin, Holte, Lenderking, & Heagerty, 2000); with the provision of targeted educational strategies such as reading informational booklets (Buchbinder et al., 2004); over time with a prototype informed consent procedure (Coletti et al., 2003); and with simplification of vocabulary, sentence structure, reading ease and use of illustrations to depict concepts (Murphy

et al., 2007). Previous studies have shown a positive relationship between knowledge of HIV vaccines/vaccine trial concepts and WTP (Dhalla et al., 2009; Dhalla et al., 2007), although there are few studies examining this relationship in IDU.

Among male HIV-negative IDU with a high knowledge score for vaccine trial concepts (for example, seven of 10 answers correct), increases in knowledge reduced the likelihood of becoming unwilling at 18 months (adjusted odds ratio [AOR] = 0.90, 95% CI = 0.83–0.96) (Koblin et al., 2000). However, Halpern et al. (2003, 2001) found no relationship in IDU between declining WTP and trial knowledge, using the same knowledge scale (Halpern, 2003; Halpern, Metzger, Berlin, & Ubel, 2001).

One methodological challenge concerns the distinction between WTP in a hypothetical vs. an actual trial. Several studies have examined actual compared with hypothetical WTP. In one study, stated WTP in IDU was the single best predictor of actual enrolment (Halpern et al., 2001). However, in an extension of this study, only 20% of those stating hypothetical WTP during the vaccine preparedness study (VPS) actually enrolled in the HIVNET 014 trial (Buchbinder et al., 2004). In one study in Vancouver, Canada, self-reported WTP in MSM did not translate into enrolment into the AIDSVAX B/B (VaxGen) trial (O’Connell et al., 2002). HIV VPS also indicate that concerns about vaccine-induced infection, side effects, false HIV-positives, and trial-related discrimination are associated with lower WTP in actual trials and that addressing barriers may improve WTP (Mills et al., 2004; Newman et al., 2006).

For future vaccine trials in IDU, HIV clades, HIV incidence rates (IR), and cohort retention are

important factors. The HIV-1 virus has genetic diversity, although it is mainly infection with subtype B that occurs in IDU (Geretti et al., 2009). The HIV IR in our IDU population was 1.25 per 100 person-years with a retention rate of 82% for the period of 2007–2008. In a vaccine trial, an IR of >2% and a retention rate of >90% are important for trial feasibility (Yin et al., 2008), as otherwise a larger sample size required would be required for an effect to be shown.

4.1.4 Objectives and Hypotheses

The present study sought to examine these selected cognitive factors in relation to WTP in a hypothetical HIV preventive vaccine trial. We also sought to examine independent predictors of WTP in such trials, and subsequently, to determine the effects of high-risk factors for seroconversion in relation to WTP. We hypothesize that higher self-efficacy will be positively related to a greater WTP. We also hypothesize that the cognitive factors of treatment optimism and knowledge will also be associated with WTP, although we cannot predict the direction of these hypotheses. In addition, we hypothesize that high-risk factors for seroconversion will be associated with an increased WTP, as this has been shown in previous studies in IDU.

4.2 METHODS

4.2.1 Study participants

Participants were part of the Vancouver Injection Drug Users' Study (VIDUS), a prospective open cohort study that began in May 1996. Persons who had injected illicit drugs at least once in the previous month, resided in the Greater Vancouver Area, and provided informed written consent (Appendix B) were eligible. The VIDUS study design has been described previously (Kerr et al., 2004). Participants were recruited through self-referral and street outreach, and completed an interviewer-administered standardized questionnaire. Participants were reimbursed \$20 CDN for the visit, at which time referrals were provided for universal medical care, HIV/AIDS care, and available drug and alcohol treatment.

In 2005, VIDUS became a open cohort consisting only of HIV-negative active injectors.

Inclusion criteria are the same as in the original study: age greater than 14 years; use of injection drugs at least once in the month prior to enrolment; provision of informed consent. Between October 2007 and May 2008, 276 HIV-negative IDU were recruited for participation in the present substudy. The sample size for the total VIDUS study in May 2008 was 1063 individuals.

Study participants provided blood samples and completed interviewer-and nurse-administered questionnaires. The instruments assess demographic data, information about recent drug use patterns, HIV risk behaviors, and experiences in addiction treatment. For this particular study, a set of supplementary questions specific to cognitive factors and WTP were administered. The study has been approved on an annual basis by the Providence Health Care/University of British Columbia Research Ethics (Appendix C).

4.2.2 Predictor variables

The explanatory variables examined were part of the main VIDUS questionnaire.

These variables were defined based on a previous study by Strathdee et al. (2000) who examined factors such as sociodemographics, drug use and risk behaviors, measures of health service utilization, and psychosocial variables in relation to WTP in an HIV vaccine trial (Table 4.1).

Aboriginal ethnicity was defined as: First Nations (native), Métis or Inuit. The CES-D scale was used to measure depressive symptomology. The scale has been used with drug-using samples with high internal consistency (Cronbach's $\alpha = 0.89$) (Tobin & Latkin, 2003). The presence of depressive symptoms was evaluated using a well-defined cut-off (CES-D ≥ 16 [yes] versus CES-D < 16 [no]) (McDowell, 2006). As per the study by Strathdee et al. (2000), educational level was defined as \geq high school graduation vs. $<$ high school graduation.

4.2.3 Measurement scales and supplemental information

Eight educational points and a WTP question were administered after the conclusion of the main VIDUS questionnaire as supplemental items (Appendix A). Trained interviewers first administered the educational points specific to vaccine trials (Koblin et al., 2000) (with permission, Koblin, November 2007) that focused on concepts such as randomization, blinding, placebos, safety, adverse reactions, and vaccine-induced seropositivity (Appendix A). Previous work in this area presented vaccine trials as being likely without giving respondents the impression that they were being invited to a specific trial (Koblin et al., 1998), and our script was

written to be consistent with this precedent. If participants did not know what a vaccine was, the definition was explained by the interviewer. The definition of a vaccine was not scripted.

The participants were then asked to rate their WTP in an HIV vaccine trial using a 5-point Likert scale. Individuals responding “definitely” or “probably” were considered to be WTP, while those responding “probably not” or “definitely not” were considered not WTP.

Cognitive Factor Scales

Trained interviewers administered three measurement scales addressing HIV treatment optimism (two items administered as part of the main VIDUS questionnaire) (Appendix A), self-efficacy (five items) (Appendix A), and knowledge (10 true/false items) (Appendix A) of HIV vaccine trial concepts. The self-efficacy and knowledge scales were administered as supplemental items.

The optimism scale consisted of two items (Appendix A), which were summed to obtain a HIV treatment optimism total score (Table 4.1). The scale was based on a treatment optimism scale which used similar items (Van de Ven et al., 2000). HIV treatment optimism in our study referred specifically to optimism regarding the effect of HIV treatment on transmission of HIV.

The self-efficacy scale was modified from a study by Kerr et al. (2005) who used a similar 8-item scale in a study examining determinants of highly active antiretroviral therapy (HAART) continuation among HIV-positive IDU in Vancouver, Canada. In the study by Kerr et al. (2005), the scale had predictive validity and high internal consistency (Cronbach’s alpha = 0.82). As is common in the measure of self-efficacy, items were tailored to reflect the specific behaviors

under study (Kerr et al., 2005), which in our study referred to WTP in a vaccine study. In the present study, five self-efficacy questions were rated on an anchored 11-point continuous scale ranging from “0” to “100” (Appendix A). Composite self-efficacy scores were calculated by adding the subscale scores and dividing the sum by the total number of subscale items (Kerr et al., 2005).

The knowledge items were taken from two studies that used a common knowledge scale (Halpern, Metzger, Berlin, & Ubel, 2001; Koblin et al., 2000). Although there was no specific validation that was conducted with the knowledge items that we used from Koblin’s study, the focus was on areas that those authors thought were most critical for participants to know with regards to vaccine trial concepts (Koblin, personal communication, November 2007). The knowledge items were categorized as correct vs. incorrect/do not know. Corrected item-total correlations were calculated for the knowledge items.

4.2.4 Outcome variable

Willingness to participate was the outcome variable and was asked in the following manner: “If an HIV vaccine study were available, would you be willing to participate in it?” (Appendix A). Five possible answers were provided: “definitely not”, “probably not”, “do not know”, “probably”, “definitely”. The outcome variable was dichotomized into “definitely/probably” vs. “definitely not/probably not”.

4.2.5 Statistical Analysis

Data analysis was undertaken using the Statistical Package for Social Scientists (SPSS) Version

17.0. We summed the data within a single cognitive factor to get the cognitive factor total, and these individual sums were used in our analysis. Exploratory analysis for each sum was conducted with histograms, Quantile-Quantile (Q-Q) plots, and the Kolmogorov-Smirnov (K-S) test to assess normality of distribution. The t-test was used for continuous normally distributed variables, and the Mann-Whitney test was used for skewed continuous variables. Spearman's correlation coefficient was used to test the correlation between variables that were not normally distributed.

Contingency table analysis was used to compare willing with unwilling subjects (Table 4.1). A multivariate logistic regression model created for all variables that were significant in the univariate model ($p < 0.05$) was used to analyze the data with WTP as the dependent variable.

4.3 RESULTS

The mean age of participants was 42.3 years (median = 43.2 years; standard deviation [SD] = 8.5 years; range 21 to 65 years). The number of people who were “definitely willing” to participate in an HIV vaccine trial was 79 (29%), “probably willing” was 75 (27%), “probably not willing” was 42 (15%), and “definitely not willing” was 47 (17%), and “do not know” was 33 (12%). When those responding “do not know” were omitted, 243 participants remained for the analysis. The percentage of men in the analyzed sample was 65%, and the percentage who were of Aboriginal ethnicity was 29%. The follow-up rate in the VIDUS participants was 82% during the period of 2007-2008.

4.3.1 HIV treatment optimism

On exploratory analysis, histograms showed that both WTP and non-WTP participants tended to be low in HIV treatment optimism (most values < 4/10 for both); Q-Q plots and the Kolmogorov–Smirnov test (K-S) test ($p < 0.01$) showed that the distribution of the treatment optimism sum was significantly non-normal. The mean treatment optimism score was 3.7 / 10. The Mann-Whitney test showed that the sum was not significantly related to WTP ($p = 0.40$). Using Spearman’s rho, the correlation of the two HIV treatment optimism items with each other was 0.62.

4.3.2 Self-efficacy

Histograms showed that people that both WTP and non-WTP participants tended to be high in self-efficacy (most values ≥ 80 of a possible 100 for both); Q-Q plots and the K-S test ($p < 0.01$) showed that the self-efficacy composite score was significantly non-normal. The mean self-

efficacy score was 82.5/100. Using the Mann-Whitney test, higher self-efficacy was significantly related to a greater WTP ($p < 0.01$). Spearman's rho showed that the individual items were highly correlated with each other (range = 0.42 to 0.86) and Cronbach's alpha was also high ($\alpha = 0.86$).

4.3.3 Knowledge of HIV vaccine trial concepts

The sum of correct responses was normally distributed on histograms and Q-Q plots. The mean knowledge score was 4.4/10. The individual items assessed in the chi-square analysis were not significantly related to WTP (Table 4.1). In terms of vaccine safety, item #7 "Once a large-scale HIV vaccine trial begins, we can be sure the vaccine is completely safe" (correct answer = false) was responded correctly by 37% of participants. Cronbach's alpha was 0.61 for the knowledge scale. The corrected item-total correlations indicated that the knowledge scale was not fully reliable (Table 4.2).

In a multivariate logistic regression analysis (Table 4.3), a 20-unit increase in self-efficacy on a 100-point composite scale was significantly related to a greater WTP (AOR = 1.95, 95% CI = 1.40-2.70, $p < 0.01$). Aboriginal ethnicity (AOR = 3.47, 95% CI = 1.68-7.18), and a higher educational level (\geq high school) (AOR = 1.96, 95% CI = 1.07-3.59) were positively related to WTP (Table 4.3). The variance inflation factors (VIF) indicated that there was no multicollinearity, as the largest VIF was less than 10.0 (Field, January 2009) (VIF for Aboriginal ethnicity = 1.03; = 1.05 for educational level; = 1.03 for self-efficacy).

