5-2007

Implementing partially effective HIV prevention programs: changes in sexual risk behavior and epidemic impact in Sub-Saharan Africa

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Implementing Partially Effective HIV Prevention Programs: Changes in Sexual Risk Behavior and Epidemic Impact in Sub-Saharan Africa

A Dissertation
Presented to the Faculty of the Graduate School
of
Yale University
in Candidacy for the Degree of
Doctor of Philosophy

by
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Dissertation Director: A. David Paltiel

May 2007

ABSTRACT

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2007

While there is no magic bullet that can completely prevent HIV transmission and halt the HIV/AIDS pandemic, governments and policy makers have an array of partially-effective HIV prevention programs from which to choose, including the use of existing interventions (e.g. education and condom use) and technologies under development (e.g. microbicides and vaccines). Complex decisions regarding if, when, and how to implement various programs with partial efficacy must be made, often in the absence of data on program outcomes. Additionally, the quantitative tradeoff between program-related decreases in HIV transmission and the effects of risk behavior change is often unknown. The potential for changes in risk behavior to influence outcomes at the individual and population levels raises significant operational and ethical concerns regarding the magnitude of program benefits.

Epidemiological data collection of sexual risk-taking behavior and mathematical modeling of population HIV transmission dynamics are used here in a multidisciplinary approach to examine the implications of risk behavior change surrounding the implementation of HIV prevention programs with less than 100% efficacy. This topic is explored within a South African context—specifically, the urban township of Soweto,

which has a generalized, predominantly heterosexual HIV epidemic representative of populations throughout sub-Saharan Africa.

The subject of risk behavior change associated with prevention program implementation arises most frequently in discussions regarding HIV vaccine development and use. The first and second papers contain analyses of self-reported data on current and anticipated sexual risk-taking behavior from adults undergoing screening and enrollment into HIV vaccine trials. The third paper describes a mathematical model to simulate the dynamics of heterosexual HIV transmission, including gender differences in the negotiation of safe sexual practices, in these populations. The potential impact of future HIV vaccination programs is considered, focusing on the interactions between vaccine efficacy and risk behavior change. The analysis is extended in the fourth paper by adapting the framework developed for HIV vaccines, likely not available for at least a decade, to consider adult male circumcision—another potential, partially-effective HIV prevention program for which clinical trial efficacy data have recently been released and for which the technology is available immediately.

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ACKNOWLEDGEMENTS

I owe my sincere gratitude to my dissertation committee for their superb guidance: Linda Niccolai, Doug Owens, and David Paltiel. I appreciate how accessible and approachable they have been throughout this process, and I really look forward to calling them my colleagues. In addition to the technical aspects of supervising my dissertation research, they provided a tangible foundation of support from afar which was invaluable during the several years I spent in South Africa navigating the world of international field research. Most importantly, David has been a phenomenal dissertation advisor—he let me create my own research agenda but helped to shape it professionally, providing guidance and insight every step of the way. By bringing energy, enthusiasm, and humor to our meetings and communications, he also helped to make this a fun process. And of course, how many dissertation advisors can say they went on a big game walking safari (rifle-toting guides included) with their graduate student in Africa?

This research would not have been possible without many other people and programs. I thank the MD/PhD Program at Yale for believing in the importance of public health as an appropriate avenue for dissertation research in training medical scientists. I thank the Yale School of Medicine for providing an environment for medical education which allows students to explore their interests outside of clinical medicine, whatever they may be (my interest in HIV policy and South Africa began as a medical student!). And I thank the many administrators and professors in the School of Medicine and the Department of Epidemiology and Public Health I have encountered over the past eight

years who have been so generous with their assistance, advice, and teaching. I also thank the many staff members at the Perinatal HIV Research Unit in South Africa who assisted me with my dissertation research, as well as the nearly 500 residents of Soweto who participated in these surveys. Their dedication to furthering research on HIV/AIDS has been an inspiration to me.

Finally, I want to thank my friends and family with all my heart—I could never have done this without you! To my oldest friends—Beata, Kim, Janka, Jen, Melody, Patrick, and Shannah—you have helped to shape me and my choices in life, including these years at Yale. To my medical school pals—Bertrand, Clare, Dan, Grace, Jane, Jason, Jennie, Lucas, Matt, Paola, and Ryan—I can't believe how lucky I was to find such a fantastic group of friends here. To Julie and Sarah—after everyone I knew moved on to residency training, you are wonderful proof that life goes on and new friendships blossom. To my friends in South Africa—thank you for providing such a wonderful community abroad, filled with fun times and new experiences. To my fiancé and biggest cheerleader, Richard—I never imagined that research so far away would also lead me to you, and I am so happy that you came along on this adventure with me. And finally, to my mother, Josie, and my grandparents, Bob and Carol—you made all of this possible and there are simply no words for how much I appreciate your constant love and support over the years. I dedicate this dissertation to you.

INTRODUCTION

Overview and rationale for dissertation research

While there is no magic bullet that can completely prevent HIV transmission and halt the HIV/AIDS pandemic, governments and policy makers have an array of partially effective HIV prevention programs from which to choose. Program interventions to prevent sexually-transmitted HIV infection include both existing methods, such as those increasing education, access to volunteer counseling and testing (VCT), condom use, socioeconomic empowerment, and treatment of other sexually transmitted diseases[1], as well as technologies still in development, such as microbicides, vaccines, and pre-exposure prophylaxis regimens[2]. None of these prevention methods are perfect, and the evolving policy notion is that 'cocktails' of imperfect prevention programs will be required to fight the epidemic[3]. Complex decisions regarding if, when, and how to implement these various programs must be made, often in the absence of data on program outcomes.

Although some prevention programs may have only positive outcomes, such as those promoting HIV awareness education, the majority of prevention programs can not guarantee success: they may prevent HIV infections, but they also risk a potential rebound effect—the notion that sex might be considered 'safer' in light of individual or population reductions in HIV transmission. There are significant operational and ethical concerns regarding the use of partially effective HIV prevention programs and whether individuals will increase their risk-taking behavior because of presumed decreases in risk of HIV infection[3,4]. At the individual level, a person who increases their risk behavior might increase their own likelihood of HIV infection, while at the population level increased risk behavior could lead to increased HIV incidence, thus worsening the

epidemic overall. Conversely, decreases in risk behavior would have beneficial effects at both the individual and program outcome levels. For many prevention programs, the quantitative tradeoff between decreases in HIV transmission and potential increases in risk behavior is unknown.

I employed both epidemiological data collection of sexual risk-taking behavior and mathematical modeling of population HIV transmission dynamics in a multidisciplinary approach to examine the implications of risk behavior change surrounding the implementation of HIV prevention programs with less than 100% efficacy. The subject of risk compensation is most frequently discussed within the context of vaccine trials and the use of vaccines with only partial efficacy in future mass vaccination campaigns[5-9]. Thus, to explore the potential benefits or harms of partially effective programs, I examined risk behavior associated with the use of vaccines in current clinical trials and future vaccination programs. I then extended the analysis by adapting the framework developed for predicting the impact of partially effective HIV vaccines, which may not be available for at least a decade, and applied it to adult male circumcision—another potential partially effective HIV prevention program for which new clinical trial efficacy data have recently been released and for which the technology is available immediately. I explored these research areas within a South African context, specifically in the urban township of Soweto, which has a generalized, predominantly heterosexual HIV epidemic and high rates of risky sexual behavior similar to many populations throughout sub-Saharan Africa.

Numerous clinical trials designed to test various HIV prevention technologies are currently being conducted in Soweto, including the first HIV vaccine trials on the African

continent. When clinical trials for prevention technologies are concluded and show significant efficacy in reducing HIV transmission, immediate decisions must be made regarding their use. Given the various HIV prevention trials being conducted in Soweto, local and national authorities in South Africa may need to consider implementation of large prevention programs in the near future. Because there will be no data on program outcomes initially, policy makers must rely on available empirical and modeling data for decisions regarding program implementation. I addressed this need in two ways for my dissertation research: (1) I collected current and anticipated sexual risk behavior data from participants actively undergoing screening and enrollment into HIV vaccine trials in Soweto; and, (2) I employed epidemic modeling to estimate the potential impact of partially effective HIV prevention programs for vaccines and male circumcision on the entire population of Soweto.

Background information

The greatest concentration of HIV infections worldwide lies in sub-Saharan Africa[1] and, for both practical and ethical reasons, controlling the global HIV/AIDS epidemic must include interventions which specifically address prevention of infections in this region[10,11]. Within the sub-Saharan region, countries in Southern Africa have the highest estimates of national HIV prevalance: Mozambique (16%), Zambia (17%), South Africa (19%), Namibia (20%), Zimbabwe (20%), Lesotho (23%), Botswana (24%), and Swaziland (33%)[1]. South Africa has the highest number of infected individuals in the world, and is representative of most countries in the Southern African region in having regional variations in HIV prevalence rates as high as 30-50%[1,12,13].

In South Africa, detailed national surveys have been conducted on the factors and behaviors which place individuals at risk of HIV infection[14-19]. Despite the existence of several national surveys, sexual practices and HIV risk vary widely by geography and culture in South Africa. For example, the national Nelson Mandela household survey revealed that the percentage of males reporting more than one sexual partner in the previous year varied widely: by location, from 9% in 'rural formal' localities to 20% in 'urban informal' localities; by ethnicity, from 4% in Whites and Indians to 11% in Coloreds and 19% in Africans; and by age, from 27% in young men aged 15-24 to 10% in men 50 years or older[18]. These differences in reported risk behaviors contribute to the variation in HIV risk from exposure to HIV, with HIV prevalence found to be 9% for individuals living in 'urban formal' localities compared to 18% in 'urban informal' localities; 13% for African individuals compared to 1-2% for other populations; and, 11% for individuals living in Gauteng Province, the province where Soweto is located[18]. For studies of risk behavior, these variations emphasize the importance of collecting data for specific populations or geographic regions.

Many tools already exist for the prevention of sexual HIV transmission and are being used in prevention programs in Southern Africa. Although increasing the allocation of resources for existing prevention program packages to coverage levels of 80% could prevent half of the infections projected for sub-Saharan Africa in the next decade[20], the majority of programs focus on (1) condom distribution and education surrounding correct condom use and (2) education on reduction in sexual partners, including abstinence and monogamy[1]: Current prevention technologies work, but they do not provide complete or lifelong protection and they are largely related to risk-

reduction behaviors which must be practiced effectively and consistently with every sex act. These prevention programs must be implemented on a widespread basis with continuous funding for an indefinite period of time, and eventually experience decreased responsiveness to program messages. Compounding these problems, current prevention tools require that women and girls have the power to negotiate safe sexual practices where, for cultural and economic reasons, in many low- and middle-income country settings they do not. The lack of practical female-controlled methods, such as microbicides and diaphragms, to prevent HIV transmission is in part responsible for the higher prevalence of HIV seen in younger women.

Current prevention efforts have not been adequate to control the HIV epidemic, but numerous prevention technologies are under development[2]; in particular, the design of an HIV vaccine to prevent HIV transmission which remains a realistic objective. At least 35 potential preventive HIV vaccine candidates are in various stages of human testing around the world[21], and numerous additional strategies for effective preventive HIV vaccines are under development in laboratories worldwide[22]. When a potential vaccine candidate is approved for human testing, three successive phases of evaluation are required[23]. Phase I testing involves the evaluation of vaccine safety—whether it causes any severe reactions or side effects—in a small group of volunteers and usually lasts for approximately one year. Phase II testing involves the evaluation of vaccine immunogenicity—whether it stimulates an immune response—in several hundred volunteers and lasts approximately two years. Phase III testing involves the evaluation of vaccine efficacy—whether it can prevent HIV transmission and/or HIV infection—in several thousand volunteers and can last for three to four years. The majority of clinical

trials being conducted are currently in Phase I testing, however eight candidates are in Phase II testing, two candidates are in Phase III testing, and two candidates are in Phase IIb testing—a hybrid between Phase II and III that provides an earlier indication of potential vaccine efficacy[21]. For Phase II, Phase IIb and Phase III testing, clinical trials are generally conducted at the multi-country level. In sub-Saharan Africa, seven countries are already participating in international clinical trials testing HIV vaccine candidates and more will soon follow[21,24,25].

Increases in risk behavior associated with small HIV vaccine trials[26], large Hepatitis B vaccine efficacy trials[27], and treatment of HIV-infected individuals with anti-retroviral therapy[28] have already been observed. Although several large HIV vaccine efficacy trials have been conducted worldwide and showed no increase in risk behavior[29-33], none have been completed in sub-Saharan Africa where little is known regarding potential HIV vaccine trial-related risk behavior change[34,35]. In South Africa, which is conducting more trials than any other African nation, baseline sexual practices, risk behavior, and attitudes towards a partially effective vaccine have not been fully assessed in the populations from which vaccine trial participants will be drawn[36-38].

Although there are many vaccine candidates progressing through the global HIV vaccine pipeline, extensive time is required to complete multiple phases of testing and clinical trials. Therefore it is probable that the first preventive HIV vaccine will be licensed only within the next decade. While eventually the hope is to develop a highly effective vaccine, the first licensed vaccine will likely have only moderate efficacy and could even have an efficacy as low as 30%[8,22,39]. Previous modeling studies have shown that even a partially effective HIV vaccine with minimal efficacy could have enormous

population impact on the HIV epidemic in high-risk groups or areas with a high prevalence of HIV[40-46], but that the magnitude of this impact depends on a fine balance between the efficacy of the vaccine, the vaccine coverage level, and the change in risky behavior[43,45,47-51]. For this reason, whether individuals might increase their sexual risk behavior in response to future mass vaccination campaigns represents a significant concern[7-9,52]. This concern is even greater for the majority of African nations, with substantial HIV epidemics and limited resources, which may implement the first generation of HIV vaccines. However, only a small number of studies exist that have addressed either epidemic modeling or the potential for risk behavior change specific to the African setting[35,40-43,45,53].

Summary of dissertation projects[i]

In the first paper, I collected data on current sexual risk-taking behavior from adults who are undergoing screening and enrollment into multiple Phase I/II HIV vaccine trials in Soweto. Baseline sexual risk behavior characteristics have not been well-documented in the township of Soweto, from which individuals are recruited for HIV vaccine trials. Further, sexual risk behavior has not been characterized in the individuals who are volunteering for screening and enrollment into HIV vaccine trials in Soweto. These issues are true for many sites across sub-Saharan Africa which are conducting or preparing for HIV vaccine trials. In addition, any analysis of sexual risk behavior change depends on the ability to collect accurate behavioral data at these sites. This paper addresses the need for a detailed risk behavior assessment tool and for the risk behavior characterization of participants enrolling into HIV vaccine trials in South Africa.

[i] This section also specifies my role in the design and conduct of this research. Because this dissertation uses the collected manuscript format, I have written the four individual papers in the plural narrative to account for multiple authorship, consistent with scientific publishing standards.

After conducting focus groups amongst patients and staff at the Perinatal HIV Research Unit (PHRU) in South Africa, I developed a survey using culturally-appropriate language for use in this population to collect self-reported data on participant sociodemographics, substance use, sexual history, and partnership-specific sexual behaviors for the previous 6 months. I incorporated my survey into the existing protocol for adults undergoing screening for HIV vaccine trials, known as the Pre-Screening Protocol, at the PHRU[54,55]. I pilot-tested several versions of my survey on participants in the Pre-Screening Protocol. Then, working with the PHRU data management team, I converted all of the Pre-Screening Protocol forms—including my survey—into a format for automated data scanning and entry. I worked with the PHRU data management team to create a database for all of the Pre-Screening Protocol data, including the data collected by my survey, and I coordinated a team of PHRU nurses and physicians to transcribe all data collected prior to the initiation of the automated format data collection. I then trained counselors to administer my survey using a combination of group and individual teaching sessions, and provided additional guidance and feedback over several years.

As part of the overall Pre-Screening Protocol, the PHRU staff collected data with my survey and performed manual reviews of the data for accuracy. Following automated data entry, the PHRU data management team performed three levels of data validation and then generated quality control reports. I supervised the resolution of incomplete or missing data in these reports by PHRU nurses and physicians in order to generate the final data collected for the Pre-Screening Protocol. I created a data analysis plan and then, working with a PHRU statistician and de-identified data from the database, I

cleaned the data and conducted statistical analyses. In addition to providing a detailed description of this cohort and baseline levels of sexual risk behavior, I used these data further to identify predictors of higher levels of risk behavior which could be used for both present HIV vaccine trial screening and future vaccination programs.

The second paper considers anticipated sexual risk behavior changes in response to receiving a hypothetical low-efficacy vaccine. In the absence of actual data on risk behavior change, this study addresses the need to estimate the magnitude of potential changes in behavior that could occur in the future. Using the same methods described above, I developed and implemented an additional survey for use in the same population of individuals volunteering for current HIV vaccine trials in Soweto and analyzed the data which were collected. I designed the survey and associated script to collect data on comprehension of the hypothetical low-efficacy vaccine concept, on anticipated changes in condom use behaviors with sex partners, and on anticipated changes in frequency of sex with non-primary sex partners. The survey and results provide a foundation for examining potential behavior change in individuals contemplating participation in a future vaccination program. Although I conducted this study to assess anticipated change in behavior following vaccination, the results may be applicable to other HIV prevention programs with partial efficacy.

For the third and fourth papers, I developed a mathematical model[ii] to simulate the dynamics of heterosexual HIV transmission in adult populations where gender differences in negotiation of safe sexual practices exist. As such, the model is pertinent

[ii] Compartmental models are an established methodology for analyzing epidemics and hypothetical program intervention scenarios. Their use entails the delineation of various health 'states' in a population as well as differential equations that specify flow between these various states. Mathematical models allow for sensitivity analyses on a variety of parameters and are helpful in situations where a historical precedent for program implementation is lacking.

to heterosexual transmission of HIV throughout much of sub-Saharan Africa. I collected detailed input parameters and assumptions from various sources, including data from published literature and communication with scientists and government officials in South Africa, to initialize the model for the high-risk heterosexual transmission of HIV that occurs within the population of Soweto. I adapted the model to estimate the impact of various partially effective HIV prevention program scenarios on the epidemic, in terms of HIV infections prevented and changes in population HIV prevalence over time.