4.4 DISCUSSION

The aim of our study was to determine if cognitive factors among IDU were related to WTP in a preventive HIV vaccine trial. In total, of 276 HIV-negative IDU, 56% of participants reported WTP. A 5-item self-efficacy scale was developed, and there was a positive relationship between self-efficacy and WTP in an HIV vaccine trial. Cronbach's alpha indicated high reliability for this scale.

The relationship of educational level and WTP differed from previous results, where generally low educational levels (<high school) were positively related to WTP (Dhalla et al., 2009; Dhalla et al., 2007). The opposite relationship in our study may reflect differences between our study population and those previously studied or may be due to unmeasured confounders in our study including vaccine awareness or motivation. Vaccine awareness refers to knowledge of childhood immunizations, the purpose of vaccination, and some knowledge of HIV vaccine development (Celentano et al., 1995).

4.4.1 Cognitive factors

HIV treatment optimism was unrelated to WTP, though specific vaccine optimism was not examined. Given the improved predictability of cognitive factors related to more specific behaviors (Fishbein & Azjen, 1975), the examination of vaccine-specific optimism may be warranted. A positive relationship between vaccine optimism and high-risk behavior would underline the need for ongoing risk-reduction counseling and behavioral interventions.

As demonstrated in our study, self-efficacy was positively related to WTP. Our results suggest

that the relationship of self-efficacy to WTP in our study may be relevant in an actual vaccine trial in IDU in our setting where recruitment strategies are similar. The sparse data at lower values makes it difficult to comment on the relationship between self-efficacy and WTP at these values. Generalizability would be expected assuming that the relationship between self-efficacy and WTP is similar in those different populations and settings. The scale or a modified version should also be tested in other populations and settings to examine its validity in relation to WTP.

The present study found no relationship between knowledge of vaccine-related concepts and WTP in an HIV vaccine trial. At the same time, low educational levels (<high school) have been positively related to WTP (Dhalla et al., 2009; Dhalla et al., 2007). In contrast, vaccine awareness has been correlated with WTP (Jaspan et al., 2006; Kiwanuka et al., 2004; Sahay et al., 2005), and educational programs to address lack of knowledge or misconceptions may improve WTP. Further investigation is needed, therefore, to more clearly understand the relationship between knowledge and WTP. This understanding can inform the need for and nature of interventions to increase that knowledge.

4.4.2 High-risk variables

Aboriginal ethnicity was found to be positively related to WTP in HIV vaccine trials. A possible confounder in the relationship between Aboriginal ethnicity and WTP is educational level (i.e., \geq high school vs. <high school). However, with or without educational level in the final multivariate model, the strength of the association between Aboriginal ethnicity and WTP in an HIV vaccine trial was largely unchanged. Perceived risk (of seroconversion) is another potential confounder, but this variable was not available in the questionnaire. Therefore, exactly what

explains the relationship between Aboriginal ethnicity and WTP is not clear in our dataset.

Further research is needed, therefore, into the relationship between factors that place one at high-risk for HIV infection and that individual's WTP in an HIV vaccine trial.

4.4.3 Comparison of studies

In the present study, approximately 56% of an IDU cohort were willing to participate in a hypothetical HIV vaccine trial, whereas a 1997 study in Vancouver, Canada, found that 83% of IDU respondents were willing to participate (Strathdee et al., 2000). As Strathdee et al. (2000) point out in their paper, the methodology used may have overestimated WTP, as participants were given little information beyond the definition of a vaccine. Moreover, in the latter study, the possible answers consisted only of a yes/no response option. The reasons for the decrease in WTP relative to the earlier survey may also be related to the development of more efficacious and less toxic HAART medications with simplified regimens (Hammer et al., 2008).

Conversely, with these advances, participants could be more optimistic about vaccine development (Gagnon & Godin, 2000), although optimism was not linked to WTP in our study. The decrease in WTP may also be due to the recent results of the STEP study (Buchbinder et al., 2008), although one knowledge item in the present study "Once a large-scale HIV vaccine trial begins, we can be sure the vaccine is completely safe" was responded to correctly by only 37% of participants.

4.4.4 Limitations

There were several limitations in our study. VIDUS is a non-random sample and this could affect generalizability. The present study was cross-sectional, and we could not examine changes

in cognitive factors, retention rates, or WTP over time. The oral interviews used might have resulted in socially desirable reporting. For example, one study found that the level of understanding of vaccine trial concepts was overestimated by self-report and forced-choice checklists, and this could be due to social desirability (Lindegger et al., 2006). There is also a possibility that the answers on the knowledge test were not based on true understanding, but on rote memorization. The way vaccines were described by the interviewers may have affected knowledge and stated WTP. Furthermore, there was limited power to detect interactions between self-efficacy and other variables in our dataset due to small numbers of participants. In addition, the treatment optimism scale consisted of only two items, thereby decreasing the reliability of the scale. Finally, we could not examine construct validity (ie. the correlation between our self-efficacy questions and those by Kerr et al. [2005]), as the latter scale was not available in the present questionnaire.

4.5 CONCLUSIONS

This study addresses gaps in the present knowledge of cognitive factors related to WTP in an HIV vaccine trial. To our knowledge, the relationship between self-efficacy and WTP in IDU has not previously been examined. In our particular setting in IDU, the self-efficacy result may be useful for identifying participants who would be WTP in an HIV vaccine trial. The cognitive factors examined in this study deserve further exploration in other settings and populations such as MSM and heterosexuals, and also other items relating more specifically to vaccine trials. Finally, in spite of the recent positive results of the Thailand HIV vaccine trial (US Military [HIV] Research Program), the potential impact of the STEP study on WTP needs to be assessed.

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Table 4.1 Factors associated with willingness to participate in an HIV vaccine trial among HIV-negative injection drug users (n=243)

Variable	WTP (n=154) n (%)	not WTP (n=89) n (%)	p-value*
Sociodemographics			
Age mean (median) (IQR)**	42.1 years (42.9) (36.8-47.7)	42.8 years (44.9) (35.8-50.4)	0.51 (t-test)
Gender			
Female (reference)	60 (39)	26 (29)	0.13
Male	94 (61)	63 (71)	
Aboriginal ethnicity***	54 (35)	17 (19)	0.01
Education \geq high school	90 (58)	38 (43)	0.02
Employment	46 (30)	22 (25)	0.39
Unstable Housing†	107 (69)	59 (66)	0.61
Risk variables			
Borrowed needles†	9 (6)	6 (7)	0.79¥
Lent needles†	4 (3)	6 (7)	0.18¥
Heroin day \geq daily‡	43 (28)	27 (30)	0.69
Cocaine day \geq daily‡	13 (8)	7 (8)	0.88
Crack day \geq daily‡	58 (38)	36 (40)	0.67
Sex trade involvement†	25 (16)	8 (9)	0.11
Incarceration†	31 (20)	12 (13)	0.19
Health Service Utilization			
Attended NEP (ever vs. never)	118 (77)	63 (71)	0.32
NEP \geq 1/week	68 (44)	35 (39)	0.46
Injecting in Insite (ever vs. never)	109 (71)	70 (79)	0.18
Injecting in Insite†	89 (58)	65 (73)	0.81
Drug / alcohol treatment†	75 (49)	47 (53)	0.54
Psychosocial variables			
Depression ■	87 (66)	53 (65)	0.88
Cognitive factors			
Treatment optimism			
By taking HIV medicines, an HIV+ person reduces the chance of infecting someone with HIV through sharing needles	-	-	0.95

Table 4.1 Factors associated with willingness to participate in an HIV vaccine trial among injection drug users (n=243)

Variable	WTP (n=154) n (%)	not WTP (n=89) n (%)	p-value*
By taking HIV medicines, an HIV+ person reduces the chance of infecting someone with HIV through unprotected sex	-	-	0.14
Treatment optimism sum	-	-	0.40
Knowledge items Correct vs. incorrect / do not know			
1	35 (23)	27 (30)	0.19
2	44 (29)	21 (24)	0.40
3	77 (50)	36 (40)	0.15
4	90 (58)	52 (58)	1.00
5	19 (12)	13 (15)	0.63
6	94 (61)	49 (55)	0.36
7	52 (34)	39 (44)	0.12
8	71 (46)	40 (45)	0.86
9	76 (49)	33 (37)	0.06
10	125 (81)	71 (80)	0.71

* Two-tailed probability.

**IQR, Interquartile range.

*** First Nations, Métis, or Inuit.

†Activities in past 6 months.

‡Current activities.

¥Fisher's exact test.

■ CES-D standard cut-off score of 16 or greater.

Table 4.2 Corrected item-total correlations of knowledge scale (n = 243)

Item number	Knowledge item	Corrected item-total correlation
1	An HIV vaccine could weaken the immune system's ability to fight off HIV infection	0.13
2	Only vaccines that are known to be at least 50% effective at preventing HIV will be tested	0.21
3	The vaccine will have no effect on a participant's HIV test results	0.25
4	If people test HIV-positive after the vaccine, they may really be infected with HIV, or they may just be having a reaction to the vaccine	0.24
5	People in these studies will receive health care for any medical problems they have	0.13
6	People in a vaccine study will know whether or not they got the placebo because only the vaccine will cause side effects	0.45
7	Once a large-scale HIV vaccine trial begins, we can be sure the vaccine is completely safe	0.35
8	People in these studies are guaranteed to be in any future vaccine studies	0.39
9	The study nurse will decide who gets the real vaccine and who gets placebo	0.40
10	Some participants will get the real vaccine and some will get a placebo	0.27

Table 4.3. Multivariate logistic regression model showing independent predictors of willingness to participate in an HIV vaccine trial among injection drug users (n=243)

Variable	AOR	95% CI	p-value
Self-efficacy	1.95	1.40 – 2.70	p<0.01
Aboriginal ethnicity	3.47	1.68 – 7.18	p< 0.01
Educational level (higher vs. lower)	1.96	1.07 – 3.59	p<0.05

AOR, adjusted odds ratio; CI, confidence interval.

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Chapter 5

Cognitive factors and willingness to participate in an HIV vaccine trial among HIV-positive injection drug users

5.1 INTRODUCTION

Currently, there is a need for the development and implementation of both a therapeutic and prophylactic vaccine (Perrin, 2002). Therapeutic vaccination has been investigated with the aim to increase immune responses in order to delay or reduce highly active antiretroviral therapy use (HAART) and prevent disease development (Puls & Emery, 2006).

At present, there is no licensed therapeutic vaccine for HIV. One phase 3 therapeutic HIV vaccine trial (Study 806) has been conducted in 77 centers in the United States (US) using the Salk HIV-1 immunogen (Remune) in the presence of antiretroviral therapy (ART) or no ART (Kahn, Cherng, Mayer, Murray, & Lagakos, 2000). This trial was unsuccessful with respect to HIV progression-free survival and overall mortality.

A recently conducted phase 2 study in HIV-positive individuals incorporated a psychological sub-study as part of a 3-arm trial (ALVAC+Remune vs. ALVAC alone vs. placebo) (Balfour et al., 2006). The goal of the sub-study was to examine HIV patients' baseline motivation for participating in a therapeutic HIV vaccine trial using a risk / benefit analysis. It was found that

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patients enrolled in the trial felt that the potential social and personal benefits of participating outweighed potential social and personal risks.

Nevertheless, more vaccine research is needed in HIV-positive individuals, and their willingness to participate (WTP) in such research must be better understood. Cognitive factors can be examined as predictors of WTP in an HIV vaccine trial, and the present study focused on such factors, including HIV treatment optimism, self-efficacy beliefs surrounding an HIV vaccine trial, and knowledge of vaccine concepts. To our knowledge, these cognitive factors have not previously been examined in the context of a therapeutic HIV vaccine preparedness study (VPS).

5.1.1 Cognitive factors

Optimism has been defined as the “hopefulness and confidence about the future or the success of something” (Soanes & Stevenson, 2005). Optimism in the context of a therapeutic trial would be important to examine as HIV treatment optimism may potentially be associated with high or low vaccine/vaccine trial optimism.

Self-efficacy is concerned “not with the skills themselves but with the judgements about what one can do with those skills” (Bandura, 1986). Self-efficacy is important because a person’s belief that he/she can comply and adhere to a protocol could be important in a multi-dose regimen vaccine trial. To our knowledge, there has been no self-efficacy scale developed in injection drug users (IDU) for an HIV vaccine trial. However, in a study of South African adolescents who were untested for HIV (Kagee, personal communication, September 2009), self-efficacy (called perceived behavioral control) was unrelated to WTP in a hypothetical HIV

vaccine trial (Giocos, Kagee, & Swartz, 2008).