I examined the potential impact of future vaccination programs on the HIV epidemic in Soweto in the third paper. Although a vaccine will not be available for some time, this paper addresses the need for a detailed consideration of the dynamics of risk behavior change in preparation for the eventual use of low-efficacy HIV vaccines in African populations. I adapted the model to incorporate the effects of prevention programs using HIV vaccines with varying levels of protection against HIV and post-vaccination changes in sexual risk-taking behavior. I compared various program outcomes to two base-case scenarios: one with no vaccination or one using a 40% effective vaccine with no post-vaccination change in behavior. The simulations consider vaccination programs which cover a significant proportion of the population over a 10-year period, and program outcomes are given during the same time period.

In the fourth paper, I explored the potential impact of programs to expand the number of adult males who are circumcised in Soweto. This paper addresses the urgent need for research to inform decisions regarding the immediate implementation of expanded adult male circumcision programs in the African setting. I adapted the model to specify the influence of current levels of circumcision on female-to-male HIV

transmission and to examine the impact of programs which circumcised an additional proportion of adult males. The simulations consider expanded adult male circumcision programs with only modest increases in the level of circumcision coverage over a 5-year period, and the program outcomes are estimated over a 20-year period. I compared the program outcomes with scenarios in which male circumcision levels remained the same over time.

While these two HIV prevention technologies are similar on a general level—both preventive vaccines and male circumcision can reduce HIV transmission with a certain degree of effectiveness—there are substantial differences that exist at both the modeling and policy levels: (1) Although vaccines will not be available in the near future, the efficacy of circumcision has recently been proven and the technology is available now. (2) Vaccination programs require giving a population of men and women a vaccine that may not provide lifelong protection and may not be fully immunogenic, whereas circumcision programs involve a one-time procedure, performed only on men, which is presumed to provide lifelong benefits. (3) No one has yet received an HIV vaccine whereas many men are already circumcised. (4) Increasing levels of vaccine efficacy directly influence the benefits of vaccination programs, which contrasts with the situation for circumcision. The fourth paper demonstrates that increasing levels of circumcision efficacy do not necessarily increase the benefits of circumcision programs. (5) Vaccination provides equal benefits to men and women whereas circumcision provides a direct benefit to men and a lesser, indirect benefit to women. (6) For potential risk behavior change in individuals who have received the intervention (a direct, or primary effect), risk behavior change resulting from vaccination programs would entail only those

vaccinated whereas risk behavior change resulting from circumcision programs would entail both those men who are circumcised as well as those men who were previously circumcised. (7) With vaccination programs, women receive direct protection against increases in male risk behavior, whereas with circumcision programs, they do not. This difference is particularly important when considering societies in which the male partner may dominate risk behavior decisions such as condom use. (8) Finally, high coverage levels would be desirable for vaccination programs whereas more modest coverage level goals would be sufficient for expanded adult male circumcision programs.

REFERENCES

1. UNAIDS. 2006 report on the global AIDS epidemic. Joint United Programme on HIV/AIDS, May 2006. Available at: http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp.

2. Camp R, Jefferys R, Swan T and Syed J. What's in the pipeline: new HIV drugs, vaccines, microbicides, HCV and TB therapies in clinical trials. Treatment Action Group, August 2006. Available at: http://www.treatmentactiongroup.org.

3. Cohen J. Prevention cocktails: combining tools to stop HIV's spread. *Science* 2005; **309**:1002-1005.

4. Cassell MM, Halperin DT, Shelton JD and Stanton D. Risk compensation: the Achilles' heel of innovations in HIV prevention? *BMJ* 2006; **332**:605-607.

5. Frey SE. Unique risks to volunteers in HIV vaccine trials. *J Investig Med* 2003; **51(Suppl 1)**:S18-20.

6. Lurie P, Bishaw M, Chesney MA, Cooke M, Fernandes ME, Hearst N, Katongole-Mbidde E, Koetsawang S, Lindan CP and Mandel J. Ethical, behavioral, and social aspects of HIV vaccine trials in developing countries. *JAMA* 1994; **271**:295-301.

7. Cohen J. The HIV vaccine paradox. *Science* 1994; **264**:1072-1074.

8. Anonymous. Future access to HIV vaccines. Report from a WHO-UNAIDS Consultation, Geneva, 2-3 October 2000. *AIDS* 2001; **15**:W27-44.

9. Newman PA, Duan N, Rudy ET and Anton PA. Challenges for HIV vaccine dissemination and clinical trial recruitment: if we build it, will they come? *AIDS Patient Care STDS* 2004; **18**:691-701.

10. Crewe M. AIDS in Southern Africa. *Postgrad Med J* 2002; **78**:127-128.

11. Crewe M. Spectacular failure--a view from the epicenter. *Yale J Health Policy Law Ethics* 2004; **4**:157-163.

12. Dorrington R, Bradshaw D and Budlender D. *HIV/AIDS profile in the provinces of South Africa: indicators for 2002.* Cape Town: University of Cape Town Centre for Actuarial Research, South African Medical Research Council Burden of Disease Research Unit, & Actuarial Society of South Africa; 2002.

13. Dorrington R, Bradshaw D, Johnson L and Budlender D. *The demographic impact of HIV/AIDS in South Africa: national indicators for 2004.* Cape Town: University of Cape Town Centre for Actuarial Research, South African Medical Research Council Burden of Disease Research Unit, & Actuarial Society of South Africa; 2004.

14. Simbayi L, Strebel A, Wilson T, Andipatin M, Msomi N, Potgieter C, Ratele K and Shefer T. *Sexually transmitted diseases in the South African public sector*: National Department of Health's Directorate of Health Systems Research and Epidemiology in conjunction with the Directorate of HIV/AIDS and STDs; August 1999.

15. Simbayi LC, Chauveau J and Shisana O. Behavioural responses of South African youth to the HIV/AIDS epidemic: a nationwide survey. *AIDS Care* 2004; **16**:605-618.

16. Pettifor AE, Rees HV, Steffenson A, Hlonga-Madikizela L, MacPhail C, Vermaak K and Kleinschmidt I. *HIV and sexual behavior among young South Africans: a national survey of 15-24 year olds.* Johannesburg: Reproductive Health Research Unit, University of the Witwatersrand; April 6 2004.

17. Pettifor AE, Rees HV, Kleinschmidt I, Steffenson AE, MacPhail C, Hlongwa-Madikizela L, Vermaak K and Padian NS. Young people's sexual health in South Africa: HIV prevalence and sexual behaviors from a nationally representative household survey. *AIDS* 2005; **19**:1525-1534.

18. Shisana O, Rehle T, Simbayi LC, Parker W, Zuma K, Bhana A, Connolly C, Jooste S and Pillay V. *South African national HIV prevalence, HIV incidence, behaviour and communication survey, 2005.* Cape Town: HSRC Press; 2005.

19. Anonymous. HIV Prevalence, Incidence, Behavior and Communication Survey 2005. Centre for AIDS Development, Research and Evaluation, 2006. Available at: www.cadre.org.za.

20. Stover J, Bertozzi S, Gutierrez J-P, Walker N, Stanecki KA, Greener R, Gouws E, Hankins C, Garnett GP, Salomon JA, Boerma JT, De Lay P and Ghys PD. The global impact of scaling up HIV/AIDS prevention programs in low- and middle-income countries. *Science* 2006; **311**:1474-1476.

21. IAVI database of AIDS vaccines in human trial [database online]. New York, NY: International AIDS Vaccine Initiative, 2006. Updated June 13, 2006.

22. Garber DA, Silvestri G and Feinberg MB. Prospects for an AIDS vaccine: three big questions, no easy answers. *Lancet Infect Dis* 2004; **4**:397-413.

23. Anonymous. AIDS Vaccine Blueprint 2006. International AIDS Vaccine Initiative, Available at: http://www.iavi.org/blueprint.

24. HIV Vaccine Trials Network current vaccine trials [database online]. Seattle, WA: HIV Vaccine Trials Network, 2006. Updated September 2006.

25. Sandstrom E and Birx D. HIV vaccine trials in Africa. *AIDS* 2002; **16(Suppl 4)**:S89-95.

26. Chesney MA, Chambers DB and Kahn JO. Risk behavior for HIV infection in participants in preventive HIV vaccine trials: a cautionary note. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; **16**:266-271.

27. Szmuness W, Stevens CE, Harley EJ, Zang EA, Oleszko WR, William DC, Sadovsky R, Morrison JM and Kellner A. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. *N Engl J Med* 1980; **303**:833-841.

28. Crepaz N, Hart TA and Marks G. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. *JAMA* 2004; **292**:224-236.

29. Francis DP, Heyward WL, Popovic V, Orozco-Cronin P, Orelind K, Gee C, Hirsch A, Ippolito T, Luck A, Longhi M, Gulati V, Winslow N, Gurwith M, Sinangil F and Berman PW. Candidate HIV/AIDS vaccines: lessons learned from the world's first phase III efficacy trials. *AIDS* 2003; **17**:147-156.

30. Bartholow BN, Buchbinder S, Celum C, Goli V, Koblin B, Para M, Marmor M, Novak RM, Mayer K, Creticos C, Orozco-Cronin P, Popovic V, Mastro TD and the Vision Vax Study Team. HIV sexual risk behavior over 36 months of follow-up in the world's first HIV vaccine efficacy trial. *J Acquir Immune Defic Syndr* 2005; **39**:90-101.

31. van Griensvan F, Keawkungwal J, Tappero JW, Sangkum U, Pitisuttithum P, Vanichseni S, Suntharasamai P, Orelind K, Gee C, Choopanya K and the Bangkok Vaccine Evaluation Group. Lack of increased HIV risk behavior among injection drug users participating in the AIDSVAX B/E HIV vaccine trial in Bangkok, Thailand. *AIDS* 2004; **18**:295-301.

32. Lampinen TM, Chan K, Remis RS, Merid MF, Rusch M, Vincelette J, Logue K, Popovic V, Alary M, Schechter MT and Hogg RS. Sexual risk behaviour of Canadian participants in the first efficacy trial of a preventive HIV-1 vaccine. *Can Med Assoc J* 2005; **172**:479-483.

33. Rerks-Ngam S, Pitisuttithum P, Nitayaphan S, Kaewkungwan J, Kim J, Benenson M, Gurunathan S, Gurwith M, Brown AE and Birx D. An update of progress in the Thai HIV prime boost vaccine trial: VCP1521 (ALVAC-HIV) + GP120 B/E (AIDSVAX B/E) [31]. Paper presented at: AIDS Vaccine International Conference; 2005; Montreal.

34. Baeten JM, Richardson BA, Martin HL, Jr., Nyange PM, Lavreys L, Ngugi EN, Mandaliya K, Ndinya-Achola JO, Bwayo JJ and Kreiss JK. Trends in HIV-1 incidence in a cohort of prostitutes in Kenya: implications for HIV-1 vaccine efficacy trials. *J Acquir Immune Defic Syndr* 2000; **24**:458-464.

35. Jackson DJ, Martin HL, Jr., Bwayo JJ, Nyange PM, Rakwar JP, Kashonga F, Mandaliya K, Ndinya-Achola JO and Kreiss JK. Acceptability of HIV vaccine trials in high-risk heterosexual cohorts in Mombasa, Kenya. *AIDS* 1995; **9**:1279-1283.

36. Shefer T, Strebel A, Wilson T, Shabalala N, Simbayi L, Ratele K, Potgieter C and Andipatin M. *The social construction of sexually transmitted infections (STIs) in South African communities* 2002.

37. Lindegger G, Slack C and Vardas E. HIV vaccine trials in South Africa--some ethical considerations. *S Afr Med J* 2000; **90**:769-772.

38. Slack C, Lindegger G, Vardas E, Richter L, Strode A and Wassenaar D. Ethical issues in HIV vaccine trials in South Africa. *S Afr J Sci* 2000; **96**:291-295.

39. Self S. Vaccine efficacy trial design: role of Phase IIb vs. Phase III trials [56]. Paper presented at: AIDS Vaccine International Conference; 2005; Montreal.

40. Anderson RM and Garnett GP. Low-efficacy HIV vaccines: potential for community-based intervention programmes. *Lancet* 1996; **348**:1010-1013.

41. Anderson RM, Swinton J and Garnett GP. Potential impact of low efficacy HIV-1 vaccines in populations with high rates of infection. *Proc Biol Sci* 1995; **261**:147-151.

42. Stover J, Garnett GP, Seitz S and Forsythe S. The epidemiological impact of an HIV/AIDS vaccine in developing countries [World Bank Policy Research Working Paper No. 2811]. The World Bank Development Research Group, March 2002. Available at: http://papers.ssrn.com/sol3/papers.cfm?abstract_id=636094.

43. Gray RH, Li X, Wawer MJ, Gange SJ, Serwadda D, Sewankambo NK, Moore R, Wabwire-Mangen F, Lutalo T, Quinn TC and the Rakai Project Group. Stochastic simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission; Rakai, Uganda. *AIDS* 2003; **17**:1941-1951.

44. Owens DK, Edwards DM and Shachter RD. Population effects of preventive and therapeutic HIV vaccines in early- and late-stage epidemics. *AIDS* 1998; **12**:1057-1066.

45. Anderson R and Hanson M. Potential public health impact of imperfect HIV type 1 vaccines. *J Infect Dis* 2005; **191(Suppl 1)**:S85-96.

46. Blower SM, Koelle K, Kirschner DE and Mills J. Live attenuated HIV vaccines: predicting the tradeoff between efficacy and safety. *Proc Natl Acad Sci U S A* 2001; **98**:3618-3623.

47. Blower SM and McLean AR. Prophylactic vaccines, risk behavior change, and the probability of eradicating HIV in San Francisco. *Science* 1994; **265**:1451-1454.

48. Bogard E and Kuntz KM. The impact of a partially effective HIV vaccine on a population of intravenous drug users in Bangkok, Thailand: a dynamic model. *J Acquir Immune Defic Syndr* 2002; **29**:132-141.

49. Edwards DM, Shachter RD and Owens DK. A dynamic HIV-transmission model for evaluating the costs and benefits of vaccine programs. *Interfaces* 1998; **28**:144-166.

50. Smith RJ and Blower SM. Could disease-modifying HIV vaccines cause population-level perversity? *Lancet Infect Dis* 2004; **4**:636-639.

51. Davenport MP, Ribeiro RM, Chao DL and Perelson AS. Predicting the impact of a nonsterilizing vaccine against human immunodeficiency virus. *J Virol* 2004; **78**:11340-11351.

52. Newman PA, Duan N, Rudy ET, Roberts KJ and Swendeman D. Posttrial HIV vaccine adoption: concerns, motivators, and intentions among persons at risk for HIV. *J Acquir Immune Defic Syndr* 2004; **37**:1393-1403.

53. Bishai D, Pariyo G, Ainsworth M and Hill K. Determinants of personal demand for an AIDS vaccine in Uganda: contingent valuation survey. *Bull World Health Organ* 2004; **82**:652-660.

54. Vardas E, Mlungwana ON, Van Niekerk RM, Mesesan K, Mogale M, Mayaphi S, McIntyre JA and Gray GE. Characteristics of a cohort of individuals screened for Phase I/II HIV vaccine trials in South Africa [344P]. Paper presented at: AIDS Vaccine International Conference; 2005; Montreal.

55. Vardas E, Gray GE, Van Niekerk R, Schwarz R, McIntyre J, Mlungwana O, Mogale M and the HIV Vaccine Trial Network. Recruiting into phase I/II HIV vaccine trials in Soweto, South Africa: a model for developing countries [OA06-04]. Paper presented at: AIDS Vaccine International Conference; 2006; Amsterdam.

PAPER 1

Sexual Risk Behavior of the First Cohort Undergoing Screening for Enrollment into Phase I/II HIV Vaccine Trials in South Africa

INTRODUCTION

A major concern regarding the conduct of HIV vaccine trials is that individuals may increase their risk-taking behavior, assuming that they are protected from HIV infection when, in actuality, they might not be[1-4]. In addition to putting individual vaccine trial participants at greater risk for HIV infection, changes in risk-taking behavior can also affect both the sample size and efficacy calculations that determine trial outcomes and, ultimately, whether a vaccine candidate is licensed for use[5-8]. Further, despite multiple HIV vaccine trials being conducted globally, appropriate methods for assessing risk are still under debate and are particularly important in low- and middle-income countries and communities where baseline sexual practices and customs are not well known. For these reasons, appropriate and accurate assessment of risk behavior during vaccine trials remains a priority.

Data on the sexual risk behaviors of African cohorts entering HIV vaccine trials are scarce and no effective tools have been published that measure risk behavior in low- and middle-income country populations. Seven countries on the African continent—Rwanda, Kenya, Uganda, Tanzania, Zambia, Botswana and South Africa—are enrolling volunteers and conducting HIV vaccine trials to date, while site development is underway in Malawi and Côte d'Ivoire[9-11]. As the first African country to initiate HIV vaccine trials, South Africa provides an important example for studying African risk behavior in potential HIV vaccine trial participants. The baseline sexual risk behaviors of South Africans enrolling into HIV vaccine trials, both individually and in the communities from which they originate, have not been characterized to date. Although one study has characterized the risk behavior of participants in an observational cohort group examining incidence and

retention in preparation for vaccine trials,[12] further research is needed on participants being actively enrolled into vaccine trials, characterizing different communities, and examining sexual risk behaviors within specific partnerships.

In this study[iii], we report the initial results of risk behavior monitoring of a predominantly heterosexual cohort of potential vaccine trial participants undergoing screening and enrollment into Phase I and Phase II HIV vaccine trials in Soweto, using a detailed risk behavior assessment tool adapted to South African language and customs developed for this purpose[13-16]. The results we report here provide one of the first characterizations of risk behaviors in an African population participating in HIV vaccine trials. In addition, these baseline data represent a first step in determining whether sexual risk behavior could change in South Africans volunteering to participate in early Phase I/II HIV vaccine clinical trials.

[iii] Partial data from this manuscript have been previously reported at the XV International AIDS Conference (Bangkok, 2004), the AIDS Vaccine International Conference (Montreal, 2005), and the AIDS Vaccine International Conference (Amsterdam, 2006).