Knowledge is defined as the “information and understanding of a specific topic or of the world in general, usually acquired by experience or by learning” (VandenBos, 2007) (*the subset of beliefs that have been objectively proven to be true*). Knowledge is ethically necessary for informed consent and may be associated with WTP in a vaccine trial. Various knowledge scales exist for these purposes (Koblin et al., 1998; Koblin, Holte, Lenderking, & Heagerty, 2000; Smit et al., 2006; Starace et al., 2006).

5.1.2 Objectives and Hypotheses

The present study examines the relationship between selected cognitive factors and WTP in a hypothetical HIV therapeutic vaccine trial in IDU in Vancouver, Canada. We sought to determine the effects of HIV treatment optimism, self-efficacy regarding a vaccine trial, and knowledge of HIV vaccine trial concepts in relation to WTP in an HIV vaccine trial. We also examined the effects of sociodemographic variables, drug use and risk behaviors, measures of health service utilization, and psychosocial factors in relation to WTP. We hypothesized that higher self-efficacy would be positively related to a greater WTP in a therapeutic HIV vaccine trial. We also hypothesized that treatment optimism and knowledge would be associated with WTP, though we could not predict the direction of this hypothesis in our study.

5.2 METHODS

5.2.1 Procedure

Participants in the present cross-sectional study were IDU who were also part of the AIDS Care Cohort to Evaluate Exposure to Survival Services study (ACCESS), a prospective open cohort study in HIV-positive IDU that began in December 2005. A detailed description of this cohort is provided elsewhere (Uhlmann et al. [in press]). Participants completed an interviewer-administered questionnaire assessing demographic data, information about recent drug use patterns, HIV risk behaviors, and experiences in addiction treatment. Participants were reimbursed \$20 Canadian (CDN) dollars for the study visit, at which time referrals were provided for universal medical care, HIV/AIDS care, and available drug and alcohol treatment. The study has been approved on an annual basis by the Providence Health Care/University of British Columbia (UBC) Research Ethics Board (Appendix C).

Data collection for the present study took place within the larger context of ACCESS. Opportunities to administer the questionnaire used to collect data between the dates of June 2007 and May 2008 yielded a sample size of 85 participants. Notably, a similar study with a larger sample size of 276 HIV-negative participants yielded close to equivalent results for the cognitive factor data in relation to WTP (Dhalla et al., 2010).

5.2.2 Educational points

After the conclusion of the main questionnaire, trained interviewers administered eight points pertaining to knowledge of HIV vaccine trial concepts (Koblin et al., 2000) (with permission, Koblin, November 2007) (Appendix A). These items focused on concepts such as

randomization, blinding, placebos, safety, adverse reactions, and vaccine-induced seropositivity (Appendix A). If participants did not know what a vaccine was, the definition was explained by the interviewer. Previous work in this area presented the prospect of vaccine trials as being likely without giving respondents the impression that they were being invited to a specific trial (Koblin et al., 2000), and our script was written to be consistent with this precedent.

5.2.3 Explanatory variables

Factors examined in relation to WTP were based on a previous VPS conducted in Vancouver, Canada (Strathdee et al., 2000) (Table 5.1). For our study, Aboriginal ethnicity was defined as: First Nations (native), Métis, or Inuit. To assess depression, the Center for Epidemiologic Studies Depression Scale (CES-D) score was used, and a standard cut-off score of ≥ 16 to define depression was applied (McDowell, 2006).

5.2.4 Measurement scales

As part of a larger interview, trained interviewers administered three measurement scales addressing HIV treatment optimism (2 items) (Appendix A), self-efficacy (5 items) (Appendix A), and knowledge of HIV vaccine trial concepts (10 true/false items) (Appendix A). The HIV treatment optimism scale was part of the main questionnaire.

In terms of validation of the optimism scale, Van De Ven et al. in 2000 developed a 12-item treatment optimism scale in gay men (15.2% reported they were HIV-positive) which was shown to have predictive validity and generalizability (Van de Ven, Crawford, Kippax, Knox, & Prestage, 2000). For the present study, two HIV treatment optimism items, similar to those used

by Van de Ven et al. (2000), were summed to obtain an HIV treatment optimism total score (Table 5.1).

The self-efficacy scale was a supplemental scale administered after the conclusion of the main questionnaire (Appendix A). The self-efficacy items were based on a previous self-efficacy scale in HIV-positive individuals that had predictive validity for HAART continuation and high internal consistency ($\alpha = 0.82$) (Kerr et al., 2005). In the present study, composite self-efficacy scores were calculated by adding the subscale scores and dividing the sum by the total number of subscale items (Kerr et al., 2005).

The knowledge scale was also a supplemental scale administered after the conclusion of the main questionnaire (Appendix A). The 10 knowledge true/false items were taken from a study in HIV-negative individuals (Halpern, Metzger, Berlin, & Ubel, 2001; Koblin et al., 2000) (with permission, Koblin, November 2007), although the scale has knowledge items also pertaining to preventive trials. The knowledge questions were categorized as correct vs. incorrect/do not know. Corrected item-total correlations for the knowledge items were also examined.

5.2.5 Outcome variable

Willingness to participate was the outcome variable and was assessed via the question: “If an HIV vaccine study were available, would you be willing to participate in it?” (Appendix A).

Five possible answers were provided: “definitely not”, “probably not”, “don’t know”, “definitely/probably” vs. “definitely not/probably not”. Those who answered “don’t know” for WTP were excluded from the analysis.

5.2.6 Statistical Analysis

Data analysis was undertaken using Statistical Package for Social Scientists (SPSS) Version 17.0. Contingency table analysis was used to compare willing with unwilling subjects (Table 5.1). The t-test was used for normally distributed continuous variables, while the Mann-Whitney test was used for skewed continuous variables. The p-value of self-efficacy ($p \leq 0.07$, 1-tailed test) was the criterion for variable inclusion in a logistic regression model, as self-efficacy was the primary variable that we chose to examine in the present study.

5.3 RESULTS

Between June 2007 and May 2008, 85 HIV-positive individuals were recruited for participation in this study. The number of people who were “definitely willing” to participate in a therapeutic HIV vaccine trial was 24 (28%), “probably willing” was 22 (26%), “probably not willing” was 15 (18%), and “definitely not willing” was 14 (17%). Ten people (12%) responded “don’t know”, leaving 75 participants for our analysis. Overall, 54% of individuals were WTP. For the sample analyzed, the percentage of men was 57%, and similarly, those who were of Aboriginal ethnicity numbered 48%. The follow-up rate in the ACCESS participants was 82% during the period of 2007-2008.

5.3.1 HIV treatment optimism

Participants tended to be low in HIV treatment optimism (most values < 3/10). The mean HIV treatment optimism score was 3.9/10. For the first optimism question (“By taking HIV medicines, an HIV-positive person reduces the chance of infecting someone with HIV through sharing needles”), 56% of the participants replied “strongly disagree” and were least optimistic, and only 11% replied “strongly agree” and were most optimistic (Table 5.1). Similarly, for the second optimism question (“By taking HIV medicines, an HIV-positive person reduces the chance of infecting someone with HIV through unprotected sex”), 55% replied “strongly disagree” while 13% replied “strongly agree” (Table 5.1). The Mann-Whitney test showed that the HIV treatment optimism sum was not significantly related to WTP ($p = 0.95$). As well, the HIV treatment optimism sum was unrelated to Aboriginal ethnicity ($p = 0.44$) and sex ($p = 0.12$). The correlation between the two HIV treatment optimism items was 0.49.

5.3.2 Self-efficacy

Participants tended to be high in self-efficacy (most values >80/100). The mean self-efficacy score was 79.8/100. In a logistic regression analysis, a 20-unit increase in self-efficacy on a 100-point composite scale was positively associated with WTP (OR = 1.61, 95% CI = 1.04-2.46, $p < 0.05$). The self-efficacy items were highly correlated with each other (range = 0.44 to 0.92) and Cronbach's α was 0.89, indicating high reliability. Scores above 0.7 are the usual criteria for adequate internal consistency (Horne et al., 2004). The sum of efficacy expectations items #1 to #4 in our self-efficacy scale yielded a self-efficacy mean value of 85.1 for WTP, and 72.0 for not WTP. These are similar values to the mean values of efficacy expectations in the study by Kerr et al. (2005), which showed the mean values to be 87.6 for no HAART discontinuation, and 70.5 for HAART discontinuation.

5.3.3 Knowledge of HIV vaccine trial concepts

Participants tended to be low in knowledge with a mean knowledge score of 4.1/10. In general, the knowledge items were unrelated to WTP. In light of the STEP study results, we paid particular attention to item #7, which stated "Once a large-scale HIV vaccine trial begins, we can be sure the vaccine is completely safe" (correct answer = false). This item was responded to correctly by only 35% of participants (Table 5.1). Cronbach's alpha was 0.64 for the knowledge items, slightly higher than in our study in HIV-negative individuals (alpha = 0.61) (Dhalla et al., 2010). Corrected item-total correlations calculated as part of a reliability analysis showed several items below a recognized cut-off of 0.3, indicating low correlation with the overall scale (Table 5.2) (Field, 2009).

Being on HAART treatment was not significantly related to WTP in a therapeutic HIV vaccine trial ($p = 0.60$) and HIV treatment optimism (Mann-Whitney = 0.25). As well, removing crack use \geq daily from the analysis did not result in a significant change in the relationship between self-efficacy and WTP. Knowledge item #10 (some people will get a real vaccine and some will get a placebo) for which $p=0.05$ on chi-square analysis (Table 5.1) was not included in our model, as we did not have justification to include only one knowledge item. The sum of knowledge was unrelated to WTP in a therapeutic HIV vaccine trial (Table 5.1).

5.4 DISCUSSION

To our knowledge, this is among the first therapeutic phase 3 HIV VPS conducted to determine factors associated with WTP in an HIV vaccine trial in IDU. Willingness to participate in a hypothetical therapeutic HIV vaccine trial was found to be 54%. A 20-unit increase in self-efficacy was positively related to WTP (AOR = 1.61, 95% CI = 1.04-2.46, $p < 0.05$). HIV treatment optimism, and the knowledge sum were unrelated to WTP. These results are similar to our recent VPS in HIV-negative individuals (Dhalla et al., 2010).

We were unable to identify a previous study examining the relationship between HIV treatment optimism and WTP in an HIV vaccine trial, in HIV-positive individuals. However, in a previous study in a Swedish general population, it was found that optimism surrounding an HIV vaccine developed in the next 5 years was positively related to the belief that treatment with highly active antiretroviral therapy (HAART) reduced infectivity (Herlitz & Steel, 2001). Further studies could be developed to discover the important relationship specifically between vaccine optimism and WTP, as well as the longitudinal relationship between optimism and sexual behavior.

Given previous findings (Kerr et al., 2005), it is reasonable that self-efficacy may factor into decisions such as WTP. Therefore, from our study, high self-efficacy scores may be useful in the enrolment of individuals into a phase 3 therapeutic HIV vaccine trial. However, as there was a lack of data at lower values of self-efficacy, the relationship between self-efficacy and WTP at lower levels of self-efficacy was inconclusive. Cognitive-behavioral interventions could be used to increase self-efficacy, potentially increasing WTP (Barclay et al., 2007). For example, it

could be explained to participants that as they are able to follow-up in the ACCESS study, they would in effect be capable of following up in an actual HIV vaccine trial.

Knowledge item #7, which assessed HIV vaccine safety (Appendix A), could also be asked more specifically with respect to the STEP study results (von Bubnoff A & Jefferys R., 2009). A recent study by Newman et al. (2008) in Toronto, Canada, found that concerns about vaccine safety were associated with uncertainty in WTP with respect to the phase 2B STEP study, though the respondents in Toronto were mainly gay men.