METHODS

Study Setting

We assessed sexual risk behavior within the context of ongoing screening and enrollment into Phase I/II adult HIV vaccine trials at the Perinatal HIV Research Unit (PHRU). The PHRU is affiliated with the University of the Witwatersrand in Johannesburg and is located at the Chris Hani Baragwanath Hospital in Soweto. Soweto is the largest black urban township in South Africa with a population of approximately 1.1 million[17] (calculated from census data, with assistance from the Johannesburg City Council) and antenatal HIV prevalence of 30% (personal communication, Avy Violari, PHRU); it is situated southwest of Johannesburg in Gauteng province, which has an overall HIV prevalence of 16% in residents 15-49 years of age[18].

The positioning of the PHRU provides important access to the Soweto population, as the hospital serves a vast majority of the area and is the location for both medical and community activities. The HIV/AIDS Vaccine Division (HAVD), within the PHRU, is the location of all adult HIV vaccine research and clinical trials. The HAVD provides free access to HIV voluntary counseling and testing (VCT), and identifies HIV-negative Soweto residents in this manner for recruitment into clinical trials. Seroprevalence of HIV infection among potential participants screened is between 50% and 60%; of those that test HIV-negative, approximately 20% volunteer to undergo screening for enrollment into HIV vaccine trials[19].

Potential HIV-negative vaccine trial volunteers are recruited from VCT into a generic "Pre-Screening Protocol" which was designed to allow the accumulation of suitably informed, healthy, low-risk HIV-negative cohorts for Phase I/II HIV vaccine

trials being conducted at HAVD[20,21]. The Pre-Screening Protocol provides information sessions about HIV vaccines, baseline and follow-up assessments of understanding, as well as risk behavior assessment and clinical screening for physical health. HIV prevention services are offered to participants at each visit including VCT, provision of free condoms, risk-reduction counseling, and referral for treatment of sexually transmitted infections (STI). Following completion of the Pre-Screening Protocol, potential volunteers may be referred to one of several Phase I/II HIV vaccine trials being conducted at HAVD.

Administration of the risk behavior survey described here has been included in the Pre-Screening Protocol since June 2003. This study represents a cross-sectional analysis of the initial risk behavior assessment at the first clinical visit for each potential vaccine trial volunteer enrolled into the Pre-Screening Protocol, thereby providing a baseline characterization of the sexual risk behavior of this cohort.

Study Participants

Eligibility criteria for enrollment into the Pre-Screening Protocol included having a minimum of 12 years of schooling (irrespective of education level achieved), being a resident of Soweto, 18-60 years of age, HIV-negative, healthy, able to provide informed consent, and, for women, not pregnant or planning to become pregnant. To remain in the Pre-Screening Protocol and to be eligible for Phase I/II HIV vaccine trials, volunteers had to remain HIV-negative, be in general good health, not become pregnant, not engage in high-risk behaviors (determined by PHRU nurses and physicians, from patient interviews and chart reviews), demonstrate good understanding of vaccine trials, and attend all appointments consistently.

All participants gave written informed consent for the study and received nominal financial compensation for transportation costs at each study visit, under the auspices of the Pre-Screening Protocol. The Committee for Research on Human Subjects at the University of the Witwatersrand in Johannesburg approved this study as an addendum to the original Pre-Screening Protocol. The Human Investigations Committee at the Yale University School of Medicine approved this study under exemption category 45CFR46.101(b)(2); this category includes the use of survey procedures in which information is obtained in such a way that participants can not be identified.

Risk Behavior Assessment

We developed the risk behavior assessment tool for use in South Africa following six focus groups at HAVD conducted with experienced HIV counselors and staff focusing on appropriate local language, specific practices and customs of the population, and question content and clarity[iv]. We pilot-tested preliminary versions of the survey with 20 participants for comprehension, feasibility and cultural appropriateness. We trained interviewers to accurately administer the survey in a non-judgmental manner using a combination of individual and group teaching sessions on interviewing techniques as well as practice survey administration with observation and feedback.

We administered the risk behavior survey to participants in a structured, face-to-face private interview using trained, multilingual interviewers. The survey took approximately 45 minutes to complete per individual and was generally conducted in a mixture of Sotho, Zulu, and English according to the language needs of the participant. We collected the risk behavior data presented in this analysis from surveys administered

[iv] Relevant questions were adapted from existing unpublished surveys addressing similar research questions used in ongoing research and modified as needed.

at the first clinic visit in the Pre-Screening Protocol; however, participants received prior risk-reduction counseling and education from VCT services in the preceding month.

Basic sociodemographic information collected included age, gender, race and ethnicity, education, marital status, employment status, migrant labor status, number of residents in the household, occupation of the major breadwinner in the household and overall household income. We collected general risk behavior information including history of receiving blood products, substance use (alcohol and recreational drug use), history of STIs, age of sexual debut, history of forced sex, and reasons for choosing recent sexual partners. We then collected partnership data, which involved a structured recall of sexual partners in the prior six months and specific risk behavior information for each sexual partner identified. This included the type of sexual relationship (anonymous, casual, or steady/stable) and the partner's gender, age, migrant labor status, additional sex partners, and HIV status as well as the numbers of oral, vaginal, and anal sex acts with each partner, whether or not a condom was used and additional sexual activities. The full survey is contained in the Appendix.

Statistical Analyses

We formatted the risk behavior questionnaire and coded it for use with DataFax software (Clinical DataFax Systems, Inc., Hamilton, Canada). Following a manual clinic review and automated data entry, data were then subjected to automated edit checking as well as manual review by three separate individuals trained in data validation. Clinic staff routinely resolved quality control reports listing incomplete or incorrect data entries.

We conducted all statistical analyses with SAS Version 9.1 software (SAS Institute Inc., Cary, North Carolina). We created additional variables to describe per capita

household income, having a partner with an age difference of 15 years or more, percentage condom use, and numbers of unprotected sex acts. For statistical comparisons, we used *t* tests for continuous variables and either the chi-square or Fisher's exact test for categorical variables.

For bivariate and multivariate analyses, we employed logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) using covariates from the sociodemographic, sexual history, and sexual risk data. We created four outcome variables and dichotomized them to reflect higher and lower participant risk behavior in the previous six months: (1) engaging in any unprotected vaginal or anal sex, (2) engaging in any unprotected vaginal or anal sex with a known or suspected HIV-positive partner, (3) reporting any casual or anonymous sexual partners, and (4) reporting 3 or more sexual partners. Analyses for outcomes (1) and (2) used only the participants sexually active in the previous six months with complete data on reported sex acts. Analyses for outcome (3) used only participants sexually active in the previous six months. Analyses for outcome (4) used all participants ever sexually active.

We dichotomized continuous covariates at the median and categorical covariates evenly to the extent possible. We first used the covariates in bivariate models to determine independent predictors of higher risk behavior for each of the four outcomes. We included covariates that were associated with an outcome of p-value < 0.20 in multivariate models for each of the four outcomes. We then eliminated covariates not significantly associated with the outcome at level p-value < 0.05 from the model one at a time, using a manual backwards selection procedure. The final multivariate model

contained covariates with statistical significance of p-value < 0.05. All multivariate models retained age and gender covariates due to their potential role as confounders.

RESULTS

Participant characteristics

We administered an initial risk behavior survey to a total of 488 participants in the Pre-Screening Protocol between June 11, 2003 and February 13, 2006 for this analysis. Table 1 presents the results of the sociodemographic portion of the survey. The participants included 219 men and 269 women, with a mean age of 26.8 years (median 25; range 18-59). The majority of participants comprised a multi-ethnic sample of Zulu, Xhosa, Northern Sotho, Southern Sotho, Swazi, Venda, Tsonga, Tswana, and other black Africans. Most participants were single and had never been married. Almost all of the participants had already achieved at least a high school education and 22% of the participants had completed either a technical college or a university degree. Only 24% of the participants were currently employed. The mean household per capita income in South African rands (ZAR) was ZAR695 (median ZAR450; range ZAR25-4,450) per month (1 USD ≈ 6 ZAR during this time period). Half of the participants (51%) were from households with a monthly per capita income below poverty level (defined as ZAR500 per capita). There were no significant gender differences in sociodemographic information except as noted.

Substance use, sexual history and general sexual risk behaviors

Male participants reported higher levels of alcohol and drug use than female participants. Overall, 62% of men reported at least one day of heavy drinking[v] in the past six months compared with 33% of women ($p < 0.001$). Men reported more days of heavy drinking in the past six months than women overall (16.6 vs. 3.4 days; t = 5.8; $p < 0.001$)

[v] Defined as consumption of >5 alcoholic beverages, with one beverage defined as 6 oz. wine, 12 oz. beer, or 1 oz. liquor

as well as amongst just those men and women reporting at least one episode of heavy drinking (26.6 vs. 10.4 days; $t = 4.3$; $p < 0.001$). More men than women reported marijuana use (19% vs. 3%, $p < 0.001$) and other recreational drug use (4.1% vs. 0.4%, $p < 0.01$) in the past six months. Only two participants reported injection drug use.

Most participants (97%) reported prior sexual activity (defined as vaginal, anal, or oral sex). Prior STIs were reported by 30% of participants overall, with 7% of participants reporting an STI diagnosis in the past six months. Additionally, 35% of all males and 24% of all females ($p < 0.01$) reported having a partner within the past six months with whom they did not have vaginal, anal, or oral sex.

Of those ever sexually active (Table 2), males reported a lower mean age of sexual debut than females (15.8 vs. 17.5 years; $t = -7.1$; $p < 0.001$). Significantly more females than males reported a forced first sexual encounter as well as forced sex within the past six months. Overall, males had a higher mean number of sexual partners than females (1.7 vs. 1.1 partners; $t = 4.8$; $p < 0.001$) in the past six months. Of participants who were ever sexually active, 13% reported abstinence during the preceding six months. While more males than females had no sexual partners in the past six months, significantly more males than females reported 3 or more sexual partners. 'Attracted to that person' was the most common reason (65%) reported for choosing a recent sexual partner.

Six-month sexual partner history and risk behaviors

Analysis of risk behaviors for participants sexually active during the previous six months revealed further gender differences (Table 3). More men reported at least one casual and/or anonymous sex partner (55% vs. 20%, $p < 0.001$), 'one night stand' (29% vs. 4%, $p < 0.001$), known or suspected HIV-infected sex partner (18% vs. 7%, $p <$

0.001), and sex partner at least 15 years older or younger (6% vs. 2%, $p = 0.03$). There were no significant gender differences in participants reporting at least one sex partner with known HIV infection (3% overall), who must travel away from their homes for one or more nights at a time because of their job (18% overall), and who is of the same gender (4% overall).

For sexually active participants reporting steady partners in the past 6 months (Table 4), 96.4% of men but 99.5% of women ($p < 0.05$) reported vaginal sex, 6% reported anal sex, 40% reported oral sex, and 11% reported other sex acts (dry sex, rimming, fisting, or sharing sexual toys). Specifically, mean condom use for vaginal sex with steady partners was 53% (median 50%) per participant, with 32% of participants reporting never using condoms and 37% reporting always using condoms. Participants reported an average of 32.0 unprotected vaginal sex acts (median 5.0, range 0-300) with steady partners in the previous six months. Mean condom use for anal sex with steady partners was 50% (median 40%) per participant, with an average of 3.4 unprotected anal sex acts (median 1, range 0-48) with steady partners in the previous six months. Overall, 4% of participants with steady partners reported unprotected vaginal or anal sex with at least one partner with known or suspected HIV infection.

For sexually active participants reporting casual or anonymous partners in the past six months (Table 4), 96% reported vaginal sex, 9% reported anal sex, 33% reported oral sex, and 9% reported other sex acts. Specifically, mean condom use for vaginal sex with casual/anonymous partners was 73% (median 100%) per participant, with 18% of participants reporting never using condoms and 60% reporting always using condoms. Participants reported an average of 7.2 unprotected vaginal sex acts (median 0, range 0-

192) with casual/anonymous partners in the previous six months. Mean condom use for anal sex with casual/anonymous partners was 73% (median 100%), with an average of 0.8 (median 0, range 0-6) unprotected sex acts over the previous six months. Overall, 9% of participants reported unprotected vaginal or anal sex with at least one casual/anonymous partner with known or suspected HIV infection.

In general, when comparing risk behaviors in the previous 6 months by partner type, mean condom use was higher and the number of unprotected sex acts were lower for casual/anonymous sex partners as compared to steady partners. Further, more participants reported unprotected vaginal or anal sex with known or suspected HIV-positive casual/anonymous partners as compared to steady partners.

Predictors of higher risk sexual behavior

Predictors for higher risk sexual behaviors for the following four outcomes were first assessed in bivariate analyses, followed by multivariate analyses: (1) "<100% condom use", any incidence of unprotected vaginal or anal sex in the previous six months; (2) "<100% condom use with HIV+", any incidence of unprotected vaginal or anal sex with a known or suspected HIV-positive partner in the previous six months; (3) "casual sex partners", any incidence of vaginal, anal, or oral sex with a casual or anonymous partner in the previous six months; and (4) ">2 sex partners", having had three or more sex partners in the previous six months. For these outcomes, 55% reported <100% condom use, 4% reported <100% condom use with a known or suspected HIV-positive partner, 35% reported sex with a casual or anonymous partner, and 13% reported having 3 or more sex partners.

In bivariate analyses, individual factors associated ($p < 0.05$) with <100% condom use were age 25 years or older and reporting an STD in the previous 6 months. In the adjusted model, factors associated with <100% condom use were female gender (OR = 0.6 for male gender; OR = 1.7 for female gender, 95% CI = 1.1, 2.6), age 25 years or older (OR = 0.6 for age < 25 years; OR = 1.7 for age ≥ 25 years, 95% CI = 1.1, 2.5), and any recreational drug use (OR = 2.3, 95% CI = 1.1, 4.8).

Having more than five people in the household and any recreational drug use were each associated with <100% condom use with a known or suspected HIV-positive partner. Both of these were retained in the adjusted model as the only significant predictors. Thus, factors associated with <100% condom use with a known or suspected HIV-positive partner were having more than five people in the household (OR = 4.2, 95% CI = 1.2, 13.9) and reporting any recreational drug use (OR = 5.1, 95% CI = 1.4, 18.4).

Male gender, any heavy alcohol use, any recreational drug use, sexual debut before the age of 18 years, choosing a partner without concern for HIV/personal safety, having a partner older or younger by 15 years or more, and having a partner who works away from home were individually associated with sex with a casual or anonymous partner. However, in the adjusted model, factors associated with sex with a casual or anonymous partner were male gender (OR = 4.8, 95% CI = 2.9, 7.8), any heavy alcohol use (OR = 3.0, 95% CI = 1.9, 4.9), choosing a partner without concern for HIV/personal safety (OR = 2.1, 95% CI = 1.2, 3.8) and having a partner who works away from home (OR = 2.4, 95% CI = 1.3, 4.3).

Male gender, any heavy alcohol use, any recreational drug use, sexual debut before the age of 18 years, having a partner older or younger by 15 years or more, and having a

partner who works away from home were each associated with having 3 or more sex partners. In the adjusted model, factors associated with having 3 or more sex partners were male gender (OR = 12.3, 95% CI = 4.7, 32.4), any heavy alcohol use (OR = 3.1, 95% CI = 1.4, 6.9), having a partner older or younger by 15 years or more (OR = 6.0, 95% CI = 1.5, 23.1), and having a partner who works away from home (OR = 4.5, 95% CI = 2.1, 10.0).

DISCUSSION

Our study has described the sexual risk-taking behavior profile of potential Phase I and II HIV vaccine trial volunteers undergoing pre-screening in Soweto, South Africa for the first HIV vaccine trials being conducted in Southern Africa. We designed a survey adapted for local use, which is an important component of measuring risk behavior in HIV vaccine trials in low- and middle-income countries[2,22]. We assessed risk behavior by self-reported condom use and self-reported numbers and types of sex acts, which have been shown to be appropriate, reliable, and accurate indicators for the risk of acquiring an STD[23,24]. We administered this survey as a component of the Pre-Screening Protocol, a generic protocol applied to all HIV-negative potential volunteers expressing an interest in participating in Phase I/II HIV vaccine trials at the vaccine trial site in Soweto, regardless of which HIV vaccine trial they might be enrolled into and which risk assessment tool was used by that particular vaccine trial.

South Africa is extraordinarily diverse, with eleven national languages and a variety of cultures. Although risk behaviors have been well documented on a national level, little has been published on Soweto in particular, and even less on the residents of Soweto who actually volunteer to enroll in various clinical trials for HIV prevention and treatment. In our study, we showed this to be a young, predominantly single and unemployed, multi-ethnic population, of whom half reside in households with incomes below poverty level. While almost all reported prior sexual activity, 13% of these participants reported abstinence over the preceding six months. Although this might have represented a personal risk-reduction strategy, 18% of participants reported sex partners who must spend nights away from home for work and it is possible that the reported abstinence may

be due to the migratory labor practices in South Africa.

Our analysis demonstrated that men in Soweto reported higher levels of risk behaviors than females overall during the previous six months, as indicated by the higher numbers of total sex partners, casual or anonymous sex partners, sex partners known or suspected to be HIV-positive, and 'one night stands'; the higher levels of heavy alcohol and recreational drug use; and, the lower mean age of sexual debut. In adjusted models for risk behaviors in the previous six months, men were five times more likely than women to have casual or anonymous sex partners (OR = 4.8; 95% CI 2.9, 7.8) and twelve times more likely to have three or more sex partners (OR = 12.3; 95% CI 4.7, 32.4). While it is possible that men throughout Soweto have higher levels of risky sexual behavior than women, it is also possible that men with higher risk behaviors or women with lower risk behaviors were more likely to attend VCT services and subsequently enroll in this screening protocol for future HIV vaccine trials. Regardless of the explanation for these findings, the trend for higher risk behaviors amongst male participants may indicate that they should be targeted for increased risk-reduction counseling during the course of future African HIV vaccine trials.

Male gender was not the only predictor of higher levels of reported risk behavior. Reporting any incidence of heavy alcohol use, choosing a partner without regard to personal safety or HIV status, and reporting at least one partner who traveled away from home for employment were also significant predictors of having had sex with a casual or anonymous partner. Any incidence of heavy alcohol use, reporting one or more partners with an age difference of at least 15 years, and reporting at least one partner who traveled away from home for employment were additional significant predictors of having had

three or more sex partners. These outcomes are consistent with research showing that South African youth with partners with an age difference of only five years were at increased risk of HIV infection[25] and that rural South African migrant men and their partners were at an increased risk of contracting STDs compared with non-migrant men[26].

In adjusted models, female gender, age greater than 25 years, and reporting any recreational drug use were significant predictors of having had any incidence of unprotected vaginal or anal sex in the previous six months. Female gender and older age are not necessarily associated with increased risk behavior, because this relationship might indicate married older women having unprotected sex with monogamous HIV-negative partners. But this association may be an indication of a form of 'passive' high risk behavior, in which married older women, for example, are forced into having unprotected sex with husbands who subsequently infect them with HIV[27]—a concept reinforced by studies showing that married older women are more likely to use condoms inconsistently[28]. Refinement of the survey tool to gather information regarding whether participants engaged in unprotected sex of their own volition or by force would help to clarify this association further. Recreational drug use, on the other hand, is clearly associated with higher risk behavior and was also a significant predictor for having had any incidence of unprotected vaginal or anal sex with a known or suspected HIV-positive partner in the previous six months.

Although some of these predictors occurred more frequently in male participants, they were independently associated with higher risk behavior and might also be used to target vaccine trial participants for increased risk-reduction counseling. In particular, the

substance use predictors were associated with all four classifications for increased risk behavior and may be particularly useful in risk stratification of vaccine trial volunteers: participants reporting any history of recreational drug use were twice as likely to have had unprotected sex (OR = 2.3; 95% CI 1.1, 4.8) and five times as likely to have had unprotected sex with a known or suspected HIV-positive partner (OR = 5.1; 95% CI 1.4, 18.4), while participants reporting any history of heavy alcohol use were three times as likely to have had sex with casual or anonymous partners (OR = 3.0; 95% CI 1.9, 4.9) and three times as likely to have had more than two partners (OR = 3.1; 95% CI 1.4, 6.9) in the previous six months.

A study of the risk behavior patterns in a cohort of participants, observed for evaluating HIV incidence and study retention rates in preparation for HIV vaccine trials, showed that the cohort engaged in higher levels of sexual risk behavior than similar participants from the same community[12]. It is difficult to ascertain how closely our sample represents the sexual risk-taking behavior of the general population of Soweto. Even amongst different populations attending the same hospital, risk behavior patterns can vary greatly. For example, in a study of HIV-positive adults who were receiving primary care services at the Chris Hani Baragwanath hospital, reported 'always' condom use was 76% with steady partners and 70% with casual partners[29]. In contrast, participants in our study at the same hospital reported 'always' condom use of only 37% with steady partners and 60% with casual partners, which is consistent with a national survey in which men in South Africa were shown to determine their condom use by whether they perceived their partner as 'risky' or 'safe', despite the fact that there is little correlation between an individual's perception of whether a partner is high risk and

whether that partner is indeed high risk[30,31]. There may have been a potential bias in participant enrollment, as knowledge of VCT services and screening for HIV vaccine trials is communicated by both structured community outreach programs and word of mouth in Soweto. These discrepancies might be explained by the differences in motivation and HIV status—participants in our study were initially recruited because they had sought HIV VCT and were subsequently found to be HIV-negative—but we were unable to determine whether this is indeed the causative factor. Compared to the general population, our methods may have selected a group of participants which practices riskier sex, because individuals at greater risk for HIV infection sought VCT services, or a group of participants which practices safer sex, because individuals at lower risk for HIV infection sought assurance that they were not infected. Regardless, it underscores the need to characterize the baseline behaviors of the actual populations that are participating in HIV vaccine trials, which was the intent of this study.

While heterosexual vaginal intercourse was the most reported sex act in our study, care was taken to include all possible categories of sexual activity. In national surveys, the prevalence of reported anal sex was 2.2% overall[32] and 3.6% amongst South African youth aged 15-24[33]. Participants in our study reported anal sex with both steady partners (6%) and casual partners (9%). In another survey of sexually active South African youth, 0.8% of men and 1.6% of women reported a partner of the same gender within the past year[32]. Several participants from Soweto in our study also reported sexual activity with partners of the same gender, which reinforces the need for both gender-neutral and comprehensive sex act risk behavior questioning techniques.

Our study used self-reported condom use as an important assessment of risk

behavior in the survey that we developed. While there is a general scientific consensus that the use of condoms prevents HIV transmission[34], the validity of self-reported condom use as an accurate measure of behavior has, until recently, been more contentious. Early studies found that self-reported condom use was not significantly associated with protection from incident STIs, but postulated that a true association might be masked by improper condom use, over-reporting due to recall bias or social desirability bias, and most importantly, by confounding[31,35-37]. On this issue, Peterman *et al.* observed that "persons appear to be more likely to have safe sex with risky partners and risky sex with safe partners"[37]. However, a definitive study which controlled for confounding by analyzing only patients with known exposure from infected partners found that self-reported condom use and incident STIs were indeed significantly associated[23]. It is now generally agreed that self-reported condom use is an appropriate indicator of behavior that puts one at risk of acquiring STIs.

There are several limitations that are inherent to the survey procedures used in this study. Both the assessment of personal information in a face-to-face interview and the risk-reduction counseling offered with VCT services prior to risk behavior survey administration may have influenced the social desirability bias of reported behaviors. Additionally, although the counselors administering the survey were periodically trained and monitored, the administration of the survey by multiple interviewers over time and in a mixture of languages (English, Sotho, Zulu) might have varied between participants. These problems could be resolved with the future use of audio computer-assisted self-interviewing (ACASI) technology. ACASI has been shown in a longitudinal randomized trial within an HIV risk behavior study to improve behavior data collection, likely by

decreasing social desirability bias, removing interviewer bias and error, and standardizing the interview questions[38]. Another limitation is that participant recall bias might have prevented accurate risk assessment, although studies have shown that structured interviews to recall information for the previous three to six months are preferable to recalling shorter or longer time periods[36]. A further limitation is that behavior may have been accurately reported by the participant, but not have completely represented true risk. For example, a person might have reported 100% condom use but not have used condoms correctly during that time, which would under-represent risky sexual behavior.

In conclusion, our study provides the first sexual risk behavior data for an African population participating in HIV vaccine trials to date as well as a baseline reference for determining whether sexual risk behavior might change in response to participation in South African HIV vaccine trials. In addition to increased risk-reduction counseling for the prevention of HIV transmission in targeted groups, the predictors of higher risk behavior described in this study might also be used to differentiate between participants more suitable for Phase I and II safety and immunogenicity studies, which require volunteers at relatively low risk for HIV infection, or Phase III efficacy studies, which require volunteers at relatively high risk for HIV infection.

Despite multiple HIV vaccine trials being conducted globally, appropriate methods for assessing risk are still under debate and are particularly important in areas where baseline sexual practices and customs are not well known. Given the implications for risk behavior change to adversely affect the potential benefits of a vaccination campaign, this and other studies stress the importance of observing risk behavior patterns during

clinical trials. Further, even if population-level risk behavior were to remain unchanged in a clinical trial overall, individual-level risk behavior change is still important to monitor. Research on risk behavior and HIV vaccines must proceed together, and risk behavior education must be an integral part of any future HIV prevention program that includes an HIV vaccine[3,4].

REFERENCES

1. Frey SE. Unique risks to volunteers in HIV vaccine trials. *J Investig Med* 2003; **51(Suppl 1)**:S18-20.

2. Lurie P, Bishaw M, Chesney MA, Cooke M, Fernandes ME, Hearst N, Katongole-Mbidde E, Koetsawang S, Lindan CP and Mandel J. Ethical, behavioral, and social aspects of HIV vaccine trials in developing countries. *JAMA* 1994; **271**:295-301.

3. Cohen J. The HIV vaccine paradox. *Science* 1994; **264**:1072-1074.

4. Anonymous. Future access to HIV vaccines. Report from a WHO-UNAIDS Consultation, Geneva, 2-3 October 2000. *AIDS* 2001; **15**:W27-44.

5. Halloran ME, Longini IM, Jr., Haber MJ, Struchiner CJ and Brunet RC. Exposure efficacy and change in contact rates in evaluating prophylactic HIV vaccines in the field. *Stat Med* 1994; **13**:357-377.

6. Blower SM, van Griensven GJ and Kaplan EH. An analysis of the process of human immunodeficiency virus sexual risk behavior change. *Epidemiology* 1995; **6**:238-242.

7. Schaper C, Fleming TR, Self SG and Rida WN. Statistical issues in the design of HIV vaccine trials. *Annu Rev Public Health* 1995; **16**:1-22.

8. Turner CF and Sheon AR. Behavioral studies relevant to vaccine trial preparation: an introduction. *AIDS Res Hum Retroviruses* 1994; **10(Suppl 2)**:S273-276.

9. HIV Vaccine Trials Network current vaccine trials [database online]. Seattle, WA: HIV Vaccine Trials Network, 2006. Updated September 2006.

10. IAVI database of AIDS vaccines in human trial [database online]. New York, NY: International AIDS Vaccine Initiative, 2006. Updated June 13, 2006.

11. Sandstrom E and Birx D. HIV vaccine trials in Africa. *AIDS* 2002; **16(Suppl 4)**:S89-95.

12. Smit J, Middelkoop K, Myer L, Seedat S, Wood R, Stein DJ and Bekker L-G. Sexual risk factors associated with volunteering for HIV vaccine research in South Africa. *AIDS Care* 2006; **18**:569-573.

13. Mesesan K, Bogoshi M, Niccolai LM, Gray GE, McIntyre JA and Vardas E. Measuring the sexual risk behavior of a cohort undergoing screening and enrollment into multiple Phase I/II HIV vaccine trials in Soweto, South Africa [ThPeC7438]. Paper presented at: XV International AIDS Conference; 2004; Bangkok.

14. Bogoshi M, Mesesan K, Niccolai LM, McIntyre JA, Gray GE and Vardas E. Circumstances and choice of first and subsequent sexual encounters in potential Phase 1 HIV Vaccine participants in Soweto [ThPeC11322]. Paper presented at: XV International AIDS Conference; 2004; Bangkok.

15. Mesesan K, Van Niekirk RM, Niccolai LM, Mlungwana ON, Holdsworth IM, Bogoshi M, McIntyre JA, Gray GE and Vardas E. Self-reported sexual risk behaviors of a cohort being prepared for multiple Phase I/II HIV vaccine trials in Soweto, South Africa [OA06-05]. Paper presented at: AIDS Vaccine International Conference; 2006; Amsterdam.

16. Mesesan K, Van Niekerk R, Niccolai LM, Mlungwana O, Holdsworth IM, Bogoshi M, McIntyre JA, Gray GE and Vardas E. Self-reported sexual risk behaviors of the first cohort undergoing screening for Phase I/II HIV vaccine trials in Soweto, South Africa [351P]. Paper presented at: AIDS Vaccine International Conference; 2005; Montreal.

17. Anonymous. 2001 South African Census. Statistics South Africa, 2004. Available at: www.statssa.gov.za.

18. Shisana O, Rehle T, Simbayi LC, Parker W, Zuma K, Bhana A, Connolly C, Jooste S and Pillay V. *South African national HIV prevalence, HIV incidence, behaviour and communication survey, 2005.* Cape Town: HSRC Press; 2005.

19. Vardas E, Mogale M, Masshego T, Molapo-Matsoso M, Martin G, McIntyre J, Khambule V, Mabunda M, Nuwe N, Mateboge O and Gray G. Prescreening protocol to

develop a well informed, low risk, healthy cohort in preparation for enrollment in Phase I/II HIV vaccine trials [505]. Paper presented at: AIDS Vaccine International Conference; 2003; New York.

20. Vardas E, Mlungwana ON, Van Niekerk RM, Mesesan K, Mogale M, Mayaphi S, McIntyre JA and Gray GE. Characteristics of a cohort of individuals screened for Phase I/II HIV vaccine trials in South Africa [344P]. Paper presented at: AIDS Vaccine International Conference; 2005; Montreal.

21. Vardas E, Gray GE, Van Niekerk R, Schwarz R, McIntyre J, Mlungwana O, Mogale M and the HIV Vaccine Trial Network. Recruiting into phase I/II HIV vaccine trials in Soweto, South Africa: a model for developing countries [OA06-04]. Paper presented at: AIDS Vaccine International Conference; 2006; Amsterdam.

22. Slack C, Lindegger G, Vardas E, Richter L, Strode A and Wassenaar D. Ethical issues in HIV vaccine trials in South Africa. *S Afr J Sci* 2000; **96**:291-295.

23. Warner L, Newman DR, Austin HD, Kamb ML, Douglas JM, Jr., Malotte CK, Zenilman JM, Rogers J, Bolan G, Fishbein M, Kleinbaum DG, Macaluso M, Peterman TA and the Project RESPECT Study Group. Condom effectiveness for reducing transmission of gonorrhea and chlamydia: the importance of assessing partner infection status. *Am J Epidemiol* 2004; **159**:242-251.

24. Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, Wabwire-Mangen F, Lutalo T, Li X, vanCott T, Quinn TC and the Rakai Project Team. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet* 2001; **357**:1149-1153.

25. Pettifor AE, Rees HV, Kleinschmidt I, Steffenson AE, MacPhail C, Hlongwa-Madikizela L, Vermaak K and Padian NS. Young people's sexual health in South Africa: HIV prevalence and sexual behaviors from a nationally representative household survey. *AIDS* 2005; **19**:1525-1534.

26. Zuma K, Lurie MN, Williams BG, Mkaya-Mwamburi D, Garnett GP and Sturm AW. Risk factors of sexually transmitted infections among migrant and non-migrant sexual partnerships from rural South Africa. *Epidemiol Infect* 2005; **133**:421-428.

27. Ackermann L and de Klerk GW. Social factors that make South African women vulnerable to HIV infection. *Health Care Women Int* 2002; **23**:163-172.

28. Pettifor AE, Measham DM, Rees HV and Padian NS. Sexual power and HIV risk, South Africa. *Emerg Infect Dis* 2004; **10**:1996-2004.

29. Martinson N, Pronyk P, Mhlongo N, Heyer A, Steyn J, McIntyre J and Gray G. Characteristics of rural and urban HIV-infected adults attending primary care services in South Africa [MoPeC3542]. Paper presented at: XV International AIDS Conference; 2004; Bangkok.

30. Simbayi L, Strebel A, Wilson T, Andipatin M, Msomi N, Potgieter C, Ratele K and Shefer T. *Sexually transmitted diseases in the South African public sector*: National Department of Health's Directorate of Health Systems Research and Epidemiology in conjunction with the Directorate of HIV/AIDS and STDs; August 1999.

31. Fishbein M and Jarvis B. Failure to find a behavioral surrogate for STD incidence--what does it really mean? *Sex Transm Dis* 2000; **27**:452-455.

32. Simbayi LC, Chauveau J and Shisana O. Behavioural responses of South African youth to the HIV/AIDS epidemic: a nationwide survey. *AIDS Care* 2004; **16**:605-618.

33. Lane T, Pettifor A, Pascoe S, Fiamma A and Rees H. Heterosexual anal intercourse increases risk of HIV infection among young South African men. *AIDS* 2006; **20**:123-125.

34. Anonymous. *Workshop summary: scientific evidence of condom effectiveness for sexually transmitted disease (STD) prevention.* Herndon, Virginia: National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services; June 12-13 2000.

35. Zenilman JM, Weisman CS, Rompalo AM, Ellish N, Upchurch DM, Hook EW, 3rd and Celentano D. Condom use to prevent incident STDs: the validity of self-reported condom use. *Sex Transm Dis* 1995; **22**:15-21.

36. Pequegnat W, Fishbein M, Celentano D, Ehrhardt A, Garnett G, Holtgrave D, Jaccard J, Schachter J and Zenilman J. NIMH/APPC workgroup on behavioral and biological outcomes in HIV/STD prevention studies: a position statement. *Sex Transm Dis* 2000; **27**:127-132.

37. Peterman TA, Lin LS, Newman DR, Kamb ML, Bolan G, Zenilman J, Douglas JM, Jr., Rogers J, Malotte CK and the Project RESPECT Study Group. Does measured behavior reflect STD risk? An analysis of data from a randomized controlled behavioral intervention study. *Sex Transm Dis* 2000; **27**:446-451.

38. Metzger DS, Koblin B, Turner C, Navaline H, Valenti F, Holte S, Gross M, Sheon A, Miller H, Cooley P, Seage GR, 3rd and the HIVNET Vaccine Preparedness Study Protocol Team. Randomized controlled trial of audio computer-assisted self-interviewing: utility and acceptability in longitudinal studies. *Am J Epidemiol* 2000; **152**:99-106.