The knowledge scale in our study had a Cronbach's $\alpha = 0.64$, indicating the scale could be further refined, or other more reliable knowledge scales could be used (Smit et al., 2006). In previous studies by Koblin et al. who developed the knowledge scale used in the present study, internal consistency was not measured (Koblin et al., 2000). Knowledge in relation to WTP in IDU has yielded contradictory results in separate studies also using Koblin's scale (Halpern et al., 2001; Koblin et al., 2000). The variability in study findings could be attributable, in part, to a lack of internal consistency in the measures used. Other studies have used various knowledge scales in IDU (Harrison, Vlahov, Jones, Charron, & Clements, 1995) and other populations (Smit et al., 2006; Starace et al., 2006). Koblin et al. (1998) developed another similar scale used in the present study, although the scale consisted of more items than the scale used in the present study.

A large percentage of the ACCESS cohort were on HAART treatment (65% of the analyzed participants in the present study claimed they were on HAART), but in our analysis, being on

treatment did not affect their WTP. Treatment with HAART is not without complications such as toxicities and necessity for long-term adherence (Hammer et al., 2008). Given this, potential participants may be duly concerned about the short-term and long-term side effects of adding another medical intervention in the form of an HIV therapeutic vaccine.

The percentage of Aboriginals in the sample in the present therapeutic HIV VPS study was 48%, compared to 29% in our previous study in HIV-negative individuals (Dhalla et al., 2010). These numbers in HIV-positive individuals and HIV-negative individuals are representative numbers of Aboriginal individuals in the Downtown Eastside of Vancouver, Canada. Aboriginal people are known to be over-represented in the HIV epidemic in Canada (Public Health Agency of Canada, 2008).

In reference to WTP, it should be noted that the progression to development of AIDS may potentially be a concern to these HIV-positive individuals, but this may be offset by the fact that many participants were already on HAART. The discouraging results of the STEP study (Buchbinder et al., 2008) may also negatively affect WTP, although the study was in HIV-negative individuals. Only 35% of individuals were aware that there may be issues surrounding vaccine safety in general, and this suggests that individuals should be educated prior to conducting a therapeutic HIV vaccine trial in this case.

Limitations

There were several limitations in our study. The ACCESS cohort is a non-random sample and only a small subsample of the cohort was included in this particular study. These issues could

affect generalizability and increase the likelihood of a Type 2 error. The study could not examine changes in cognitive factors over time. Oral interviews might have resulted in socially desirable reporting. Treatment optimism may also not necessarily be a proxy for vaccine optimism. In addition, there were only two items in the treatment optimism scale, and more items would be required to improve the reliability of the scale. Although we found no effect of confounding, the sample size ($n = 75$) to detect confounders was limited. In addition, it is possible that the answers on knowledge were not based on true understanding of vaccine trial concepts but on rote recall. The psychometrics of Koblin's scale were also not strong ($\alpha=0.64$). It should also be kept in mind that trials at specific sites depend on local cultural and social environments (Lau, Stansbury, Gust, & Kafaar, 2009), and that hypothetical WTP may also overestimate actual enrolment.

5.5 CONCLUSIONS

This study addresses gaps in knowledge regarding cognitive factors and WTP in HIV vaccine trials. In this study, HIV treatment optimism and knowledge of vaccine trial concepts were unrelated to WTP in a therapeutic HIV vaccine trial. At higher values, self-efficacy may be useful in increasing WTP in a therapeutic HIV vaccine trial. The self-efficacy scale that we have developed may be validated to determine the relationship to WTP in other populations and settings. A prediction model could be developed to quantify the contribution of self-efficacy to variations in WTP. To build on a recent study which examined factors associated with non-enrolment in the phase 2B STEP study (Newman et al., 2008), quantitative (e.g., Likert-type scales) and qualitative (e.g., focus groups) research in IDU could further examine WTP in an HIV vaccine trial, as well as knowledge and beliefs surrounding vaccine trial concepts in IDU.

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Table 5.1 Factors associated with willingness to participate in an HIV vaccine trial among HIV-positive injection drug users (n=75)

Variable	WTP (n=46) n (%)	not WTP (n=29) n (%)	p-value*
Sociodemographics			
Age mean (median) (IQR)**	42.3 years (43.7) (35.6-48.0)	41.7 years (43.1) (36.9-46.9)	0.76* (t-test)
Female (reference)	19 (41)	13 (45)	0.76
Male	27 (59)	16 (55)	
Aboriginal ethnicity***	20 (43)	16 (55)	0.32
Education ≥ high school	24 (52)	13 (45)	0.54
Employment	9 (20)	4 (14)	0.76¥
Unstable Housing†	37 (80)	21 (72)	0.42
Risk variables			
Borrowed needles†	2 (4)	1 (3)	1.00¥
Lent needles†	1 (2)	0	1.00¥
Injection heroin ≥ daily‡	9 (20)	7 (24)	0.64
Injection cocaine ≥ daily‡	5 (11)	2 (7)	0.70¥
Smoking crack ≥ daily‡	25 (54)	9 (31)	0.05
Sex trade involvement†	4 (9)	5 (17)	0.30¥
Incarceration†	7 (15)	2 (7)	0.47¥
Health Service Utilization			
Attended needle-exchange program (ever vs. never)	34 (74)	16 (55)	0.09
Needle-exchange program ≥ 1/week	17 (37)	10 (34)	0.83
Injecting in Insite (ever vs. never)	34 (74)	19 (66)	0.44
Injecting in Insite†	24 (52)	13 (45)	0.54
Drug / alcohol treatment†	23 (50)	15 (52)	0.88
Psychosocial variables			
Depression (≥ 16)§ (n = 62)	26 (67) (n=39)	14 (61) (n=23)	0.65
Cognitive factors			
By taking HIV medicines, an HIV+ person reduces the chance of infecting someone with HIV through sharing needles■	-	-	0.73

Table 5.1, cont'd. **Factors associated with willingness to participate in an HIV vaccine trial among HIV-positive injection drug users (n=75)**

Variable	WTP (n=46) n (%)	not WTP (n=29) n (%)	p-value*
By taking HIV medicines, an HIV+ person reduces the chance of infecting someone with HIV through unprotected sex■	-	-	0.74
Treatment optimism sum	-	-	0.95
Knowledge items Correct vs. incorrect / do not know			
1	12 (26)	10 (34)	0.44
2	11 (24)	8 (28)	0.72
3	16 (33)	13 (45)	0.38
4	24 (52)	16 (55)	0.80
5	4 (8)	9 (31)	0.03¥
6	25 (51)	12 (41)	0.27
7	13 (27)	13 (45)	0.14
8	17 (35)	13 (45)	0.50
9	18 (39)	13 (45)	0.63
10	39 (85)	19 (66)	0.05
Knowledge sum			0.41 (t-test)
HAART^Δ treatment	29 (63)	20 (69)	0.60

* Two-tailed probability.

**IQR, Interquartile range.

*** First Nations (native), Métis, or Inuit.

†Activities in past 6 months.

‡Current activities.

¥Fisher's exact test.

§ CES-D standard cut-off score of ≥ 16 .

■ 5-point optimism scale ranging from “strongly disagree” to “strongly agree”.

Δ Highly-active antiretroviral therapy

Table 5.2 Corrected item-total correlations of knowledge scale (n = 75)

Item Number	Knowledge item	Corrected item- total correlation
1	An HIV vaccine could weaken the immune system's ability to fight off HIV infection	0.05
2	Only vaccines that are known to be at least 50% effective at preventing HIV will be tested	0.29
3	The vaccine will have no effect on a participant's HIV test results	0.49
4	If people test HIV-positive after the vaccine, they may really be infected with HIV, or they may just be having a reaction to the vaccine	0.19
5	People in these studies will receive health care for any medical problems they have	0.14
6	People in a vaccine study will know whether or not they got the placebo because only the vaccine will cause side effects	0.48
7	Once a large-scale HIV vaccine trial begins, we can be sure the vaccine is completely safe	0.30
8	People in these studies are guaranteed to be in any future vaccine studies	0.43
9	The study nurse will decide who gets the real vaccine and who gets placebo	0.49
10	Some participants will get the real vaccine and some will get a placebo	0.22

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Chapter 6

Conclusion

This chapter is divided into 5 sections: (1) a description of the dissertation and background information (2) a summary of the findings of the studies and comparisons between the studies (3) overall strengths and weaknesses of the studies (4) implications and (5) future directions. A table of the most recent vaccine preparedness studies (VPS) that were not covered in Chapter 2 and 3 has also been included (Tables 6.1 and 6.2).

6.1 BACKGROUND

The purpose of this thesis was to investigate the cognitive factors of HIV treatment optimism, self-efficacy beliefs, and knowledge of vaccine trial concepts in relation to willingness to participate (WTP) in an HIV vaccine trial. Chapters 2 and 3 consist of review articles of HIV vaccine preparedness studies (VPS) in the Organization for Economic Co-operation and Development (OECD) countries and in the non-OECD countries, respectively. A large number of preventive (in HIV-negative individuals) VPS have taken place in the OECD and non-OECD countries, for example in injection drug users (IDU) and those at sexual risk (Dhalla, Nelson, Singer, & Poole, 2009; Dhalla, Woods, Strathdee, Patrick, & Hogg, 2007). Assessing cognitive and high-risk factors in VPS may assist in planning and implementation of HIV vaccine trials and thus contribute to studies of vaccine preparedness.

Chapter 4 examines cognitive factors and high-risk variables in relation to WTP in HIV-negative IDU from the Vancouver injection drug users' study (VIDUS). Chapter 5 examines cognitive factors in relation to WTP in HIV-positive IDU from the the AIDS Care Cohort to evaluate

Exposure to Survival Services study (ACCESS). We examined WTP in both HIV-negative and HIV-positive individuals for a comparison of variables associated with WTP and differences in these populations.

In general, VPS are conducted to identify populations that would be suitable for HIV vaccine trials in different settings, to develop recruitment and retention strategies, to develop and evaluate education strategies for vaccine efficacy trials, to measure attitudes towards HIV vaccine efficacy trials, and to measure behavior change in high-risk cohorts (Sheon, 1994). As such, HIV VPS are a precursor to HIV vaccine trials, as they assess feasibility of large-scale vaccine trials (Strathdee et al., 2000). Criteria that have been suggested to determine this feasibility in target populations include: HIV seroprevalence, HIV seroconversion, risk behaviors, WTP in a vaccine trial, and compliance/retention (Meyers et al., 1995). HIV incidence rates (IR) specifically can also reflect non-vaccine interventions: education, counseling, condom use, and treatment of sexually transmitted diseases (STDs) (Djomand et al., 2008; Heyward, Osmanov, & Esparza, 1996).

Even if the factors delineated above are all indicate that conducting HIV vaccine trials may be feasible, other factors such as unavailability of medical care during and after a trial might indicate that it is not, in fact, feasible to conduct a vaccine trial (Newman, 2009). This is particularly predominant in resource-limited settings. As well, significant structural-level challenges are posed by criminalization of behaviors associated with HIV transmission (with, for example, extrajudicial killing of IDU) and of evidence-based HIV preventive measures including syringe exchange programs (Newman, 2009).

6.2 STUDY RESULTS

In the OECD countries, VPS have been conducted mainly in IDU, men who have sex with men (MSM), and women at heterosexual risk (WAHR) (Dhalla et al., 2007). Populations examined in the VPS in non-OECD countries have included IDU, MSM, commercial sex workers (CSW), sexually transmitted diseases (STD) clinic attendees, army conscripts, factory workers, police officers, and discordant couples (Dhalla et al., 2009).

Studies have shown that WTP rates have varied, ranging from 41-86% in IDU in the OECD countries, and between 23%-100% in the non-OECD countries. Subsequent to the studies featured on our published reviews, other VPS have taken place more recently in 2008/2009 (Tables 6.1 and 6.2) (de Bruyn, Skhosana, Robertson, McIntyre, & Gray, 2008; Djomand et al., 2008; Etcheverry et al., 2008; Giocos, Kagee, & Swartz, 2008; Middelkoop et al., 2008; Ruzagira et al., 2009; Saterren et al., 2006; Suhadev et al., 2006; Valente et al., 2009; Yin et al., 2008) with results that have been largely consistent with previous studies. Generally, high-risk factors in HIV-negative individuals were positively associated with WTP. This is important as HIV seroconversion rates also need to be adequate (>2%) if a difference between the vaccine and placebo can be detected in an actual HIV vaccine trial. Willingness to participate was found to be 56% in the VIDUS study, while it was found to be 54% in the ACCESS study.