TABLE 1. Participant sociodemographics (n = 488)

Characteristic	n (%)[a]
Gender	
Men	219 (44.9)
Women	269 (55.1)
Mean age [median age 25; range 18-59]	26.8 years
Race	
Black, categorized by ethnicity	485 (99.4)
Zulu	195
Xhosa	52
Northern Sotho	26
Southern Sotho	87
Swazi	4
Venda	14
Tsonga	35
Tswana	62
Other	10
Colored	2 (0.4)
White	1 (0.2)
Highest level of education completed	
Primary school	17 (3.5)
High school	361 (74.4)
Technical college/trade school	86 (17.7)
University	21 (4.3)
Currently in school	111 (22.9)
Marital status	
Married	35 (7.2)
Single, never married	429 (88.5)
Divorced/Widowed/Separated	21 (4.3)
Employed, categorized by migrant labor	117 (24.2)
Requires nights away from home	39
Does not require nights away from home	76
Mean number of residents in household	5.3 persons**
Occupation of main breadwinner in household	
No income for household	28 (5.8)
Government grant <ZAR500[b]	13 (2.7)
Unskilled labor	55 (11.3)
Government grant >ZAR500	46 (9.5)
Small business owner	57 (11.8)
Skilled labor	118 (24.3)
Large business owner	42 (8.7)
Professional	126 (26.0)

Mean household monthly per capita income[c]	ZAR695
Participants from households below poverty level[d]	215 (51.3)

** Statistically significant difference between male and female participants ($p < 0.01$)
[a] Results specified as n (%) and sample size within 1% of total n = 488 unless otherwise noted
[b] ZAR, South African rands (1 USD ≈ 6 ZAR)
[c] n = 419; median monthly per capita income ZAR450, range ZAR25-4,450
[d] n = 419; poverty level defined as ZAR500 per capita

TABLE 2. Characteristics of participants reporting ever sexually active (n = 471)[a,b]

Sexual history variable	Men (%)	Women (%)	*p*
Mean age of first sexual encounter (years)	15.8 y	17.5 y	< 0.001**
Forced first sexual encounter	15.5	23.6	0.028*
Main rationale for partner choice in past 6 months[c]			0.10
Knowing their HIV status	14.6	19.4	
Knowing the partner was faithful	5.3	8.7	
Forced to because of favors/gifts from the partner	0.5	1.2	
Forced to because of marriage/commitment to the partner	7.8	11.1	
Attracted to the partner	71.8	59.7	
Reported number of sexual partners in past 6 months			< 0.001**
0	15.5	8.2	
1	43.7	73.2	
2	19.3	16.3	
3 or more	21.6	2.3	
Mean number of sexual partners in past 6 months	1.7 p	1.1 p	< 0.001**[e]
Reporting forced sex in the past 6 months[d]	0.5	3.3	0.044*

* $p < 0.05$, ** $p < 0.01$

[a] Sex and sexual activity are defined as any incidence of vaginal, anal, or oral sex

[b] Sample size within 1% of total n = 471 unless otherwise noted

[c] n = 459

[d] n = 449

[e] Males also had a higher mean number of sexual partners than females amongst just those participants with at least one sex partner in the past six months (2.0 vs. 1.2 partners, t = 6.2, p < 0.001)

TABLE 3. Sexual partnership risk behaviors in the previous 6 months (n = 408)

Participants reporting at least one of the following:	Men (%)	Women (%)	*p*
A steady sex partner	82.3	94.0	< 0.001**
A casual sex partner	49.1	17.2	< 0.001**
An anonymous sex partner	13.7	2.6	< 0.001**
A casual or anonymous sex partner	54.9	19.7	< 0.001**
A one-night stand	29.1	4.3	< 0.001**
A partner with an age difference of 15 years or greater[a]	5.7	1.7	0.028*
A partner of the same gender[b]	3.4	3.9	0.80
A partner who spends nights away from home for work	16.6	19.7	0.41
A partner with known HIV	4.6	1.7	0.09
A partner with known or suspected HIV	17.7	6.9	< 0.001**

* $p < 0.05$, ** $p < 0.01$
[a] Including both older men with younger women and older women with younger men
[b] n = 406

TABLE 4. Sexual partnership risk behaviors in the previous 6 months

Sexual risk behavior	With steady partners (n = 358)[a]	With casual or anonymous partners (n = 141)[b]
Participants reporting vaginal sex	350 (98.3%)[c]	134 (95.7%)
Mean condom use during reported vaginal sex[d]	53.3%	73.0%
Average number unprotected sex acts per participant reporting vaginal sex[e]	32.0 acts	7.2 acts
Participants reporting anal sex	22 (6.2%)	13 (9.2%)
Mean condom use during reported anal sex[f]	49.5%	73.1%
Average number unprotected sex acts per participant reporting anal sex[g]	3.4 acts	0.8 acts
Participants reporting oral sex	142 (40.0%)	46 (32.9%)
Participants reporting other sex acts	38 (11.0%)	12 (8.8%)
Participants reporting unprotected vaginal or anal sex with at least one partner with known or suspected HIV	13 (3.7%)	13 (9.4%)

[a] Sample size for responses: n = 356 (vaginal sex), n = 358 (anal sex), n = 357 (oral sex), n = 347 (other sex acts), and n = 353 (unprotected sex with known/suspected HIV+ partner)
[b] Sample size for responses: n = 140 (vaginal sex), n = 141 (anal sex), n = 140 (oral sex), n = 136 (other sex acts), and n = 139 (unprotected sex with known/suspected HIV+ partner)
[c] Male participants less likely than female participants, 96.4% vs. 99.5% ($p = 0.037$)
[d] Median condom use was 50% for steady partners and 100% for casual/anonymous partners
[e] Median (range) unprotected sex acts was 5(0-300) for steady partners and 0(0-192) for casual/anonymous partners
[f] Median condom use was 40% for steady partners and 100% for casual/anonymous partners
[g] Median (range) unprotected sex acts was 1(0-48) for steady partners and 0(0-6) for casual/anonymous partners

TABLE 5. Multivariate predictors of higher risk sexual behavior in the previous 6 months, Adjusted OR (95% CI)

Covariate	<100% condom use (55.2%, n = 397)[a]	<100% condom use w/ HIV+ (3.6%, n = 391)[b]	Casual sex partners (34.6%, n = 399)[c]	>2 sex partners (12.5%, n = 399)[d]
Gender[e]				
Male (vs. female)	0.59 (0.39, 0.90)[f]*	1.44 (0.43, 4.87)	4.75 (2.88, 7.81)**	12.33 (4.70, 32.40)**
Age[e]				
< 25 years (vs. ≥ 25 years)	0.60 (0.40, 0.90)[g]*	1.04 (0.35, 3.16)	0.97 (0.60, 1.55)	1.47 (0.73, 2.97)
Marital status				
Single (vs. married, divorced, separated, or widowed)	NS[h]	NI	NS	NI
Education				
High school or less (vs. college or university degree)	NS	NI	NI	NI
Household occupants				
> 5 residents (vs. ≤ 5 residents)	NS	4.15 (1.24, 13.89)*	NS	NI
Per capita household income				
Below poverty level (vs. at or above poverty level)	NI[i]	NI	NI	NI
Employment status				
Unemployed (vs. employed)	NI	NI	NS	NI
Alcohol use				
≥1 day of heavy drinking in past 6 months (vs. 0 days)	NS	NS	3.01 (1.86, 4.87)**	3.09 (1.39, 6.87)**
Drug use				
Any recreational drug use in past 6 months (vs. no use)	2.27 (1.08, 4.78)*	5.09 (1.41, 18.37)*	NS	NS
Age of sexual debut				
< 18 years (vs. ≥ 18 years)	NI	NS	NS	NS
Sexual debut				
Forced first encounter (vs. not forced)	NI	NI	NI	NI
STD history, ever				
Yes (vs. no)	NS	NI	NI	NI
Rationale for partner choice				
Not HIV knowledge/safety oriented (vs. HIV protection oriented)	NI	NI	2.09 (1.16, 3.76)*	NI

Partner age				
≥ 1 partner older or younger by at least 15 years (vs. 0 partners)	NI	NI	NS	5.97 (1.54, 23.13)**
Partner's migrant labor				
Travels for work (vs. does not travel for work)	NS	NI	2.40 (1.33, 4.34)**	4.53 (2.05,9.99)**
Sex act profile				
Includes dry sex, fisting, rimming, or sharing sexual toys (vs. not)	NI	NI	NS	NS

* $p < 0.05$, ** $p < 0.01$
[a] Defined as having any incidence of unprotected vaginal or anal sex in the previous 6 months
[b] Defined as having any incidence of unprotected vaginal or anal sex in the previous 6 months with a known or suspected HIV-positive partner
[c] Defined as having any incidence of vaginal, oral, or anal sex with a casual or anonymous sex partner in the previous 6 months
[d] Defined as having 3 or more sex partners in the previous 6 months
[e] Included in final multivariate model as a potential confounder regardless of significance level
[f] OR for female gender = 1.7 (1.1, 2.6)
[g] OR for age ≥ 25 years = 1.7 (1.1, 2.5)
[h] NS = not significant, $p \geq 0.05$ for adjusted OR in final multivariate model
[i] NI = not included in initial multivariate model because $p \geq 0.20$ in bivariate analysis

APPENDIX

The following pages contain the risk behavior assessment survey developed for use in this study.

Visit Code ☐.☐

Pre-Screening Protocol (039) LSQ #200

01 – S☐☐☐☐ LifeStyle Questionnaire Interview Date ☐☐ ☐☐ ☐☐

Site Number Participant Number dd mm yy

We are going to ask you some personal questions about your sexual activities in this survey that might be embarassing. This information will be kept confidential and will not be seen by anyone except for the relevant clinical staff and people who review our research to make sure that it is conducted ethically. If at any point you become uncomfortable and you do not want to continue, please tell me and we will stop the survey at that point. Because we need this information for the phase I/II vaccine trials, for your own safety we may not be able to enroll you in a future vaccine trial if you are unable to answer these questions.

We will now start the interview. This survey will take about forty minutes or less to complete. I will read each question and response to you. If a question is confusing, please ask me to explain it better. Please answer the questions as best as you can. There are no right or wrong answers and we are not looking for you to give us specific answers.

Q1. Interviewer's initials: ☐☐ **Q2. Participant's initials:** ☐☐

Q3. Participant's Date of Birth: *dd* ☐☐ *mm* ☐☐ *yyyy* ☐☐☐☐

Q4. Participant's current age: ☐☐ **Q5. Sex:** *male* ☐ *female* ☐

Q6. Which of the following best describes you:

☐ Colored ☐ Black specify: → ☐ Zulu ☐ S. Sotho ☐ Tsonga

☐ White ☐ Other ☐ Xhosa ☐ Swazi ☐ Tswana

☐ Indian/Asian ☐ N. Sotho ☐ Venda ☐ Other: _____

Q7. What is the highest level of schooling you *completed*:

☐ No schooling ☐ College / 'technikon' school

☐ Primary school ☐ University

☐ Secondary / high school / 'matric' / grade12

Q8. Are you still in school? *yes* ☐ *no* ☐

Visit Code ☐.☐

Pre-Screening Protocol (039) LSQ #205

0 1 – S ☐☐☐☐

Site Number Participant Number

LifeStyle Questionnaire continued...

Q9. Are you married or have you ever been married?

☐ Married (includes Western and African/customary marriages) ☐ Widowed

☐ Single / never married (includes living in relationship) ☐ Separated

☐ Divorced

If 'no' go to Q12

	yes	no
Q10. Do you currently have a job and receive money for the work that you do?	☐	☐
Q11. Does your job require you to travel away from your home and sleep elsewhere for more than one night at a time?	☐	☐

Q12. Including yourself, what is the total number of people who live in your household? ☐☐

Q13. What type of work does the main breadwinner - the person who earns the most money - in your household do?
(Interviewer: ask this question and then decide which of the below answers is closest to what the participant says.)

☐ No one in the household is employed and there is no income

☐ Child support grant or other small monthly grant (under R500)

☐ Unskilled labor (e.g. gardener or domestic worker)

☐ Disability grant or old-age pension or other large monthly grant (more than R500)

☐ Small business enterprise (e.g. spaza shop, hawker, renting out rooms in household)

☐ Skilled labor (e.g. builder, mechanic)

☐ Large business enterprise (all business owners that are not 'small business enterprises')

☐ Professional

Visit Code ☐.☐

Pre-Screening Protocol (039) LSQ #210

0 1 – S ☐☐☐☐

Site Number Participant Number

LifeStyle Questionnaire continued...

Q14. What is the approximate *monthly* earnings for your household, including everyone that earns money?

☐	Less than R500	☐	R3000 - R3499
☐	R500 - R999	☐	R3500 - R3999
☐	R1000 - R1499	☐	R4000 - R4499
☐	R1500 - R1999	☐	R4500 - R4999
☐	R2000 - R2499	☐	More than R5000
☐	R2500 - R2999	☐	Don't know

	yes	no
Q15. In the past six months, have you received blood, blood products or organ donations?	☐	☐

The next several questions ask about drug and alcohol use. Many of the questions in this survey ask about how many times you may have done something in the past six months. If it is difficult to remember exactly how many times, just give us your best guess or tell us how many time you think you do something each month or each week on average and we will adjust for the number of months.

Q16. In the past 6 months, about how many times did you drink more than 5 alcoholic drinks in one day?
-- This includes home made alcohol, e.g. mgqombothi
-- We call 'one drink' the amount of alcohol (beer, wine, cider, mixed alcohol drink) in a can.
-- If the drink is strong alcohol such as whiskey that is not mixed with anything then 'one drink' is the same as a 'tot'.

☐☐☐

	yes	no
Q17. In the past six months, did you smoke dagga (weed, grass, marijuana, green veja, pot, matekwane)?	☐	☐
Q18. In the past six months, did you use needles to inject/shoot drugs such as cocaine (crack or mandrax) or heroine or something else?	☐	☐
Q19. In the past six months, did you use any other drugs by snorting or sniffing them, smoking them or taking them as pills such as cocaine, heroin, ecstacy, crystal meth, or other recreational drugs.	☐	☐

Visit Code ☐.☐

Pre-Screening Protocol (039) LSQ #215

01 – S☐☐☐☐

Site Number Participant Number

LifeStyle Questionnaire continued...

The next questions ask about sexually transmitted diseases (STDs) that you may have had and about your sexual activities. Some of the questions in the survey may not apply to you, but we must ask you all of the questions and we must ask them exactly as they are written. Remember that all of your answers will be kept confidential.

If participant is unsure of specific day of month for dates in this survey, ask the participant whether the event occured in the beginning, middle, or end of the month and then estimate the day by 5, 15, or 25. If the participant can not state the period of the month, estimate the day as 15.
If the participant says that something occurred many years ago and can not remember even the month, estimate month with a 6 (June) and estimate day as 15.

Q20. Have you ever in your life been told, specifically by a nurse or doctor or other health care provider, that you had a STD (sexually transmitted disease), including any genital sores, ulcers, or genital discharge that required a visit to the clinic?
Regardless of whether the answer is yes or no, we must still go over the STDs that this might include just to make sure none of them are forgotten:
-- 'drop' or any abnormal vaginal discharge that was treated with medicine (chlamydia, gonorrhea, or trichomonas)
-- herpes (explanation: a blister, similar to blisters on lips from a cold sore, but on private parts)
-- syphilis (explanation: painless sore/wound on private parts)
-- painful glands near private parts, following STD *(lymphogranuloma venereum)*
-- painful sore on private parts *(chancroid)*
-- sexually acquired hepatitis B (explanation: yellow eyes/liver disease from an STD)
-- severe lower stomach pain associated with abnormal vaginal discharge--not menstrual pains *(pelvic inflammatory disease, women only)*
-- bad - smelling vaginal discharge *(mucopurulent cervicitis, women only)*
-- testicular pain, following STD *(acute epididymitis, men only)*
-- anal pains, following STD *(acute proctitis)*

yes *no*
☐ ☐
If 'no' go to Q22

Q21. When was the *last* time that you were told that you had any sexually transmitted disease or infection?

(if the most recent STD is herpes, please give us the very *first* time you were told you had herpes)

dd *mm* *yyyy*
☐☐ ☐☐ ☐☐☐☐

☐ This occurred within the last six months

☐ This did *not* occur within the last six months

Visit Code ☐.☐

Pre-Screening Protocol (039) LSQ #220

01 – S☐☐☐☐

Site Number Participant Number

LifeStyle Questionnaire continued...

In the following questions, when I say 'sex', I mean three things: vaginal sex, when a man inserts his penis into a woman's vagina; anal sex, or 'backdoor sex/ sex from behind', when a man inserts his penis in his partner's butt, regardless of whether that person is a man or a woman; and oral sex, when a person - either a man or a woman - puts their mouth on their partner's penis or vagina. Do you have any questions about this definition of sex?

Q22. How old were you the very first time you had sex? ☐☐

Never had sex → ☐ **If checked go to 26**

Q23. Did you *choose* to first start having sex at that age, or was there some circumstance which *forced* you to have sex for the first time?

☐ Yes, there was some circumstance which forced me to have sex at that age. → **If checked, ask 'Do you want to talk about it?' before continuing.**

☐ No, I chose to start having sex at that age.

Q24. In the last six months, have you ever been *forced* to have sex with someone because of violence, money, or any other reason?

no ☐ *yes* ☐ → **If checked, ask 'Do you want to talk about it?' before continuing.**

Q25. Which of the following items was *most* important to you when choosing a sexual partner over the past six months?

☐ Knowing whether or not the partner has HIV

☐ Knowing whether or not the partner is having sex with other people besides you

☐ Feeling I have to have sex (not because I want to) because the partner took me to restaurants and/or bought me gifts

☐ Feeling I have to have sex (not because I want to) because I am married to the partner or in a commit ted relationship

☐ Feeling sexually or physically attracted to that partner

Q26. Did you have any partners in the past six months with whom you did *not* have vaginal, anal, or oral sex?

yes ☐ *no* ☐

Visit Code ☐.☐

Pre-Screening Protocol (039) LSQ #225

0 1 – S ☐☐☐☐

Site Number Participant Number

LifeStyle Questionnaire continued...

I would like you to now think of all the persons that you had sex with during the past six months. Please give us the initials of those partners.
We are only asking for these initials because we would like to ask you a series of questions about each partner, and this will help us to remember which partner you are talking about. If you do not know a partner's initials or if you do not want us to know the partner's initials, you can use any nickname of your choice (for example: 'red shirt', 'weekend party', etc) that will help us to remember which partner you are talking about.
To help you remember all of your partners, we will go through each month or holiday and think of who you were with at that time. Let's start with this month:

	Month (first 3 letters)	*List partners*	*Number of partners this month*
Q27. What are the initials or nicknames of the partners with whom you had sex this month?	☐☐☐		☐☐

	Month (first 3 letters)	*List additional partners only*	*Number of new partners this month*
Q28. Did you have sex with any additional partners *not already mentioned* the month before that? What are the initials or nicknames of these partners?	☐☐☐		☐☐
Q29. Did you have sex with any additional partners *not already mentioned* the month before that?	☐☐☐		☐☐
Q30. Did you have sex with any additional partners *not already mentioned* the month before that?	☐☐☐		☐☐
Q31. Did you have sex with any additional partners *not already mentioned* the month before that?	☐☐☐		☐☐
Q32. Did you have sex with any additional partners *not already mentioned* the month before that?	☐☐☐		☐☐
Q33. Did you have sex with any additional partners *not already mentioned* the month before that?	☐☐☐		☐☐

The following question is for the interviewer only. Do not ask this question to the participant.
Q34. What is the *total* number of sexual partners in the last six months? ☐☐☐ → **If total is zero, skip partner module and conclude survey now.**

We are now going to ask you questions about your sexual activities with each of these partners. Some of the questions are personal and might be embarrassing, but it is very important that you be honest. These questions may not apply to you, but we must ask you all the questions and we must ask them exactly as they are written. Remember that all your answers will be kept confidential.
When we ask you about sex, include all the times with or without a condom, and with or without ejaculation. When we ask you about using condoms, do not include times when the condom slipped, broke, or was not used for the entire time.

Visit Code ☐.☐

Pre-Screening Protocol (039) LSQ #230

0 1 – S ☐☐☐☐ ☐☐

Site Number Participant Number

LifeStyle Questionnaire continued... PARTNER MODULE

Partner Number ☐☐

Now, I am going to ask you questions about _____.

1. Is this partner male or female? *male* ☐ *female* ☐

2. What is the approximate age of this partner? ☐☐

3. Was this a "one night stand"? *yes* ☐ *no* ☐

4. Is this a steady/stable, casual, or anonymous partner? A steady/stable partner is someone who is special to you, like a husband/wife/boyfriend/girlfriend, or lover. A casual sex partner is a person you know but who is not your main sex partner, whether you had sex only once or many times. An anonymous sex partner is someone whose name you did not know the day before you had sex. A sex partner who is a prostitute could be either casual or anonymous.
steady/stable ☐ *casual* ☐ *anonymous* ☐

5. Does this partner have a job that involves travelling away from home and sleeping elsewhere for one or more days at a time, *or* does this partner live in a different city than you (long distance relationship)?
yes ☐ *no* ☐ *don't know* ☐

6. In the last six months, about how many times did you have oral sex with this partner? If you can not remember, you can think of the average number of times each week or each month and we will multiply it by the number of months that you were with this partner. ☐☐☐ → **If 0 skip next question**

7. Of those times you had oral sex, how many times did you use a condom or other form of protection? ☐☐☐

8. In the last six months, about how many times did you have vaginal sex with this partner? ☐☐☐ → **If 0 skip next question**

9. Of those times you had vaginal sex, how many times did you use a male or female condom before penetration? ☐☐☐

10. In the last six months, about how many times did you have anal sex with this partner? ☐☐☐ → **If 0 skip next question**

11. Of those times you had anal sex, how many times did you use a condom before penetration? ☐☐☐

12. In the last six months, about how many times did you and your partner do any of these activities?
--"dry sex" without a condom (sex with a woman without foreplay so that there is no vaginal lubrication, natural or artificial)
--share sexual toys (e.g. vibrators) between both partners
--insert an entire hand (not just the fingers) into the vagina or anus of the partner
--lick the anus of the partner ☐☐☐

13. Before the last time you had sex with this partner, had this partner had sex with other people besides you in the previous six months?
yes ☐ *no* ☐ *don't know* ☐

14. Do you know if this partner has HIV for sure?

☐ Yes, I know he/she has HIV for sure
☐ Yes, I know he/she does *not* have HIV (and I have no reason to doubt it)
☐ No, but I suspect he/she does *not* have HIV
☐ No, but I suspect he/she has HIV (regardless of what he/she has told me)

This section is to be completed for each sexual partner. Repeat module for each partner before completing interview.

PAPER 2

Anticipated Changes in Sexual Risk Behavior Following Vaccination with a Low-Efficacy Preventive HIV Vaccine: Survey Results from a South African Township

INTRODUCTION

With more than 20 millions deaths since the start of the HIV/AIDS epidemic, an estimated 39 million people currently living with HIV/AIDS globally, and 4 million new infections occurring each year[1], the development of new technologies to control this pandemic remains a priority. Potential HIV vaccine candidates are being tested in clinical trials worldwide and many more are under development; therefore, a preventive vaccine may be available within the next decade[2]. While the first HIV vaccines will likely be only partially effective in preventing transmission, even low-efficacy vaccines will be useful for populations such as those across much of sub-Saharan Africa in which the risk of HIV infection is high[3,4].

The individual and population benefits from any HIV vaccine which is not 100% effective in preventing HIV transmission will depend on whether risk compensation—the notion that individuals might change their sexual risk taking behavior in response to vaccination—occurs. Little is known about the potential for risk behavior change associated with mass vaccination campaigns[4-6]. This is particularly true in the African setting where only an isolated study in Uganda, conducting a contingent valuation survey for future HIV vaccines, asked whether individuals might change their behavior in response to hypothetical vaccination[7]. In a household survey of adults, the Ugandan study revealed that 18% of respondents did not think (or were not sure) they would need to use a condom for non-spouse sex partners if they received a 50% effective HIV vaccine.

There have been no risk behavior studies to date on the potential impact of future HIV vaccination programs in South Africa. Because of South Africa's enormous HIV

epidemic, relatively strong health infrastructure, and political support for HIV vaccine development and clinical trials, it is likely to be one of the first countries in sub-Saharan Africa to consider widespread use of a low-efficacy vaccine. Although decreases in risky sexual behaviors would enhance the benefits of programs using low-efficacy vaccines, increases in risky sexual behaviors would decrease potential program benefits and merit further investigation. We developed a survey instrument to investigate the potential for increases in sexual risk behavior in response to a hypothetical, low-efficacy preventive HIV vaccine and administered it to participants in a South African cohort undergoing screening and enrollment into current HIV vaccine trials.

METHODS

Study participants and setting

We collected data on anticipated responses to a hypothetical low-efficacy preventive vaccine from 158 participants undergoing screening for Phase I/II HIV vaccine trials in South Africa. The participants were enrolled in the Pre-Screening Protocol in the HIV/AIDS Vaccine Division of the Perinatal HIV Research Unit (PHRU), which we have described in detail previously [Dissertation Paper 1].

Briefly, the study took place at the Chris Hani Baragwanath Hospital, which is located within the township of Soweto, where antenatal HIV prevalence is 30% (personal communication, Avy Violari, PHRU). The PHRU implemented the Pre-Screening Protocol to collect participants who are healthy, reliable, at low risk of HIV infection, and informed about HIV vaccine science and clinical trials for eventual screening and enrollment into multiple HIV vaccine trials[8,9]. We obtained written informed consent from all participants under the auspices of the Pre-Screening Protocol, and this study was approved by the Committee for Research on Human Subjects at the University of the Witwatersrand in South Africa and the Human Investigations Committee at the Yale University School of Medicine in the United States.

Assessment of anticipated changes in sexual risk behavior

Sexual risk behaviors may change over time, regardless of whether an HIV vaccine is eventually available. In order to examine anticipated risk behavior change in a time-independent manner, we designed a survey in which respondents were asked to consider a hypothetical situation of immediate vaccine availability. The scripted survey described a vaccination scenario in which participants were asked to imagine that a low-efficacy

vaccine was available now, rather than at some point in the future, and questions were posed regarding how they might change their current behaviors if they were to receive such a vaccine.

We used focus groups and pilot testing to optimize the survey language; we trained multi-lingual interviewers to administer the survey in private face-to-face encounters; and, we conducted manual and automated reviews of data for accuracy, as previously described [Dissertation Paper 1]. The data presented here were collected from participants scheduled for either initial or follow-up visits in the Pre-Screening Protocol; however, no participants had prior exposure to this survey. We linked the answers from this survey to sociodemographic data collected at the same visit in the Pre-Screening Protocol [Dissertation Paper 1], including gender, age, education level, alcohol use, and recreational drug use.

The specific vaccine concept we used in this study was a 30% effective vaccine which provided 100% protection to those individuals in whom the vaccine worked; thus, the vaccine would provide 100% protection to only 30% of those vaccinated, as opposed to providing 30% protection to 100% of those vaccinated. The survey involved a scripted, structured educational component on what is meant by a 30% effective vaccine, followed by questions to assess comprehension. Similar techniques have been used elsewhere to assess anticipated changes in sexual risk behavior following hypothetical vaccination with a partially-effective HIV vaccine[7,10]. After comprehension was assessed, participants were re-educated if they answered any of the questions incorrectly or had further questions. We then asked participants questions regarding whether they predicted that they might change their condom use and number of sex partners in

response to receiving such a vaccine, as well as whether they predicted that their partners might change their condom use. Our questions differentiated responses on anticipated changes in behavior between anonymous, casual, and steady/stable sex partners. The script and questions used for vaccine comprehension and anticipated changes in sexual risk behavior are detailed in the Appendix.

Statistical analyses

We employed standard descriptive statistical methods to report frequencies and used the chi-square test for statistical comparison of categorical variables. We used logistic regression techniques to estimate odds ratios (OR) and 95% confidence intervals (CI) for bivariate and multivariate analyses, as previously described [Dissertation Paper 1]. Age and gender were retained in all final adjusted models due to their potential roles as confounders. All analyses were conducted with SAS Version 9.1 software (SAS Institute Inc., Cary, North Carolina).

For bivariate and multivariate analyses, we created covariates as follows: (1) male gender (vs. female gender); (2) age < 25 years (vs. age ≥ 25 years); (3) education level of high school or less (vs. technical college or university degree); (4) any heavy alcohol use in the past 6 months, defined as at least one day of drinking more than 5 alcoholic beverages (vs. no heavy alcohol use); (5) any recreational drug use (vs. no use); and, (6) poor initial comprehension of vaccine concept, defined as answering any of the three vaccine comprehension questions incorrectly (vs. good comprehension, defined as answering all three questions correctly). We created the following outcome variables to indicate potential increases in sexual risk behavior predicted by participants following vaccination with a hypothetical low-efficacy vaccine, dichotomized to reflect increased

risk behavior vs. unchanged or decreased risk behavior: (1) anticipated decrease in condom use by participants with either an anonymous, casual, or steady/stable sex partner; (2) anticipated increase in sex with casual or anonymous partners; and (3) anticipated decrease in condom use by sex partners of participants, including those who thought their partners would or might want to decrease condom use.

RESULTS

Participant characteristics

We collected hypothetical risk behavior responses from 158 participants (91 males, 67 females) in the Pre-Screening Protocol from June 2003 to March 2004. The mean age was 27.0 years (median, 25 years; range, 18-53 years) and 26% of the participants reported education beyond high school level. Alcohol use (at least 1 day of heavy drinking in the previous 6 months) was reported by 54% of participants and recreational drug use (any use over the previous 6 months) was reported by 18% of participants. The majority of participants (68%) completed the survey at their first full clinic visit, while the remainder completed the survey at a follow-up visit. However, results presented here represent the first time a participant was given the survey, thus there was no prior exposure to these questions that might have influenced our results.

Comprehension of low-efficacy vaccine concept

Following the scripted description of a low-efficacy vaccine, we assessed initial comprehension of this concept (Table 1). Overall, 82% of participants answered all three concept questions correctly. We included the 18% of participants who answered at least one question incorrectly in the 'poor comprehension of vaccine concept' category, used in the regression analyses described below. Although we have reported initial comprehension scores for questions answered incorrectly, we counseled all participants to assure full comprehension before completing the remainder of the survey.

Anticipated changes in sexual risk behavior

We designed this study to examine the potential for increases in sexual risk behavior predicted by survey participants following hypothetical vaccination. When

participants were asked about their anticipated behaviors with sex partners if they were to receive a low-efficacy HIV vaccine, 22% overall reported they might use condoms less frequently than at present with sex partners (anonymous, casual, or steady/stable) and 9% overall reported that they might increase their frequency of sex with casual or anonymous partners. Although significant numbers of participants predicted that they would instead decrease their risk behavior (use condoms more frequently and/or decrease their frequency of sex with casual or anonymous partners), we believe that these data are less reliable than the data on anticipated increases in risk behavior [see Discussion below]. Anticipated behavior changes for specific partner types are presented in Table 2. Additionally, when asked if their sex partners might want to use condoms less frequently if they knew the participant had received a vaccine, 37% of participants responded 'yes' and an additional 18% of participants responded 'maybe'.

Predictors of anticipated increases in sexual risk behaviors

Potential decrease in condom use by participants: A total of 22% of participants reported that they might decrease their condom use with sex partners if they received a low-efficacy vaccine. Poor vaccine concept comprehension was associated ($p < 0.01$) with an anticipated decrease in condom use by participants in bivariate analyses (OR = 3.3; 95% CI = 1.4, 7.7) whereas gender, age, education, alcohol use, and drug use showed no association. We included age, gender, and vaccine comprehension in the initial multivariate model, but poor vaccine concept comprehension was the only factor associated with an anticipated decrease in condom use by participants in the final adjusted model (OR = 3.6; 95% CI = 1.5, 8.8).

Potential increase in sex with casual or anonymous partners: Overall, 9% of participants reported that they might have sex with casual or anonymous partners more frequently if they received a low-efficacy vaccine. None of the covariates examined (gender, age, education, alcohol use, drug use, and vaccine concept comprehension) were associated with this outcome in bivariate or multivariate analyses.

Potential decrease in condom use by partners of participants: Overall, 55% of participants reported that their sex partners would or might use condoms less frequently if they knew the participant had received a vaccine, with no significant differences between male and female participant responses. Poor vaccine concept comprehension was associated ($p < 0.05$) with an anticipated decrease in condom use by the partners of participants in bivariate analyses (OR = 2.4; 95% CI = 1.04, 5.4) while male gender, young age, education of high school or less, any heavy alcohol use, and any drug use were not. We included age, gender, alcohol use, and vaccine comprehension in the initial multivariate analysis. In the final adjusted model, both poor vaccine comprehension (OR = 2.7; 95% CI = 1.2, 6.4) and young age (OR = 2.0; 95% CI = 1.03, 4.0) were associated with an anticipated decrease in condom use by the partners of the participants.

DISCUSSION

Anticipated change in sexual risk behaviors following HIV vaccination has rarely been studied within the African setting: several Kenyan studies have addressed potential changes in risk behavior surrounding participation in HIV vaccine trials[11,12], while to our knowledge only one other study in Uganda—using similar methodology to that described here—has assessed potential behavior changes surrounding future mass HIV vaccination campaigns[7]. We assessed anticipated changes in sexual risk behaviors in response to vaccination with a hypothetical low-efficacy HIV vaccine in a cohort of volunteers currently undergoing screening and enrollment into multiple Phase I/II HIV vaccine trials in South Africa. We developed a scripted, educational survey tool for this purpose, adapted for local use and pilot-tested in the same population, which also allowed us to assess comprehension of the low-efficacy HIV vaccine concept. Overall, we found evidence of the potential for sexual risk behavior to change following vaccination, even among individuals who understand the concept that a vaccine may only provide incomplete protection against HIV transmission. We base this conclusion on the anticipated changes in risk behaviors which volunteers predicted for themselves following a hypothetical vaccination scenario. Because our study provided repeated education to assure all participants understood the concept of a low-efficacy vaccine, our results may represent a lower bound on the actual amount of risk behavior disinhibition which could be expected in this population.

We found that almost all of the participants (99%) comprehended the idea that they would not get HIV infections from a low-efficacy vaccine. While this number is encouraging, it must be remembered that this survey was given to participants already

enrolled in a Pre-Screening Protocol for HIV vaccine trial screening and enrollment, which involved general education on HIV vaccines, prior to participation in this study. Comprehension of the new concept of a low-efficacy vaccine, however, was still excellent: 82% of participants overall understood that they would not know whether a low-efficacy vaccine would work at an individual level and that protection from HIV infection would depend on this factor. While these concepts were newly introduced in the survey, caution must be taken in extrapolating the ease of comprehension to the general population because participants were already well-versed in the language and basics of HIV vaccine science. However, with adequate education, introducing the concept of partially effective vaccines should be very feasible in the general population beyond those participating in HIV vaccine trials.

After education to ensure that all participants understood the concept of a low-efficacy vaccine, we assessed anticipated changes in sexual risk behaviors following hypothetical vaccination within a variety of sexual partnership scenarios. We found that 9% of participants reported that they might have sex with casual or anonymous partners more frequently if they were to receive such a vaccine, and that this behavior was not predicted by age, gender, education, alcohol use, recreational drug use, or comprehension of the vaccine concept. Poor comprehension of the low-efficacy vaccine concept was, however, significantly associated with reporting an anticipated decrease in condom use with sex partners, both for participants reporting their own anticipated condom use as well as for participants reporting anticipated condom use by their sex partners. Specifically, 22% of participants reported that they would probably decrease their condom use in sexual partnerships as a result of vaccination. For these participants

reporting their own anticipated behavior change, the majority of the decrease in condom use was expected to occur with steady or stable partners, which would not be a significant factor in HIV transmission in populations with low HIV prevalence. However, in populations where HIV prevalence is high and a generalized epidemic exists, such as Soweto and many communities in South Africa and beyond, even a decrease in condom use with stable partners will likely result in a general increase in HIV transmission. In addition, 55% of participants reported that their sex partners might want to use condoms less frequently than at present if they knew that the participant had received the vaccine. In our sample, there were no significant gender differences in this statistic, despite a body of literature suggesting that women are less likely to successfully negotiate condom use in South Africa[13-16].

Of note, the majority of participants in our study predicted that they would either maintain their risk behavior at current levels or *decrease* their risk behavior following vaccination, e.g. 34% of participants anticipated using condoms more frequently and 41% of participants anticipated having sex less frequently with casual sex partners. While any decreases in sexual risk behavior would enhance the benefits of vaccination programs, the intent of our study was to investigate the potential for *increased* sexual risk behaviors which might lessen the benefits of such vaccination programs or lead to potential harms. We believe that our data showing anticipated increases in risk behaviors are more reliable than the data showing anticipated decreases in risk behaviors because of the inherent social desirability bias in our study design. All participants had received prior risk-reduction counseling and HIV vaccine education, were motivated to participate in HIV vaccine trials, and answered our survey questions in a face-to-face interview format.

Thus, it is more reasonable to conclude that the number of participants anticipating an increase in their sexual risk behavior is in fact an underestimate, while the number of participants anticipating a decrease in their sexual risk behavior is an overestimate, of the true potential for risk behavior change in this population. Further studies in communities naïve to HIV vaccine trial-related education would assist in elucidating this relationship.