Yin et al. (2008) comment in their study that a 1-year retention of at least 90% with >2% HIV seroincidence is considered necessary for an HIV vaccine trial. In our review articles in Chapters 2 and 3, some of the retention rates at 1 year were found to be lower than 90%.

However, many of these retention rates may be adequate due to the relatively large sample sizes, and also because WTP was associated with high risk behavior.

6.2.1 Cognitive factors

In Chapters 4 and 5, cognitive factors were examined in relation to WTP in both a preventive and therapeutic HIV vaccine trial. It was determined that HIV treatment optimism and knowledge of HIV vaccine trial concepts were generally unrelated to WTP; however, self-efficacy had a positive association with WTP. In Chapter 4, using HIV-negative individuals, a 20-unit increase in self-efficacy on a 100-point composite scale was positively related to WTP (adjusted odds ratio [AOR]) = 1.95, 95% CI = 1.40-2.70, p-value <0.01). In Chapter 5 using HIV-positive individuals, a higher levels of self-efficacy for a 20-unit change was similarly related to WTP (AOR = 1.61, 95% CI = 1.04-2.46, p<0.05). These results applied only to higher levels of self-efficacy, due to the sparsity of data at lower values of the self-efficacy variable.

For the VIDUS study, the mean value for the first four “efficacy-expectation” items was 87.3 for WTP and 74.4 for not WTP. This is compared to 85.1 for WTP, and 72.0 for not WTP in the ACCESS study. These are similar values to the mean values of efficacy expectations in Kerr’s study (Kerr, 2005), which showed the mean values to be 87.6 for no highly active antiretroviral therapy (HAART) discontinuation, and 70.5 for HAART discontinuation.

As previously discussed, biomedical interventions such as HIV vaccines also require behavioral and structural interventions to be effective (Coates et al., 2008; Gupta et al., 2008; Padian et al., 2008). Willingness to participate in a vaccine trial is an important biomedical measure to predict

future enrolment in an actual vaccine trial. Furthermore, the self-efficacy scale used in the present study focused on adherence and retention components, which are important factors in an HIV vaccine trial. Behavioral strategies such as cognitive-behavioral techniques could improve self-efficacy and thus WTP. On a more macroscopic level, structural interventions are required to enhance the feasibility of vaccine trials and the likelihood that the findings of such trials would be put to good use.

6.3 STRENGTHS AND WEAKNESSES

6.3.1 Strengths

One of the strengths of our studies is that we addressed a gap in knowledge in the current HIV vaccine literature regarding cognitive factors in relation to WTP. The reviews of the VPS in Chapters 2 and 3 have also never been conducted before. In addition, to our knowledge, we have also conducted one of the first therapeutic VPS in IDU.

Another strength is that we used a well-developed cohort of a high-risk population of IDU from the VIDUS study. This gave us the opportunity to assess a high-risk cohort with good follow-up that would be a potential population used for an actual HIV vaccine trial. Injection drug users are an important group of people that would be targeted to receive an HIV vaccine.

A further strength of the study is that we used questionnaires that have previously been used or validated. The HIV treatment optimism items were already part of the main VIDUS questionnaire. The self-efficacy scale was based on a scale by Kerr et al. (2005), in which predictive validity was shown for self-efficacy and HAART continuation. The knowledge scale

was one that has previously been used in other studies (Halpern, Metzger, Berlin, & Ubel, 2001; Koblin, Holte, Lenderking, & Heagerty, 2000; Suhadev et al., 2006).

6.3.2 Weaknesses

The VIDUS and ACCESS studies were of a cross-sectional nature rather than a longitudinal nature. Therefore, changes and stability of WTP as well as changes in knowledge levels could not be examined over time, given educational efforts. How changes in knowledge contribute to changes in WTP also could not be examined (Koblin et al., 2000). Longitudinal assessment would be valuable to examine attrition rates (Bartholow et al., 1997). The sample size for the therapeutic VPS was also relatively small (85 participants) and, therefore, the results could be susceptible to a Type 2 error.

Both our studies relied on self-report and participants were reimbursed for their participation (Kerr et al., 2005); therefore, this may lead to social desirability resulting in under-reporting of drug use and sexual behaviors, and over-reporting of WTP. HIV treatment optimism was unrelated to WTP, but specific vaccine optimism was not examined. Another limitation of our treatment optimism scale was that it consisted of only two items. Longer scales for treatment optimism do exist (Van de Ven, Crawford, Kippax, Knox, & Prestage, 2000) and may improve reliability (Huebner, Rebchook, & Kegeles, 2004). The responses to the knowledge items may not be based on true understanding but on rote recall. Participants also need to believe the information they receive so that they do not simply recall information but believe it to be true (Halpern et al., 2001).

The present studies (measuring intention) may be limited in terms of predicting actual participation (measuring behavior) in vaccine efficacy trials. The validity of the WTP responses in our study depends on whether those who state they will be willing to participate actually would actually enrol in efficacy trials (Meyers, Metzger, Navaline, Woody, & McLellan, 1994). As well, the data we collected did not specify an actual candidate vaccine product or a specific trial (Koblin et al., 2000; Ruzagira et al., 2009), and this may be important in light of the recent STEP study results. Generalizability is a concern for WTP in an HIV vaccine trial, as knowledge and WTP may vary between communities and countries, and also between different risk groups (Smit et al., 2006). The findings in the present study may not be generalizable to the entire community of IDU or to other populations. Generalizability may also be a concern because in consenting to be part of the VIDUS cohort, participants have already indicated WTP in research studies, and this may positively bias WTP (Middelkoop et al., 2008).

6.4 IMPLICATIONS

The research presented in this dissertation makes a contribution to the field of HIV vaccine research. Few studies have examined cognitive factors of optimism, self-efficacy, and knowledge; for example, to our knowledge, self-efficacy in relation to WTP in IDU has never been examined. No standard or validated self-efficacy scale in IDU is available for HIV vaccine research. The review articles also offer a view of VPS in different settings and populations compared to our particular setting. Such review articles have not been published previously.

Self-efficacy may be a useful predictor of WTP and could inform recruitment and enrolment into an actual vaccine trial. The results regarding self-efficacy could also inform researchers about

participants who are unlikely to adhere or be retained.

Cognitive-behavioral interventions could be used to modify self-efficacy (Barclay et al., 2007); for example, people in the VIDUS study who are followed up could be told that they are able to manage follow-up, and this is reflecting their self-efficacy. In other words, someone who has successfully performed a behavior in the past should report a higher level of self-efficacy than another person who has either failed to perform the behavior or who has never attempted it (Smith, McGraw, Costa, & McKinlay, 1996).

Knowledge in relation to WTP in IDU has yielded contradictory results (Halpern et al., 2001; Koblin et al., 2000), and our studies were conducted to address these contradictions. The internal consistency of the knowledge scale in the preventive VPS was 0.61 and in the therapeutic VPS was 0.64, reflecting relatively low levels of internal consistency. Scores above 0.7 are the usual criteria for adequate internal consistency (Horne et al., 2004). The variability in study findings could be attributable, in part, to a lack of internal consistency in the measures used. The knowledge scale could be refined or other knowledge scales could be used that have improved internal consistency values (Smit et al., 2006).

The issue of knowledge must also take into account rote memorization vs. true understanding of vaccine trial concepts, especially among vulnerable populations (Meyers et al., 1995). Truly informed consent would require extensive education about the candidate vaccine, its potential risks, and the detailed description of trial procedures (Hays & Kegeles, 1999).

Willingness to participate in an HIV vaccine trial was found to be 56% in our preventive study in HIV-negative IDU and 54% in our therapeutic study in HIV-positive IDU. These values are within the range of WTP values in other studies (Dhalla et al., 2009; Dhalla et al., 2007). This would be favorable in this era of highly active antiretroviral therapy (HAART), in that individuals would still consider participating in an HIV vaccine trial despite the promise of effective treatment should they seroconvert (Golub et al., 2005). However, it is likely that WTP may be considerably affected with the discouraging results of the STEP study.

As mentioned previously, there is a potential for disinhibition regarding safe sexual behavior from use of condoms; and of concern, there may also similarly be a potential for disinhibition motivated by HIV vaccine trial participation.

Vaccine safety, vaccine-induced seropositivity, and possible protection from the vaccine are an important focus of participant and community education (Koblin, Avrett, Taylor, & Stevens, 1997). Community education should be in place to improve communities' knowledge base about preventive HIV vaccine trials, inform communities' perception of trial-related risks, and increase understanding of trial-related benefits (Strauss et al., 2001). Dialogue with the community in a transparent manner can be an essential prerequisite for the conducting of vaccine trials (Sahay et al., 2005). These types of community-based interventions could also lead to improvements in self-efficacy behaviors (Smith et al., 1996).

6.5 FUTURE DIRECTIONS

Over the next few years, social and behavioral research will likely become more integral to HIV

vaccine research (Lau, Stansbury, Gust, & Kafaar, 2009), as this topic has been under-researched. Such research may include application of the health belief model, the theory of planned behavior (TPB), and the theory of reasoned action (TRA) (Poole, Matheson, & Cox, 2008). For example, the cognitive factors examined in this study may deserve further exploration in other settings and populations such as men who have sex with men (MSM) and heterosexuals, and also using items that relate more specifically to vaccine trials. The self-efficacy scale could be modified and validated using items that pertain more to individual populations and settings. HIV vaccine optimism specifically can be examined to determine its relationship to WTP. HIV treatment optimism can also be examined with respect to other variables, such as sociodemographic variables of age, gender, and ethnicity. Follow-up research should be conducted on the high AOR based on the Aboriginal ethnicity variable.

For the self-efficacy construct, a prediction model can be used to quantify the contribution of this construct to WTP in a HIV vaccine trial. Longitudinal analysis could be conducted to determine changes in WTP and knowledge over time as well as factors associated with retention and HIV seroconversion.

Barriers and motivators to participation as well as misconceptions can be examined in our population to further target educational strategies. Identification of possible barriers is crucial as they have a direct relationship with the decision to participate in HIV vaccine trials (Sahay et al., 2005). Recruitment into trials is likely to be enhanced by addressing misconceptions surrounding participation, including issues such as confidentiality, discrimination, vaccine-induced seropositivity, and negative reactions from new sex partners (Van de Ven et al., 2005).

Future research could also examine other aspects of the health belief model such as cost-gain analysis and perceived vulnerability or susceptibility. In this regard, the results of the STEP study should be incorporated in VPS to determine their effect on WTP.

Examining cognitive and high-risk factors in relation to WTP may lead to useful and practical applications for enrolment into phase 3 HIV vaccine trials. Both preventive and therapeutic VPS are essential as they contribute overall to assessing feasibility of HIV vaccine trials. HIV vaccines would contribute to overall prevention and therapeutic measures to prevent acquisition of HIV and/or delay progression to AIDS.

Table 6.1 Retention rates for a hypothetical HIV vaccine study

Source	Location	Study Population	Sample size	Time period (Time interval)	Retention
Wei, 2006 (HPTN 033)	Guangxi, China	IDU (94% Han) (18-51 years)	500	2002-2003 (12 mos)	87%
Middelkoop, 2008 (HPTN 033)	Cape Town, South Africa	Adults* Adolescents* (16-40 years)	200	2003-2005 (12 months)	Adults 83%*† Adolescents 87%*†
Djomand, 2008 (HVTN 903)	Dominican Republic	FSW Male STI clinic attendees	200	2003-2007 (12 months)	97.0%
	Haiti	STI clinic attendees	201		95.0%
	Jamaica	FSW Male and female STI clinic attendees	100		89.0%
	Puerto Rico	FSW women with IDU male sexual partners	100		87.0%
	Peru	MSM (18-35 years)	200		92.5%

IDU, injection drug users; FSW, female sex workers; STI, sexually transmitted infection clinic attendees; MSM, men who have sex with men.

* no significant difference between adults and adolescents ($p=0.58$).

†female gender associated with retention on multivariate analysis (hazard ratio 0.28, 95%CI = 0.13-0.61).

Table 6.2 Willingness to participate (WTP) and determinants of participation for a hypothetical HIV vaccine study

Source	Location (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
Sateren, 2006	Kericho, Kenya	Agricultural plantation residents (18-45 years)	820 (81 HIV+ve)	97%		
Giocos, 2008	Western Cape, South Africa	Grade 10 and 11 Learners (14-21 years)	224		Subjective norms Attitudes towards participation in a vaccine trial	1.19 (1.07-1.34) 1.32 (1.00-1.74)
Middelkoop, 2008	Cape Town, South Africa	Adults Adolescents* (16-40 years)	200 HIV-ve	40% Adults 13% Adolescents (baseline) 63% Adults 40% Adolescents (12 mos)	Adults Adolescents	3.50 (1.55-8.89) 28.0 (4.63-1144)
Yin, 2008	Xinjiang, China (northwestern China)	IDU (≥18 years) 70% Uigars 25% Han ethnics	401	74.3% definitely 17.7% probably	Ever had sex with IDU Sharing needles / syringes Perceived family support for participation Perceived vaccine protection Perceived risk of stigma and isolation	1.8 (1.04-3.2) 3.7 (1.2-11.7) 7.4 (4.3-12.7) 16.1 (3.7-70.8) 0.3 (0.2-0.5)

Table 6.2, cont'd **Willingness to participate (WTP) and determinants of participation for a hypothetical HIV vaccine study**

Source	Location (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
Djomand, 2008	Dominican Republic	FSW Male STI clinic attendees	200	91.5% baseline 90.7% 12 mos		
	Haiti	STI clinic attendees	201	95.0% baseline* 89.0% 12 mos		
	Jamaica	FSW Male and female STI clinic attendees	100	92.0% baseline* 84.3% 12 mos		
	Puerto Rico	FSW women with IDU male sexual partners	100	90.0% baseline** 80.6% 12 months		
	Peru	MSM	200	96.0% baseline** 89.6% 12 mos		
de Bruyn, 2008	Soweto, South Africa	School-going youth (10-25 years)	240	52.5% definitely 35.0% probably		

Table 6.2, cont'd **Willingness to participate (WTP) and determinants of participation for a hypothetical HIV vaccine study**

Source	Location (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
Etcheverry, 2008	Barcelona Madrid, Spain	FSW IDU Non-IDU MSM	780	82% definitely or probably	Age 31-40 vs. 18-30 years Latin American origin vs. Spanish origin Homosexual Bisexual Sex with an IDU partner Sex with a partner using other drugs (cocaine, crack, marijuana, heroin) Sex with a partner with multiple sexual partners Performs sex work Non-injection drug use	1.64 (1.04-2.58) 3.77 (1.84-7.75) 4.53 (1.33-15.49) 4.83 (1.12-20.83) 2.48 (1.18-5.22) 2.92 (1.50-5.71) 2.16 (1.91-4.25) 1.89 (1.05-3.38) 1.67 (1.02-2.73)
Ruzagira, 2009	Masaka district, Uganda	Community- based cohort (18-60 years)	1013	95% WTP (2 years)	Unwilling to participate Age 35-44 vs. 18-24 years Physical harm concerns (1+ mentioned) Risk behavior index*** (low to high risk)	 3.90 (0.98-15.61) 34.9 (10.4-118) 0.09 (0.01-0.73)

Table 6.2, cont'd **Willingness to participate (WTP) and determinants of participation for a hypothetical HIV vaccine study**

Source	Location (Year of Study)	Study Population	Sample Size	WTP	Predictors	AOR (95% CI)
Valente, 2009†	Los Angeles, California	Social network members (alters) Adults (25+ years Adolescents (12-24 yrs)	348 276		Age, per year increase Awareness of index's HIV positivity (no) Drug risk	1.03 (1.00-1.05) 0.11 (0.05-0.23) 0.22 (0.08-0.65)
Suhadev, 2009	Chennai Madurai, India	Transport workers STI patients IDU MSM CSW Married women	501	88% WTP 88% 92% 74% 95% 58% 82% overall	↓ Education Married women	↓ WTP ↓ WTP

IDU, injection drug users; FSW, female sex workers; CSW, commercial sex workers; STI, sexually transmitted infection clinic attendees; MSM, men who have sex with men.

* based on number of sexual partners, history and consistency of condom use.

† factors associated with willingness to invite alters to participate in this VPS.

** statistically significant decrease from baseline to 12 months.

***defined as those 16-20 years of age.

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Wei, L., Chen, J., Rodolph, M., Beauchamp, G., Mâsse, B., Li, R., et al. (2006). HIV incidence, retention, and changes of high-risk behaviors among rural injection drug users in Guangxi, China. *Substance Abuse*, 27, 53-61.

Yin, L., Zhang, Y., Qian, H. Z., Rui, B., Zhang, L., Zhu, J., et al. (2008). Willingness of Chinese injection drug users to participate in HIV vaccine trials. *Vaccine*, 26, 762-768.

APPENDIX A: Study Measurement Scales

HIV treatment optimism items

Please indicate how much you agree with each statement, giving your first ‘gut reaction’:

RESPONSES: 1. Strongly Disagree
2. Somewhat Disagree
3. Neither agree nor disagree
4. Somewhat Agree
5. Strongly Agree

STATEMENTS:

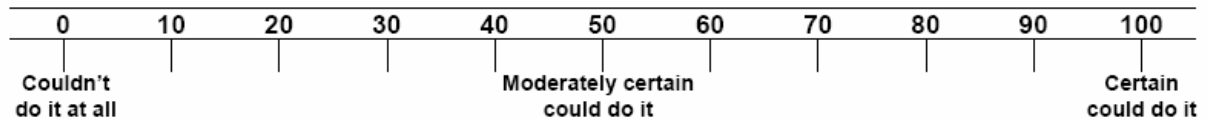
- By taking HIV medicines, an HIV+ person reduces the chance of infecting someone with HIV through sharing needles 1 2 3 4 5

- By taking HIV medicines, an HIV+ person reduces the chance of infecting someone with HIV through unprotected sex 1 2 3 4 5

Self-efficacy items

If you were in a vaccine study, how certain are you that you could do each of the following?

Please rate your level of confidence by recording in each space a number from 0 to 100 using the scale below:



a. Remember to keep appointments for the time of each vaccination, which may be frequent for the first several months.
b. Remember to keep all appointments for the rest of the study, which may be every three months, and up to four years in total.
c. Remember to also take HAART medications if HIV-positive.
d. Remember not to obtain HIV antibody tests outside of the study.
e. Take the vaccine when using intravenous drugs.

Participants were asked to indicate their level of confidence in their ability to perform the specified behaviors. Responses were given using an 11-point scale ranging from 0 to 100 (i.e. 0, 10, 20, . . . , 100), with 0 anchored as ‘Could not do it at all’ and 100 anchored as ‘Certain could do it’.

HAART refers to highly active antiretroviral therapy.

VIDUS II / ACCESS Nurse's Supplemental Questionnaire

Code:

Interviewer:

To Be Completed by the NURSE

READ:

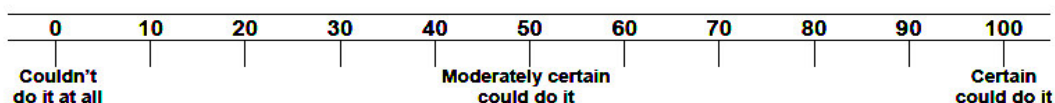
- In the next few years, more HIV vaccine studies will be started, with the hope of coming up with an HIV vaccine that works.
- The people who participate in these studies receive either a vaccine or a placebo. A placebo is a substance that can't hurt you, but can't prevent HIV either.
- The vaccine or the placebo can produce the same side effects, such as a sore arm, fever, or headache, that could last for a few days.
- People who get the vaccine will be chosen at random, like flipping a coin, and no one will know who got the vaccine and who got the placebo until after the study is over.
- Participants in vaccine studies will get counselling and tests for HIV infection about every 3 to 6 months.
- They will also be asked not to have an HIV test anywhere except at the vaccine study office. This is because the vaccine could cause a false HIV-positive test.
- Study participants might face discrimination. For example, if they tell others they are in an HIV vaccine study, people might think they are infected with HIV or have AIDS.
- Vaccine study staff are available to help vaccine study participants obtain access to health care and make sure their HIV test is accurate and up-to-date.

SQ0: If an HIV vaccine study were available, would you be willing to participate in it?

☐ Definitely Not ☐ Probably Not ☐ Don't Know ☐ Probably ☐ Definitely

SQ1: If you were in a vaccine study, how certain are you that you could do each of the following?

Please rate your level of confidence by recording in each space a number from 0 to 100 using the scale below.



**Confidence
(0 – 100)**

a. Remember to keep appointments for the time of each vaccination, which may be frequent for the first several months.	
b. Remember to keep all appointments for the rest of the study, which may be every three months, and up to four years in total.	
c. Remember to also take HAART medications if HIV-positive.	
d. Remember not to obtain HIV antibody tests outside of the study.	
e. Take the vaccine when using intravenous drugs.	

Knowledge items from nurse's supplemental questionnaire⁴

SQ2: Please identify the following statements as either "true", "false", or "I don't know".

- a. An HIV vaccine could weaken the immune system's ability to fight off HIV infection.
☐ True ☐ False ☐ I don't know
- b. Only vaccines that are known to be at least 50% effective at preventing HIV will be tested.
☐ True ☐ False ☐ I don't know
- c. The vaccine will have no effect on a participant's HIV test results.
☐ True ☐ False ☐ I don't know
- d. If people test HIV-positive after the vaccine, they may really be infected with HIV, or they may just be having a reaction to the vaccine.
☐ True ☐ False ☐ I don't know
- e. People in these studies will receive health care for any medical problems they have.
☐ True ☐ False ☐ I don't know
- f. People in a vaccine study will know whether or not they got the placebo because only the vaccine will cause side effects.
☐ True ☐ False ☐ I don't know
- g. Once a large-scale HIV vaccine trial begins, we can be sure the vaccine is completely safe.
☐ True ☐ False ☐ I don't know
- h. People in these studies are guaranteed to be in any future vaccine studies.
☐ True ☐ False ☐ I don't know
- i. The study nurse will decide who gets the real vaccine and who gets placebo.
☐ True ☐ False ☐ I don't know
- j. Some participants will get the real vaccine and some will get a placebo.
☐ True ☐ False ☐ I don't know

Adapted and used with permission from Koblin et al. Readiness for HIV vaccine trials: changes in willingness and knowledge among high-risk populations in the HIV Network for Prevention Trials. J Acquir Immune Defic Syndr 2000; 24(5): 451-7.

⁴ Permission to use obtained, Wolters Kluwer Health Permissions department, March, 2010.

APPENDIX B: Consent Forms



British Columbia Centre for Excellence in HIV/AIDS

St. Paul's Hospital
#608 – 1081 Burrard St.
Vancouver, B.C. V6Z 1Y6
Phone: 604-685-6355
Fax: 604-685-5533

The VANCOUVER Injection Drug Users Study II **INFORMED CONSENT FORM**

The Principal Investigator in this study is:

Dr. Thomas Kerr, B.C. Centre for Excellence in HIV/AIDS. Phone (604) 806 9116.

The co-Investigators in this study are:

Dr. Evan Wood, B.C. Centre for Excellence in HIV/AIDS
Dr. Julio Montaner, B.C. Centre for Excellence in HIV/AIDS
Dr. Martin Schechter, BC Centre for Excellence in HIV/AIDS
Dr. Mark W. Tyndall, B.C. Centre for Excellence in HIV/AIDS
Dr. Anita Palepu, B.C. Centre for Excellence in HIV/AIDS
Dr. Robert Hogg, B.C. Centre for Excellence in HIV/AIDS
Dr. Jo-Anne Stoltz, B.C. Centre for Excellence in HIV/AIDS
Dr. Stephanie Strathdee, BC Centre for Excellence in HIV/AIDS
Dr. Richard Harrigan, BC Centre for Excellence in HIV/AIDS
Dr. David Patrick, B.C. Centre for Disease Control
Dr. Timothy Christie, B.C. Centre for Excellence in HIV/AIDS
Dr. Patricia Spittal, B.C. Centre for Excellence in HIV/AIDS

Study Sponsors:

CIHR and NIH

Introduction

The VIDUS II study is a multi-year study examining HIV prevention and HIV treatment issues among HIV-negative injection drug users and is being conducted by researchers at the BC Centre for Excellence in HIV/AIDS. You are being invited to participate in this study because you are an HIV-negative person who has had experience injecting drugs. HIV-negative injection drug users are at risk of complications from their drug use including HIV infection. Little is known about the barriers to accessing medical and

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Participant Initials: _____

prevention services among injection drug users.