Because an HIV vaccine has not yet been licensed or used in a vaccination campaign outside of clinical trials, no data exist on the actual changes that might occur in risk behavior after widespread vaccination. Limited inferences can be made from risk behavior studies and survey techniques in HIV vaccine trial participants, as clinical trials are operated under different conditions than mass vaccination campaigns and may underestimate the true changes that might occur[4], but they represent the only alternative source of information available at present. Analysis to date of previous and ongoing large-scale HIV vaccine efficacy trials in the United States, Canada, the Netherlands, and Thailand indicates that self-reported sexual and injection drug use risk-taking behavior did not increase, and sometimes decreased, during the clinical trial period[17-21]. By contrast, though, two small HIV vaccine trials in men who have sex with men in San Francisco revealed that high-risk sexual behaviors increased significantly during the trial period[22]. This occurred despite education that these were only Phase I/II safety and immunogenicity studies with no known vaccine efficacy—implying that the risk behavior increase that would occur in a Phase III trial or in a general vaccination campaign might be even greater. And, although risk behavior was not shown to increase in the only Phase III HIV vaccine efficacy trial conducted thus far, 46% of participants gave joining to 'get protection from HIV' as one of the reasons for participating in the trial[18,23].

Only limited African data exist, from two cohort studies in Kenya, on changes or anticipated changes in risk behavior concerning HIV vaccine trial participation. First, in a cohort of female commercial sex workers (CSW) prospectively maintained in readiness for future HIV vaccine trials, there was a significant decline in risk behavior during the period of follow-up[24]. However, despite the fact that voluntary counseling and testing (VCT) and follow-up were shown to decrease the incidence of HIV via decreased risk behavior, predictions can not be made about what might happen when this same population is actually vaccinated in an HIV trial. Second, a survey of a high-risk heterosexual cohort of male truck drivers and female CSWs on anticipated participation in a Phase III HIV vaccine trial revealed that 17% of men and 9% of women thought that they would increase their risk behavior (via decreased condom use or increased sex partners) as a result of participation in the trial. This occurred despite intensive individual HIV counseling during the study, and despite being educated that half of the participants would receive a placebo[12]. Except for these few examples, there have been no other African studies either on the characterization of sexual risk behaviors in cohorts enrolling into HIV vaccine trials or on anticipated sexual risk behavior changes in response to HIV vaccine trial participation.

Our study had several limitations. We conducted our survey in a face-to-face interview format and within the context of screening for HIV vaccine trial participation, in which participants had received prior education and risk-reduction counseling; therefore, the data we collected on anticipated changes in sexual risk behaviors are susceptible to social desirability bias as described above. Our results may therefore underestimate the actual potential for risk-taking behavior to increase, at least amongst

participants reporting their own anticipated changes in behaviors. Because there was such a difference in the number of participants reporting that their partners might want to use condoms less frequently, as opposed to their own reported proposed decrease in condom use, it is possible that this line of questioning reduces such bias. More than half of the participants reported that their partners might want to use condoms less frequently, thus the true number of participants who might decrease their own condom use behaviors could be much higher. However, it is also possible that social desirability bias causes an over-estimation of anticipated changes in behaviors reported for sex partners. Future studies should address this issue, and audio computer-assisted self-interviewing (ACASI) technology may assist in reducing potential desirability bias as well as standardizing the survey encounter[25].

Another limitation of our study is that it may be difficult to generalize the results to the greater population of Soweto. Participants in this pre-screening cohort were recruited through community outreach methods which included the provision of free HIV VCT, thus possibly selecting individuals who engaged in higher or lower risk behaviors than the general population. Higher levels of risky behavior have been demonstrated in a vaccine trial preparedness cohort in a similar South African community[26]. However, this potential sample bias may have been tempered for the purposes of this survey by the risk reduction counseling and vaccine education that participants in our study had previously received.

In summary, the potential for sexual risk behavior to change following vaccination is a valid concern. In particular, we have shown that individuals predict that they may increase their risk taking behavior even after successfully understanding the concept that

a vaccine may provide only incomplete protection against HIV transmission. Our research also underscores the need for risk reduction counseling and education surrounding the implementation of future vaccination campaigns with partially effective vaccines. It may not be sufficient to provide education regarding risk behavior only to individuals who are vaccinated; their sex partners may also need risk reduction counseling and mass media education campaigns may be necessary.

REFERENCES

1. UNAIDS. 2006 report on the global AIDS epidemic. Joint United Programme on HIV/AIDS, May 2006. Available at: http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp.

2. IAVI database of AIDS vaccines in human trial [database online]. New York, NY: International AIDS Vaccine Initiative, 2006. Updated June 13, 2006.

3. Anonymous. Future access to HIV vaccines. Report from a WHO-UNAIDS Consultation, Geneva, 2-3 October 2000. *AIDS* 2001; **15**:W27-44.

4. Newman PA, Duan N, Rudy ET and Anton PA. Challenges for HIV vaccine dissemination and clinical trial recruitment: if we build it, will they come? *AIDS Patient Care STDS* 2004; **18**:691-701.

5. Cassell MM, Halperin DT, Shelton JD and Stanton D. Risk compensation: the Achilles' heel of innovations in HIV prevention? *BMJ* 2006; **332**:605-607.

6. Newman PA, Duan N, Rudy ET, Roberts KJ and Swendeman D. Posttrial HIV vaccine adoption: concerns, motivators, and intentions among persons at risk for HIV. *J Acquir Immune Defic Syndr* 2004; **37**:1393-1403.

7. Bishai D, Pariyo G, Ainsworth M and Hill K. Determinants of personal demand for an AIDS vaccine in Uganda: contingent valuation survey. *Bull World Health Organ* 2004; **82**:652-660.

8. Vardas E, Mlungwana ON, Van Niekerk RM, Mesesan K, Mogale M, Mayaphi S, McIntyre JA and Gray GE. Characteristics of a cohort of individuals screened for Phase I/II HIV vaccine trials in South Africa [344P]. Paper presented at: AIDS Vaccine International Conference; 2005; Montreal.

9. Vardas E, Gray GE, Van Niekerk R, Schwarz R, McIntyre J, Mlungwana O, Mogale M and the HIV Vaccine Trial Network. Recruiting into phase I/II HIV vaccine trials in

Soweto, South Africa: a model for developing countries [OA06-04]. Paper presented at: AIDS Vaccine International Conference; 2006; Amsterdam.

10. Blower SM and McLean AR. Prophylactic vaccines, risk behavior change, and the probability of eradicating HIV in San Francisco. *Science* 1994; **265**:1451-1454.

11. Baeten JM, Richardson BA, Lavreys L, Rakwar JP, Mandaliya K, Bwayo JJ and Kreiss JK. Female-to-male infectivity of HIV-1 among circumcised and uncircumcised Kenyan men. *J Infect Dis* 2005; **191**:546-553.

12. Jackson DJ, Martin HL, Jr., Bwayo JJ, Nyange PM, Rakwar JP, Kashonga F, Mandaliya K, Ndinya-Achola JO and Kreiss JK. Acceptability of HIV vaccine trials in high-risk heterosexual cohorts in Mombasa, Kenya. *AIDS* 1995; **9**:1279-1283.

13. Ackermann L and de Klerk GW. Social factors that make South African women vulnerable to HIV infection. *Health Care Women Int* 2002; **23**:163-172.

14. Pettifor AE, Measham DM, Rees HV and Padian NS. Sexual power and HIV risk, South Africa. *Emerg Infect Dis* 2004; **10**:1996-2004.

15. Simbayi L, Strebel A, Wilson T, Andipatin M, Msomi N, Potgieter C, Ratele K and Shefer T. *Sexually transmitted diseases in the South African public sector*: National Department of Health's Directorate of Health Systems Research and Epidemiology in conjunction with the Directorate of HIV/AIDS and STDs; August 1999.

16. Williams BG, Taljaard D, Campbell CM, Gouws E, Ndhlovu L, Van Dam J, Carael M and Auvert B. Changing patterns of knowledge, reported behaviour and sexually transmitted infections in a South African gold mining community. *AIDS* 2003; **17**:2099-2107.

17. Francis DP, Heyward WL, Popovic V, Orozco-Cronin P, Orelind K, Gee C, Hirsch A, Ippolito T, Luck A, Longhi M, Gulati V, Winslow N, Gurwith M, Sinangil F and Berman PW. Candidate HIV/AIDS vaccines: lessons learned from the world's first phase III efficacy trials. *AIDS* 2003; **17**:147-156.

18. Bartholow BN, Buchbinder S, Celum C, Goli V, Koblin B, Para M, Marmor M, Novak RM, Mayer K, Creticos C, Orozco-Cronin P, Popovic V, Mastro TD and the Vision Vax Study Team. HIV sexual risk behavior over 36 months of follow-up in the world's first HIV vaccine efficacy trial. *J Acquir Immune Defic Syndr* 2005; **39**:90-101.

19. van Griensvan F, Keawkungwal J, Tappero JW, Sangkum U, Pitisuttithum P, Vanichseni S, Suntharasamai P, Orelind K, Gee C, Choopanya K and the Bangkok Vaccine Evaluation Group. Lack of increased HIV risk behavior among injection drug users participating in the AIDSVAX B/E HIV vaccine trial in Bangkok, Thailand. *AIDS* 2004; **18**:295-301.

20. Lampinen TM, Chan K, Remis RS, Merid MF, Rusch M, Vincelette J, Logue K, Popovic V, Alary M, Schechter MT and Hogg RS. Sexual risk behaviour of Canadian participants in the first efficacy trial of a preventive HIV-1 vaccine. *Can Med Assoc J* 2005; **172**:479-483.

21. Rerks-Ngam S, Pitisuttithum P, Nitayaphan S, Kaewkungwan J, Kim J, Benenson M, Gurunathan S, Gurwith M, Brown AE and Birx D. An update of progress in the Thai HIV prime boost vaccine trial: VCP1521 (ALVAC-HIV) + GP120 B/E (AIDSVAX B/E) [31]. Paper presented at: AIDS Vaccine International Conference; 2005; Montreal.

22. Chesney MA, Chambers DB and Kahn JO. Risk behavior for HIV infection in participants in preventive HIV vaccine trials: a cautionary note. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; **16**:266-271.

23. Colfax G, Buchbinder S, Vamshidar G, Celum C, McKirnan D, Neidig J, Koblin B, Gurwith M and Bartholow B. Motivations for participating in an HIV vaccine efficacy trial. *J Acquir Immune Defic Syndr* 2005; **39**:359-364.

24. Baeten JM, Richardson BA, Martin HL, Jr., Nyange PM, Lavreys L, Ngugi EN, Mandaliya K, Ndinya-Achola JO, Bwayo JJ and Kreiss JK. Trends in HIV-1 incidence in a cohort of prostitutes in Kenya: implications for HIV-1 vaccine efficacy trials. *J Acquir Immune Defic Syndr* 2000; **24**:458-464.

25. Metzger DS, Koblin B, Turner C, Navaline H, Valenti F, Holte S, Gross M, Sheon A, Miller H, Cooley P, Seage GR, 3rd and the HIVNET Vaccine Preparedness Study Protocol Team. Randomized controlled trial of audio computer-assisted self-interviewing: utility and acceptability in longitudinal studies. *Am J Epidemiol* 2000; **152**:99-106.

26. Smit J, Middelkoop K, Myer L, Seedat S, Wood R, Stein DJ and Bekker L-G. Sexual risk factors associated with volunteering for HIV vaccine research in South Africa. *AIDS Care* 2006; **18**:569-573.

TABLE 1. Comprehension of low-efficacy vaccine concept (n = 158)

Concept evaluated	n (%) incorrect[a]
One can get HIV from a low-efficacy HIV vaccine	2 (1%)
One will know whether a low-efficacy HIV vaccine worked on one's body and is providing full protection	10 (6%)
A 30% effective vaccine will only work on 3 of every 10 people vaccinated (any incorrect answer)	17 (11%)
At least one of the above concepts incorrect	29 (18%)

[a] Sample sizes within 2% of total n = 158

TABLE 2. Anticipated changes in sexual risk behavior (n = 158)[a]

Specific risk behavior[b]	Less frequently	About the same	More frequently
Condom use with anonymous sex partners	2.5%	57.0%	40.5%
Condom use with casual sex partners	2.6%	63.7%	33.8%
Condom use with steady/stable sex partners	20.4%	65.6%	14.0%
Sex with anonymous partners	37.8%	57.1%	5.1%
Sex with casual partners	40.7%	52.9%	6.5%

[a] Sample sizes within 2% of total n = 158
[b] All questions assess anticipated risk behavior changes as compared to current levels of behavior for individual participants, following hypothetical vaccination with a 30% effective vaccine

APPENDIX

The scripted survey developed for assessing hypothetical risk behavior response to vaccination with a low-efficacy preventive HIV vaccine is detailed below.

In this questionnaire, we would like to ask some *hypothetical* questions. 'Hypothetical' means that we must imagine a situation that does not actually exist. These questions will be about what we call a partially effective HIV vaccine.

To help explain what 'partially effective' means, let us first discuss the polio vaccine, which you have probably already received when you were younger. The effectiveness of the polio vaccine, which is a very good vaccine, is 90-100%. This means that if you line up 10 people and give each of them the vaccine, it will work in 9 of them or all 10 of them. This means that they will be protected from getting polio even when they are exposed to the disease. But, it is possible that one of them is not protected from getting polio because the vaccine did not work in that person. This is because our bodies are not the same and some medicines work differently in different people, for example, drinking panados for a headache might help some people but not other people.

Before we continue, we want to make it *very* clear that there is no effective HIV vaccine available anywhere in the world, either commercially or through a research facility. But we would like to ask you some questions about what you might do if there were a vaccine. This means imagining a vaccine that has already been tested in clinical trials and approved for use—which may in reality take 10 more years to accomplish.

***Suppose* you were to receive an HIV vaccine that is known (after many tests and clinical trials in humans) to be 30% effective. This means that if you line up 10 people and give each of them the vaccine, the vaccine will only work in 3 of them. It will not work in 7 of them. This means that only 3 of them will be protected from getting HIV if they have sex without protection with a person who has HIV. It also means that if you get the vaccine yourself, you do not know if you are one of the 3 people who would be protected. You could also be one of the 7 people who are not protected because the vaccine did not work in them.**

Do you have any questions about this? To make sure that I have explained this to you well, I will now ask you three questions. Do not worry if you get a question wrong, it just means that I need to explain this better.

Q1. Please answer yes or no: If you get an HIV vaccine that is 30% effective, will you get HIV from the vaccine itself?

1 Yes

0 No

If answer is 1, more discussion is needed

Q2. Please answer yes or no. If you get an HIV vaccine that is 30% effective, will you know whether the vaccine worked on you?

1 Yes

0 No

If answer is 1, more discussion is needed

Q3. I will now read a statement and then give you four choices to complete the statement. If you get an HIV vaccine that is 30% effective, you will be protected from getting HIV _____ ? (Choose one)

1 Never

2 Every time you have sex without protection

3 3 out of 10 times you have sex without protection

4 It depends on whether you are one of the 3 out of 10 people who the vaccine worked on

If answer is 1, 2, or 3, more discussion is needed. Please explain to all participants why answer 4 is right and answers 1,2,3 are wrong before continuing.

We would now like to ask you some questions about what you *might* do if you were to get this vaccine. Remember, there is no vaccine available for HIV and there is no right or wrong answer. We are just interested in what you *might think* you would do. Again, these questions are confidential so we will not tell anyone what you have told us.

In the following questions, we refer to three types of sexual partners: steady/stable, casual, and anonymous. A steady/stable partner is someone who is special to you, like a husband/wife/boyfriend/girlfriend, or lover. A casual sex partner is a person you know but who is not your main sex partner, whether you had sex only once or many times. An anonymous sex partner is someone whose name you did not know the day before you had sex. For the following questions, if you do not currently have one of these partner types, you can answer hypothetically—what you imagine you would do.

Q4. If you received this vaccine, do you think that any of your sexual partners might want to use condoms *less* frequently with you if they knew you had received a vaccine? *(Make sure the participant is talking about their partner's behavior, not their own behavior)*

1 Yes

0 No

8 Maybe

9 Refuse to answer

For the next three questions, if you received this vaccine, how frequently would you use condoms compared to presently? *(Make sure that each answer reflects how the person would CHANGE their behavior from the way they act at present)*

Q5. With an anonymous sex partner?

1 I would probably use condoms less frequently than I do at present

2 I would probably use condoms about the same as I do at present

3 I would probably use condoms more frequently than I do at present

9 Refuse to answer

Q6. With a casual sex partner?

1 I would probably use condoms less frequently than I do at present
2 I would probably use condoms about the same as I do at present
3 I would probably use condoms more frequently than I do at present
9 Refuse to answer

Q7. With a steady/stable sex partner?

1 I would probably use condoms less frequently than I do at present
2 I would probably use condoms about the same as I do at present
3 I would probably use condoms more frequently than I do at present
9 Refuse to answer

For the next two questions, if you received this vaccine, how many partners would you have sex with compared to presently? (*Make sure that each answer reflects how the person would CHANGE their behavior from the way they act at present)*

Q8. If they were anonymous sex partners?

1 I would probably have sex with anonymous partners less frequently than I do at present
2 I would probably have sex with anonymous partners about the same as I do at present
3 I would probably have sex with anonymous partners more frequently than I do at present
9 Refuse to answer

Q9. If they were casual sex partners?

1 I would probably have sex with casual partners less frequently than I do at present
2 I would probably have sex with casual partners about the same as I do at present
3 I would probably have sex with casual partners more frequently than I do at present
9 Refuse to answer

Thank you very much for participating in this survey. Do you have any questions for us or anything you would like to discuss?