Purpose of the Study

The purpose of the study is to examine trends in HIV risk behaviors as well as patterns of medical service and social service use among HIV-negative injection drug users.

Who can participate

HIV-negative persons who have used injection drugs. Unless you have been previously enrolled in VIDUS, you will have injected drugs at least once in the past month to be eligible for this study. Please note that if you become HIV-positive during your participation in this study, you will no longer be eligible to participate. However, you will be invited to transfer to a related study, called ACCESS, which takes place at the same research site. The study procedures for ACCESS are the same as for VIDUS II (see description below), but you will be required to sign a new consent form.

Your Participation in the Evaluation

To help you decide whether or not you wish to take part, this consent form will tell you about:

- Why the research is being done
- What your participation will involve, and
- The possible benefits, risks and discomforts.

Please take time to read this information carefully. You are welcome to discuss this information with your family, friends, and doctor before you decide whether to participate or not. If you decide to participate, you will be asked to sign this form.

Study Procedures

To monitor people's drug use patterns, three techniques will be used to collect information for this study and will require 30-45 minutes of your time. Data are being collected through interviews, collection of blood, and health and social information (database) linkages. Each of these will be described below.

Interview: If you agree to participate, you will be interviewed at the beginning of the study about your health, drug use, and sexual activities. You will also be asked to participate in follow-up interviews every 6 months over the next five years for a total of 10 interviews. You may be invited to conduct additional interviews if the study receives additional funding. Your responses will be important to help us understand how drug use patterns and behaviors affect the health of injection drug users. You have the right to refuse to answer any question, and there will be no consequences for refusing to answer any questions.

Collection of Blood: At the beginning of the study, and at each 6 month follow-up visit, you will be asked to provide several tubes of blood drawn from a vein in your arm. Blood will be tested for HIV viruses, hepatitis viruses, and T-helper immune cell counts. You will receive counseling about HIV and hepatitis C before your blood is taken and when you return for your results. You may also ask any questions you have, for example about HIV/AIDS or other infections, or how to access clean needles. You have the right to

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choose not to receive your HIV and hepatitis C test results if you do not want them.

Reporting to Public Health

Both HIV and Hepatitis C virus infection are reportable illnesses, which means that doctors and nurses need to report the names of people they test positive for these infections. You may choose name-included (nominal) or nameless (non-nominal) testing for your HIV test. The HIV and Hep C testing procedures are slightly different and will be described below.

HIV testing procedures: 1. **Name-included (nominal) HIV testing.** If you choose the name-included option for your HIV testing, we are required by law to provide your name to local health officials if you test positive. If you choose the name-included option, and you test positive for HIV, public health officials may contact you to educate you about ways to prevent transmitting the virus and to ask you if you know anyone else who should be tested for HIV because of your contact with them. 2. **Nameless (non-nominal) HIV testing:** You can also choose to have your name not included with your HIV test. If you choose the nameless option for HIV, we can still provide you with your test result when you come back to the study office, and we will not have to share your name with public health officials. However, public health officials may still make an effort to contact you without knowing or using your name or address to find you. You have the option of refusing to speak with public health officials about HIV and your HIV test results. The benefits of knowing you are HIV infected include, knowing that you should see a doctor so that you can better manage your health and knowing that you need to be careful with your used needles and that you should use condoms if you are having sex.

Please also note that we may also ask you to provide a saliva sample for rapid HIV testing to confirm that you are HIV-negative prior to enrolling in the study. The sample will be taken by a study nurse. It will not be stored and the results will be kept confidential.

Hep C testing procedures: 1. **Name-included (nominal) Hepatitis C (Hep C) testing.** We are required by law to provide your name to local health officials if you test positive this virus. If you test positive for Hep C, public health officials may contact you to educate you about ways to prevent transmitting the virus and to ask you if you know anyone else who should be tested for Hep C because of your contact with them. You have the option of refusing to speak with public health officials about Hep C and your Hep C test results. The benefits of knowing you are Hep C infected include, knowing that you should see a doctor so that you can better manage your health and knowing that you need to be careful with your used needles.

Blood Storage: A small amount of blood will be stored in deep-freeze at the B.C. Centre for Excellence in HIV/AIDS and/or the BC Centre for Disease Control for the duration of the study. We will also be storing blood samples for five years after the study is ended, in order to test for previously unknown viruses that may appear (for example, a new kind of hepatitis). Before any of your blood is to be tested in the future for an agent other than those already mentioned, approval will be sought from an Ethics committee at the University of British Columbia.

Health Information (database) linkages: To obtain some health information and information about your social service use, we need your permission for access to health and social service records, which include information about your hospital visits, medical treatments, contact with social services and other agencies. This will only be done if you give your permission by signing this form. For example, we would find this information through St. Paul's ER and Hospital database; BC Centre for Excellence in HIV/AIDS Drug Treatment Program Database; PARIS Database (includes records of VCH primary care and addiction service utilization); UBC Health Linked Database; BC CDC Infectious Disease Testing Database; InSite (supervised injection site) Database; and Vital Statistics. Also, if you are a participant in VIDUS (Vancouver Injection Drug Users Study), CHASE (Community Health and Safety Evaluation), or SEOSI (Scientific Evaluation of the Supervised Injection Site), we are asking for your permission to link to the information you provided when you enrolled in those studies. Information that could be used to identify you will be kept in an electronic database that can be looked at only by the principal researcher and the research staff. They are not allowed to share your name with anyone unless required by law.

Follow-up: We are also asking for your permission to try to find you if you miss a scheduled appointment. If you enroll in the study, we will ask you where we can try to contact you. If you agree to provide contact information and the names of the agencies you visit, evaluation staff will try to reach you at your last known address or phone number, and evaluation staff may also try to reach you through agencies that you visit, such as shelters, medical services, and street nurses. We will not try and contact you at any agency without getting your permission first and we will not try to contact you at phone numbers or addresses unless this information has been provided by you.

Risks and Benefits

You should know that using street drugs is very dangerous and the staff will be willing to assist you in getting help to reduce or stop using drugs at any time. You may want to discuss the health risks of drug use with your family doctor or one of the study nursing staff.

Interview: The risks associated with being interviewed may be related to your feelings when answering the questions. This could possibly cause a negative emotional response. You may refuse, for any reason, to answer any question(s) that make you feel uncomfortable and there will be no consequences for refusing to answer any questions. If you want to speak with an interviewer or nurse, or seek counselling services after being interviewed, you may ask the interviewer for assistance, and the interviewer may ask if you need help if he or she thinks you are having difficulty.

Collection of Blood: Possible complications of drawing blood could include minor bruising, irritation, redness, minor bleeding and/or swelling where the blood is taken. There is also a very small risk of infection.

Information (database) Linkages: The investigators involved with this project have a legal and ethical duty to keep all information about you confidential unless otherwise required by law. Any identifying information about you that we use to link databases (such as your name, birth date, personal health number, etc.), will be removed and an

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VIDUS II

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Participant Initials: _____

anonymous identifier such as a code number will be attached to your data before it is used for the research. The only people who will have access to both your personal identifying information (such as your name), and your research-related information (such as number of hospital visits), will be the study database personnel. These personnel are required to sign confidentiality agreements as a condition of employment. No other study personnel except the Principal Investigator will have access to both your personal identifiers and your personal information.

Reporting to public health: To date there have been no adverse effects associated with reporting HIV or Hep C test results to public health officials, and there are benefits to getting your test results. However, once we disclose test results and individuals names, we cannot control what they do with this information. It is important to realize that if you do not want your name reported to public health, that you choose the non-name option for your HIV test.

Benefits: As noted above, the benefits to participation in the study include knowing the results of the HIV and Hep C tests that are conducted as part of the study, as well as obtaining access to health and addiction services through study referrals. In addition, participants in similar studies have expressed positive feelings about contributing to a project that will ultimately benefit others similar to them and to society as a whole.

Voluntary Participation and Withdrawal

Your participation is entirely voluntary. You have the right to refuse to participate in this study. If you decide to participate, your decision is not binding and you may choose to withdraw from the study at any time without any negative consequences to the medical care, education, or other services you may receive from this clinic or this hospital, or other services you may receive in the neighborhood. The researchers may also decide to discontinue the study at any time, or withdraw you from the study at any time, if they feel it is in your best interest.

Confidentiality

Your confidentiality will be respected. Information that discloses your identity will not be released without your consent unless required by law or regulation. However, research records and medical records identifying you may be inspected in the presence of the investigator or his or her designate, by representatives of Health Canada, and the UBC/PHC Research Ethics Board for the purposes of monitoring the research. No records that identify you by name or initials will be allowed to leave the investigator's office.

Compensation

There will be no cost to you for participation in this study. You will not be charged for any research procedures, such as blood testing. You will be offered a \$20 payment at each study visit. You will still be offered \$20 for this first visit even if you do not decide to enroll in the study.

If You Have Questions

If you have any questions or concerns about this study, you can contact Dr. Thomas Kerr

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at 604-806-9116.

Your Rights

By signing this form you are not giving up any of your rights and you do not release the study doctors or other participating institutions from their legal and professional responsibilities. If new information becomes available that may affect your willingness to remain in the study, you will be advised of this information. If you have concerns about your rights as a research subject and/or your experiences while participating in this study, you may telephone the Director, Office of Research Services at the University of British Columbia, at 604-822-8598 or the Chair of the UBC/Providence Health Care Research Ethics Board at 604-628-2344 local 62325.

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VIDUS II

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PARTICIPANT CONSENT AND SIGNATURE PAGE

Consent and Signature

I agree to participate in the Vancouver Injection Drug Users Study II, allow confidential access to my health and service records, including hospital records, emergency room visits, medical treatment records, social service and other agency records, criminal justice records, and records from other research studies; allow a sample of my blood to be tested for HIV and Hep C, give my permission to be contacted for a follow-up visit every six months, and acknowledge receiving a copy of this form.

Signed	Printed Name	Date
--------	--------------	------

Principal Investigator Or Designate	Printed Name	Date
--	--------------	------

Blood Testing Selections

HIV Testing:

I select the name included (nominal) option for my HIV testing.

Signature: _____

I select the nameless (anonymous) HIV option for my HIV testing.

Signature: _____



British Columbia
Centre for Excellence
in HIV/AIDS

St Paul's Hospital
608 - 1081 Burrard Street
Vancouver BC V6Z 1Y6
Canada

AIDS Care Cohort to Evaluate access to Survival Services (ACCESS)

INFORMED CONSENT FORM

Principal Investigator: Dr. Evan Wood, BC Centre for Excellence in HIV/AIDS
604-806-9692

Study Sponsors: Canadian Institutes of Health Research
US National Institutes of Health

INTRODUCTION -----

The ACCESS study is a multi-year study examining HIV prevention and HIV treatment issues among illicit drug users and is being conducted by researchers at the BC Centre for Excellence in HIV/AIDS. You are being invited to participate in this study because you are an HIV-positive person who has had experience using illicit drugs. HIV-positive illicit drug users are at risk of complications from their HIV disease. Little is known about the barriers to accessing medical services and HIV prevention services among HIV-positive drug users.

PURPOSE OF THE STUDY -----

The purpose of the study is to examine trends in HIV risk behaviours as well as patterns of medical service and social service use among HIV-positive illicit drug users.

WHO CAN PARTICIPATE -----

HIV-positive persons who have used illicit drugs. Unless you have been previously enrolled in VIDUS, you will have used any illicit drug (not including pot) at least once in the past 6 months to be eligible for this study.

YOUR PARTICIPATION -----

To help you decide whether or not you wish to take part, this consent form will tell you about why the research is being done, what your participation will involve, and the possible benefits, risks and discomforts.

Please take time to read this information carefully. You are welcome to discuss this information with your family, friends, and doctor before you decide whether to participate or not. If you decide to participate, you will be asked to sign this form.

STUDY PROCEDURES -----

To monitor people's drug use patterns, three techniques will be used to collect information for this study and will require 30-45 minutes of your time. Data are being

ACCESS Consent Form (H05-50233)

Version 2009-05-13

Approved 2009-05-25

Participant's Initials: _____

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collected through interviews, collection of blood, and health and social information (database) linkages. Each of these will be described below.

■ Interview

If you agree to participate, you will be interviewed at the beginning of the study about your health, drug use, and sexual activities. You will also be asked to participate in follow-up interviews every 6 months over the next 5 years, for a total of 10 interviews. You may be invited for additional interviews if the study receives additional funding. Your responses will be important to help us understand how drug use patterns and behaviours affect the health of HIV-positive drug users. You have the right to refuse to answer any question, and there will be no consequences for refusing to answer any questions.

■ Collection of Blood

At the beginning of the study, and at each 6-month follow-up visit, you will be asked to provide several tubes of blood drawn from a vein in your arm. Blood will be tested for HIV viruses, hepatitis viruses, and T-helper immune cell counts. You will receive counselling about HIV and hepatitis C before your blood is taken and when you return for your results. If you are taking antiretroviral therapy, we may also measure the level of these medications in your blood. You may also ask any questions you have, for example about HIV/AIDS or other infections, or ways to reduce the risks of illicit drug use. You have the right to choose not to receive your HIV and hepatitis C test results if you do not want them.

Reporting to Public Health: Both HIV and hepatitis C virus infection are reportable illnesses, which means that doctors and nurses need to report the names of people they test positive for these infections. You may choose name-included (nominal) or nameless (non-nominal) testing for your HIV test. The HIV and hep C testing procedures are slightly different and will be described below.

HIV testing procedures:

1. Name-included (nominal) HIV testing. If you choose the name-included option for your HIV testing, we are required by law to provide your name to local health officials if you test positive. If you choose the name-included option and you test positive for HIV, public health officials may contact you to educate you about ways to prevent transmitting the virus and to ask you if you know anyone else who should be tested for HIV because of your contact with them.

2. Nameless (non-nominal) HIV testing. You can also choose to have your name not included with your HIV test. If you choose the nameless option for HIV, we can still provide you with your test result when you come back to the study office, and we will not have to share your name with public health officials. However, public health officials may still make an effort to contact you without knowing or using your name or address to find you. You have the option of refusing to speak with public health officials about HIV and your HIV test results. The benefits of knowing you are HIV-infected include knowing that you should see a doctor so that you can better manage your health, that

you need to be careful with used needles and that you should use condoms if you are having sex.

Please also note that we may also ask you to provide a saliva sample for rapid HIV testing to confirm that you are HIV-negative prior to enrolling in the study. The sample will be taken by a study nurse. It will not be stored and the results will be kept confidential.

Hep C testing procedures:

1. Name-included (nominal) hepatitis C (hep C) testing. We are required by law to provide your name to local health officials if you test positive for this virus. If you test positive for hep C, public health officials may contact you to educate you about ways to prevent transmitting the virus and to ask you if you know anyone else who should be tested for hep C because of your contact with them. You have the option of refusing to speak with public health officials about hep C and your hep C test results. The benefits of knowing you are hep-C-infected include knowing that you should see a doctor so that you can better manage your health and knowing that you need to be careful with your used needles.

Blood Storage: A small amount of blood will be stored in deep-freeze at the BC Centre for Excellence in HIV/AIDS and/or the BC Centre for Disease Control for the duration of the study. We will also be storing blood samples for five years after the study is ended, in order to test for previously unknown viruses that may appear (for example, a new kind of hepatitis). Before any of your blood is to be tested in the future for an agent other than those already mentioned, approval will be sought from an Ethics committee at the University of British Columbia.

■ Health and Social Information (Database) Linkages

To obtain some health information and information about your social service use, we need your permission for access to health and social service records, which include information about your hospital visits, medical treatments, contact with social services and other agencies. This will only be done if you give your permission by signing this form. For example, we would find this information through St. Paul's ER and hospital database, BC Centre for Excellence in HIV/AIDS Drug Treatment Program database, PARIS database (includes records of VCH primary care and addiction services use), BC Linked Health Database, BC CDC infectious disease testing database, Insite (supervised injection site) database, and Vital Statistics. Also, if you are a participant in VIDUS (Vancouver Injection Drug Users Study) I or II, CHASE (Community Health and Safety Evaluation), SEOSI (Scientific Evaluation of the Supervised Injection Site), or ARYS (At-Risk Youth Study) I or II, we are asking for your permission to link to the information you provided when you enrolled in those studies. Information that could be used to identify you will be kept in an electronic database that can be looked at only by the principal researcher and the research staff. They are not allowed to share your name with anyone unless required by law.

■ Follow-Up

We are also asking for your permission to try to find you if you miss a scheduled appointment. If you enrol in the study, we will ask you where we can try to contact you. If you agree to provide contact information and the names of the agencies you visit, evaluation staff will try to reach you at your last known address or phone number, and evaluation staff may also try to reach you through agencies that you visit, such as shelters, medical services, and street nurses. We will not try to contact you at any agency without getting your permission first, and we will not try to contact you at phone numbers or addresses unless this information has been provided by you.

RISKS -----

You should know that using street drugs is very dangerous, and the staff will be willing to assist you in getting help to reduce or stop using drugs at any time. You may want to discuss the health risks of drug use with your family doctor or one of the study nursing staff.

Interview: The risks associated with being interviewed may be related to your feelings when answering the questions. This could possibly cause a negative emotional response. You may refuse, for any reason, to answer any question that makes you feel uncomfortable, and there will be no consequences for refusing to answer any questions. If you want to speak with an interviewer or nurse, or seek counselling services after being interviewed, you may ask the interviewer for assistance, and the interviewer may ask if you need help if he or she thinks you are having difficulty.

Collection of Blood: Possible complications of drawing blood could include minor bruising, irritation, redness, minor bleeding and/or swelling where the blood is taken. There is also a very small risk of infection.

Reporting to Public Health: To date there have been no adverse effects associated with reporting HIV or hep C test results to public health officials, and there are benefits to getting your test results. However, once we disclose test results and individuals' names, we cannot control what they do with this information. It is important, if you do not want your name reported to public health, to choose the non-name option for your HIV test.

Information (Database) Linkages: The investigators involved with this project have a legal and ethical duty to keep all information about you confidential unless otherwise required by law. Any identifying information about you that we use to link databases (such as your name, birth date, personal health number, etc.), will be removed and an anonymous identifier such as a code number will be attached to your data before they are used for the research. The only people who will have access to both your personal identifying information (such as your name) and your research-related information (such as number of hospital visits) will be the study database personnel. These personnel are required to sign confidentiality agreements as a condition of employment. No other study personnel except the Principal Investigator will have access to both your personal identifiers and your personal information.

BENEFITS -----

As noted above, the benefits to participation in the study include knowing the results of the HIV and hep C tests that are conducted as part of the study, as well as obtaining access to health and addiction services through study referrals. In addition, participants in similar studies have expressed positive feelings about contributing to a project that will ultimately benefit others similar to them and to society as a whole.

ACCESS TO HIV TREATMENT -----

Since this study is being conducted by the province's main HIV treatment provider, we would like to actively assist you to obtain HIV care. If you wish for us to actively assist you in obtaining HIV treatment, we will be required to submit your name, birth date, and care card number with your blood tests. These blood tests will also include CD4, viral load, resistance testing, and complete blood count differential. If you do not want this option, you can choose to have your blood tests done non-nominally (without your name), and we will still be happy to try to help you find an HIV doctor.

VOLUNTARY PARTICIPATION AND WITHDRAWAL -----

Your participation is entirely voluntary. You have the right to refuse to participate in this study. If you decide to participate, your decision is not binding and you may choose to withdraw from the study at any time without any negative consequences to the medical care, education, or other services you may receive from this clinic or this hospital, or other services you may receive in the neighbourhood. The researchers may also decide to discontinue the study at any time or withdraw you from the study at any time, if they feel it is in your best interest.

CONFIDENTIALITY -----

Your confidentiality will be respected. Information that discloses your identity will not be released without your consent unless required by law or regulation. However, research records and medical records identifying you may be inspected in the presence of the Principal Investigator or his designate, by representatives of Health Canada, and the UBC/PHC Research Ethics Board for the purposes of monitoring the research. No records that identify you by name or initials will be allowed to leave the investigator's office.

COMPENSATION -----

There will be no cost to you for participation in this study. You will not be charged for any research procedures, such as blood testing. You will be offered a \$20 payment at each study visit. You will still be offered \$20 for this first visit even if you decide not to enrol in the study.

IF YOU HAVE QUESTIONS -----

If you have any questions or concerns about this study, you can contact Dr. Evan Wood at 604-806-9692.

YOUR RIGHTS -----

By signing this form, you are not giving up any of your rights and you do not release the study doctors or other participating institutions from their legal and professional responsibilities. If new information becomes available that may affect your willingness to remain in the study, you will be advised of this information. If you have any concerns about your rights as a research subject and/or your experiences while participating in this study, contact the Research Subject Information Line, Office of Research Services, University of British Columbia, at 604-822-8598, or the Chair of the UBC/Providence Health Care Research Ethics Board at 604-628-2344, local 63197.

PARTICIPANT CONSENT AND SIGNATURE PAGE

Consent and Signature

I agree to participate in the ACCESS study, allow confidential access to my health and service records (including hospital records, emergency room visits, medical treatment records, social service and other agency records, criminal justice records, and records from other research studies), allow a sample of my blood to be tested for HIV and hepatitis C, give my permission to be contacted for a follow-up visit every six months, and acknowledge receiving a copy of this form.

Signed	Printed Name	Date
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Principal Investigator or Designate	Printed Name	Date
--	--------------	------

BLOOD TESTING SELECTIONS

HIV Testing

I select the name included (nominal) option for my HIV testing.

Signature: _____

or

I select the nameless (anonymous) option for my HIV testing.

Signature: _____

YOUR RIGHTS -----

By signing this form, you are not giving up any of your rights and you do not release the study doctors or other participating institutions from their legal and professional responsibilities. If new information becomes available that may affect your willingness to remain in the study, you will be advised of this information. If you have any concerns about your rights as a research subject and/or your experiences while participating in this study, contact the Research Subject Information Line, Office of Research Services, University of British Columbia, at 604-822-8598, or the Chair of the UBC/Providence Health Care Research Ethics Board at 604-628-2344, local 63197.

APPENDIX C: Ethics Certificate



PROVIDENCE HEALTH CARE
Research Institute

UBC-Providence Health Care
Research Institute
Office of Research Services
11th Floor Hornby Site - SPH
c/o 1081 Burrard St.
Vancouver, BC V6Z 1Y6
Tel: (604) 806-8567
Fax: (604) 806-8568

ETHICS CERTIFICATE OF EXPEDITED APPROVAL: ANNUAL RENEWAL

PRINCIPAL INVESTIGATOR: Gary D. Poole	DEPARTMENT: School of Population and Public Health	UBC-PHC REB NUMBER: H08-00554
INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:		
Institution Providence Health Care Other locations where the research will be conducted: Downtown Eastside Study Office		Site St. Paul's Hospital
CO-INVESTIGATOR(S): Shayesta Dhalla Thomas Kerr Evan Wood		
SPONSORING AGENCIES: Canadian Institutes of Health Research (CIHR) - "Willingness of injection drug users (IDU), both HIV-ve and HIV+ve to take part in a HIV vaccine preparedness study and a hypothetical HIV vaccine study"		
PROJECT TITLE: Willingness of Injection Drug Users, both HIV-negative and HIV-positive, to take part in an HIV vaccine preparedness study and a hypothetical HIV vaccine study.		

EXPIRY DATE OF THIS APPROVAL: April 2, 2010

APPROVAL DATE: April 2, 2009

CERTIFICATION:

1. The membership of the UBC-PHC REB complies with the membership requirements for research ethics boards defined in Part C Division 5 of the Food and Drug Regulations of Canada.
2. The UBC-PHC REB carries out its functions in a manner fully consistent with Good Clinical Practices.
3. The UBC-PHC REB has reviewed and approved the research project named on this Certificate of Approval including any associated consent form and taken the action noted above. This research project is to be conducted by the principal investigator named above at the specified research site(s). This review of the UBC-PHC REB have been documented in writing.

The UBC-PHC Research Ethics Board Chair or Associate Chair, has reviewed the documentation for the above named project. The research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved for renewal.