PAPER 3

Predicting the Impact of a Partially Effective HIV Vaccine and Subsequent Risk Behavior Change on the Heterosexual HIV Epidemic in Low- and Middle-Income Countries: a South African Example

INTRODUCTION

Despite a lack of success in HIV vaccine development to date[1], there are 35 HIV vaccine candidates currently progressing through various clinical trials around the world, and many more in development[2]. Because of the scientific challenges in vaccine design[3], clinical trials are using a minimum efficacy value of 30% for evaluating the effectiveness of potential vaccine candidates[4]. Given the urgent need for an HIV vaccine, it is likely that HIV vaccines with only partial efficacy will be used initially in populations at high risk for HIV infection[5]. The potential for post-vaccination risk-taking behavior to increase poses a significant threat to the successful use of partially effective vaccines in future vaccination programs[5-8]. Individuals might increase their risk-taking behavior, assuming they are at lower risk for HIV infection when, in reality, they might have only limited protection from HIV infection or none at all[9-14].

Models have shown that even a partially effective HIV vaccine with minimal efficacy could have enormous population impact on the HIV epidemic in areas with high HIV prevalence, such as sub-Saharan Africa[15-21], but that the magnitude of this impact depends on a fine balance between the efficacy of the vaccine, the vaccine coverage level, and the change in risky behavior[18,20,22-26]. While decreases in individual risk behavior would augment the population benefits of such vaccination programs in terms of HIV infections prevented, increases in risk behavior might negate those benefits or even worsen the HIV epidemic. Although we are unable to predict what might occur in a future mass vaccination campaign[7], results from the few completed vaccine trials to date in North America, Europe, and Asia show that risk behavior generally did not increase[27-31], despite early reports of increased risk behavior in several small trials[32]. However,

nine African countries are either preparing or already enrolling participants for HIV vaccine trials[2,33,34] and preliminary studies indicate that sexual risk behavior might increase in response to vaccination[6,35] [also, Dissertation Paper 2]. To what degree increased risk behavior might potentially offset the benefits of vaccination remains a question largely unanswered in the African setting.

The impact of partially effective vaccines and potential risk behavior change on future vaccination campaigns in South Africa has not yet been examined. With an estimated 5.5 million people living with HIV/AIDS as of 2006 and HIV prevalence in some areas as high as 30-40%[36-38], South Africa is experiencing the type of severe HIV epidemic that is present or developing in many low- and middle-income countries. Additionally, because of South Africa's burden of HIV, political support for HIV vaccines, participation in international HIV vaccine trials, and status as a middle-income country with a relatively strong health infrastructure for vaccine purchase and delivery, it may be one of the first countries in sub-Saharan Africa to consider the use of early generations of licensed HIV vaccines. Therefore, we estimated the effect of various potential preventive[vi] vaccination scenarios on the heterosexual HIV epidemic in the urban township of Soweto, South Africa with a mathematical simulation model[vii], using different levels of vaccine efficacy and changes in post-vaccination condom use[39,40].

[vi] For our study, a preventive vaccine is defined as a vaccine which prevents primary infection with HIV and a partially effective vaccine (low-efficacy vaccine, imperfect vaccine) is defined as a vaccine with less than 100% efficacy, or ability to prevent transmission of HIV

[vii] Partial data from this manuscript have been previously reported at the Annual Meeting of the Society for Medical Decision Making (Atlanta, 2004) and the 13th Conference on Retroviruses and Opportunistic Infections (Denver, 2006).

METHODS

We developed a dynamic, compartmental epidemic model for heterosexual HIV transmission and disease progression to simulate the impact of various partially effective preventive HIV vaccination scenarios and subsequent changes in risk behavior in a population at high risk for heterosexually transmitted HIV in Soweto, South Africa.

Model description

The model defines six 'compartments', each representing a particular health 'state', to simulate the process of HIV transmission and disease progression: (1) unvaccinated HIV-negative, (2) vaccinated HIV-negative, (3) unvaccinated asymptomatic HIV-positive, (4) vaccinated asymptomatic HIV-positive, (5) symptomatic HIV-positive, and (6) AIDS. There are separate states for males and females, for a total of twelve compartments overall. Rates of movement between states for individuals are specified by a set of twelve deterministic differential equations which govern allowable transitions between the population subgroups. The model considers a population of sexually active adults, who enter the simulation upon reaching sexual maturity and can leave the simulation due to death from either non-AIDS or AIDS-related causes. Only heterosexual transmission of HIV is considered in this analysis (see Appendix for further details).

The model accounts for both the immunological and behavioral effects of a preventive HIV vaccine (see Appendix for further details). HIV-negative men and women who are vaccinated will be protected from HIV infection in sexual partnerships with HIV-infected individuals a certain proportion of the time, which is the efficacy of the vaccine. Therefore, if the vaccine is 40% effective, vaccinated HIV-negative

individuals will then be protected from HIV infection in 40% of partnerships with infected heterosexual partners. Additionally, individuals may change their sexual risk-taking behavior, such as condom use, sex act type and frequency, and number of sex partners, in response to vaccination. For example, they might increase their risky behavior because they feel protected by the vaccine or they might decrease their risky behavior as a response to the counseling that may be given in a mass vaccination campaign. Specifically, we examine post-vaccination changes in male-negotiated condom use behavior.

A more detailed description of the model and the assumptions underlying its specification is provided in the Appendix.

Simulations

We conducted simulations as if a vaccine was currently available and a vaccination program was implemented for a period of 10 years. We then evaluated the effects of various vaccination scenarios by examining the total number of HIV infections averted and the change in population HIV prevalence. We calculated these values by comparing model outputs under the vaccine program simulation to a simulation without a vaccination program.

We first simulated a base-case scenario, in which a vaccination program was implemented using a vaccine with 40% efficacy and in which there was no post-vaccination change in risk behavior (male-negotiated condom use). We compared model predictions from the base-case scenario to other vaccination scenarios with varying vaccine efficacies and post-vaccination changes in male condom use. We performed all

model simulations using Excel® 2003 spreadsheet software (Microsoft Corporation, Redmond WA).

Input parameters, assumptions, and initial conditions

We derived input parameters for the model from both published data sources and assumptions. Input parameters are listed in Table 1, along with their associated model equation symbols. We modeled the urban township population of Soweto using an initial population size of 823,000 including only men and women aged 17 years or older[41], a mean age of 25.1 years[42], and a life-expectancy of 60.8 years from birth in the absence of deaths due to AIDS[43]. Based on regional and national studies of sexual debut in South Africa, we estimated that all individuals in Soweto are sexually active by this age[44-47]. Using national and province-specific HIV prevalence data for individuals aged 15-49 years[47], we estimated an initial HIV prevalence of 11.6% for males and 20.0% for females. We assumed an anti-retroviral (ARV)-naïve population.

We modeled a preventive HIV vaccine that produced an immunological effect in all recipients (100% take, $\psi = 1$), provided protection for a mean duration of 50 years ($1/\omega = 50$), and affected only HIV transmission with no effect on infectivity or disease progression in those who were HIV-positive[19,24,48,49]. For our base-case scenario, we used a 40% effective vaccine ($\varepsilon = 0.4$), a figure which was subsequently varied. We simulated a program in which vaccines were given to unvaccinated asymptomatic men and women aged 17 years or older, without testing individuals for HIV; therefore, vaccines were given to both uninfected and asymptomatic HIV-positive individuals. We assumed that none of the population were vaccinated initially and that the vaccine would be administered in a highly coordinated and effective mass-vaccination campaign, in

which 75% of those eligible for vaccination were vaccinated in the first year and in each year thereafter ($\nu(t) = 0.75$). Although a high estimate, we felt this coverage level would be feasible given the apparent devastating epidemic in South Africa and the needs of both individuals and government for additional HIV prevention methodologies. However, we also performed additional sensitivity analyses for a more modest coverage level of 50% ($\nu(t) = 0.50$).

In the model, we varied the number of sexual partners a man or woman has and the probability of HIV transmission within those sexual partnerships according to disease stage. We estimated that uninfected and asymptomatic HIV-positive men and women had on average three sexual partnerships per year ($p_0, p_1 = 3$) [Dissertation Paper 1], symptomatic HIV-positive men and women had only one sexual partnership per year ($p_2 = 1$), and individuals with AIDS had no sex partners ($p_3 = 0$). We used Ugandan data to estimate the per-partnership probability of HIV transmission from asymptomatic ($\beta_{M1,j} = 0.0684, \beta_{W1,j} = 0.1112$) and symptomatic ($\beta_{M2,j} = 0.1657, \beta_{W2,j} = 0.2697$) HIV-positive men and women[18,50-52]. We based our infectivity parameters on monogamous serodiscordant couple studies, which represent conservative estimates compared to transmission data from multiple-partnership studies[53]. Because research into the biologic and social basis for observed gender differences in HIV transmission is inconclusive to date[18,50,52-56], we performed additional sensitivity analyses in which the male-to-female (MTF) and female-to-male (FTM) infectivity rates were exchanged and in which the symptomatic FTM infectivity rate was decreased by two- and ten-fold (see Appendix for further details).

We used the median time from HIV seroconversion to AIDS in an African setting

and previously published lengths for HIV disease stages to estimate the duration of both asymptomatic HIV disease ($1/\mu_{1,j} = 6.8$ years) and symptomatic HIV disease ($1/\mu_{2,j} = 2.6$ years) in the model[19,24,57]. We used the median time from AIDS development to death of 9.2 months ($1/\mu_{3,j} = 0.8$ years) for the duration of AIDS[57]. These disease progression times were based on studies in the Rakai district of Uganda prior to the availability of ARV therapy in this area.

From studies of condom use in South Africa[44-47] [also, Dissertation Paper 1], we estimated that baseline condom use was 50% in all sexual partnerships ($h_{i,0} = 0.5$). We used a condom failure rate of 14% over the course of each sexual partnership ($f = 0.14$)[58]. For our base-case simulation, we examined a scenario in which post-vaccination condom use did not change from baseline levels of 50% (0% change in condom use, $\Delta = 1.0$); subsequent analyses examined values from 25% (50% decrease, $\Delta = 0.5$) to 75% (50% increase, $\Delta = 1.5$) to explore a wide range of potential changes in risk behavior. In addition, based on research showing a significant gender difference in the ability of women in many South African settings to successfully negotiate condom use with their sexual partners[59-62], we assumed that condom use was negotiated exclusively by the male in the relationship. Therefore, we used a likelihood function for condom use in a given partnership based entirely on the preference of the male partner (see Appendix for further details).

RESULTS

We simulated vaccination scenarios for an initial population of 823,000 sexually active, heterosexual men and women with an HIV prevalence of 12% and 20%, respectively, of whom 75% were effectively vaccinated each year with vaccines that provided 50 years of protection. In the absence of HIV prevention interventions in Soweto, the model predicted that HIV prevalence would increase over the next 50 years from 16% currently to 26%, with 743,000 new HIV infections occurring during that period (Figure 1). Within the next 10 years alone, simulations predicted the overall population prevalence would rise to 20% and 161,000 new HIV infections would occur.

For vaccination scenarios with no change in post-vaccination risk behavior, increases in vaccine efficacy produced greater numbers of HIV infections averted (Figure 2) with concurrent decreases in overall population HIV prevalence. A vaccination program using a 20% effective vaccine would avert 34,000 infections over 10 years and decrease the 10-year overall population HIV prevalence from 20% to 16%. Similarly, a 30% effective vaccine would avert 50,000 infections and decrease prevalence to 15% over 10 years. In contrast, a 100% effective vaccine would avert 135,000 infections in the same time period and decrease HIV prevalence to 6%.

We next examined specific combinations of vaccine efficacy and changes in risk behavior (Figure 3). Figure 3A shows the results for our base-case vaccination scenario using a 40% effective vaccine with no change in condom use post-vaccination. Over 10 years, this vaccination program could prevent 65,000 new HIV infections in Soweto and reduce the population HIV prevalence from 20% to 13%.

We then examined changes in risk behavior by varying post-vaccination condom use. We simulated a vaccination scenario in which a 40% effective vaccine was used, as in the base-case scenario, but in which post-vaccination condom use increased by 25% (Figure 3B). In this case, the beneficial effects of the base-case vaccination program increased: cumulative infections averted would increase from 65,000 to 80,000 and the prevalence of HIV would decrease even further, from 20% to 11%. In contrast, a vaccination scenario in which post-vaccination condom use decreased by 25% would reduce the beneficial effects of the base-case vaccination program (Figure 3C). The cumulative number of infections averted would only decrease from 65,000 to 49,000 and the prevalence of HIV would only decrease from 20% to 15%.

Depending on the particular combination of vaccine efficacy and change in risk behavior, some vaccination programs we simulated would be detrimental. As an example, we show a vaccination program which used a 20% effective vaccine but which resulted in a 50% decrease in post-vaccination condom use (Figure 3D). This scenario created a perverse outcome in which the negative behavioral effects outweighed the protective effects of the vaccine. This vaccination program would actually cause an additional 15,000 infections beyond what would be expected without any vaccination campaign and would increase the prevalence of HIV over 10 years from 20% to 22%.

Given these observations and the uncertainty of future mass vaccination campaign conditions, we then examined the relationship between varying vaccine efficacy values and levels of risk behavior change. We estimated all combinations of vaccine efficacy and changes in post-vaccination condom use for vaccination scenarios that would prevent the same 65,000 HIV infections as the base-case scenario over a period of ten years

(Figure 4A). The base-case scenario is represented by the point at which the curve crosses the horizontal axis. Other points on the curve map particular combinations of vaccine efficacy and changes in condom use behavior that would produce identical results. At one extreme, an imperfect vaccine would be less effective than a program to change condom use behavior: any HIV prevention program that could increase condom use to at least 80% (e.g. increase condom use by more than 58% over baseline levels), in the absence of a vaccine, would prevent more infections than a 40% effective vaccine in the base-case vaccination scenario. At the other extreme, an imperfect vaccine with adequate efficacy could offset the negative effects of any decreases in post-vaccination condom use: if all individuals ceased using condoms entirely after being vaccinated (e.g. condom use decreased 100%, from baseline levels of 50%), any HIV vaccine that was more than 65% effective would still prevent more infections than a 40% effective vaccine in the base-case vaccination scenario.

To examine whether various vaccination programs might be beneficial or harmful at the population level, we also estimated which combinations of vaccine efficacy and changes in post-vaccination condom use would result in a net decrease in the number of HIV infections (Figure 4B). The curve divides the graph area into all combinations of vaccine efficacy and changes in post-vaccination condom use in vaccination programs that would either increase the number of infections (the region below the curve) or, alternatively, decrease the number of infections (the region above the curve). As the efficacy of the vaccine increased, HIV infections were still reduced even with decreasing condom use. All vaccination programs which generated any increase in condom use over baseline levels would be beneficial in terms of infections prevented, regardless of the

efficacy of the vaccine used. All vaccination programs which used a vaccine with an efficacy of at least 42% would be beneficial in terms of infections prevented, regardless of changes in risk behavior—a result that is robust even if condom use were to cease entirely post-vaccination campaign. Any vaccination programs which used a vaccine with an efficacy less than 42% and which also caused a decrease in condom use from baseline levels could be beneficial or harmful in terms of infections prevented, depending on the particular combination of vaccine efficacy and risk behavior change. The example of a 20% vaccine with a 50% decrease in post-vaccination condom use, described above, is one such harmful scenario.

Despite the lack of population HIV prevalence data for Soweto, we validated the model using overall predicted trends for Gauteng province (which includes Soweto township) population HIV prevalence[63]. In the absence of vaccination programs, predicted trends for Soweto HIV prevalence in the sexually active population in our model matched predicted trends for Gauteng province HIV prevalence in adults aged 20-64 within 5-15% each year for 10 years (data not shown).

Because of the uncertainty in the published literature regarding the existence of gender differences in HIV transmission rates, we performed additional sensitivity analyses in which the MTF and FTM transmission parameters were exchanged. In addition, we performed sensitivity analyses on the symptomatic FTM infectivity parameter (0.27 probability of transmission per partnership per year) as our calculations yielded a relatively high value for this probability (see Appendix for further details). We examined outcomes for simulations in which the FTM infectivity parameter was reduced to 50% and 10% of our calculated value. We also explored the effects of a 50%

vaccination program coverage goal, rather than 75%. In all cases, while the quantitative benefits of the programs change (data not shown), the analyses remain robust to our qualitative conclusions regarding the impact of partially effective vaccines.

DISCUSSION

We designed a mathematical model to simulate heterosexual transmission and disease progression of HIV in low- or middle-income country populations. We simulated vaccination programs using preventive vaccines with varying levels of efficacy and post-vaccination changes in risk behavior, which for this study was represented by condom use. We specifically examined the impact of these vaccination programs on the HIV epidemic in Soweto, South Africa in terms of HIV infections prevented and changes in HIV prevalence over time. We found that vaccines with only 30% or 40% efficacy can confer substantial health benefits, which is significant because most vaccines in use today for other diseases have much higher efficacies than this. We also found that the effects of changes in risk behavior, post-vaccination condom use in this instance, can be significant and condom use will merit close attention in future vaccination campaigns. Finally, we found that even with increases in risk behavior, sufficiently effective vaccines could still be beneficial.

Heterosexually-transmitted HIV is responsible for more than 80% of adult HIV infections worldwide[58], and more than 98% of new HIV infections are occurring in low- and middle-income countries[38]. Our analysis represents the first simulation of the impact of preventive HIV vaccination programs on heterosexual HIV transmission and disease progression in South Africa, and is one of only a small number of HIV vaccination program simulations for heterosexually-transmitted HIV in low- and middle-income country populations[15-18,20]. We were able to utilize African data for the majority of our model input parameters, most of which were specific to this particular South African population: infectivity values and disease progression times were derived from

studies in Uganda, Kenya, and Zambia; baseline levels of condom use, mortality rates, and life expectancy data were derived from several South African studies; adolescent and adult HIV prevalence values, population mean age, age of sexual debut, and assumptions of gender differences in condom negotiation were estimated from both national and province-specific data in South Africa; population size was calculated based on district-specific census data for Soweto obtained from the city of Johannesburg; and, assumptions for contact rates, potential risk behavior change, and current condom use were derived from our studies in Soweto [Dissertation Papers 1 and 2]. Despite using different methodology and population assumptions, our findings of the beneficial impact of partially effective vaccines were consistent with previous models, both simple and complex, of the effects of preventive HIV vaccines[15,16,19,21,48] and their sensitivity to changes in risk behavior[18,22,24].

To our knowledge, this also represents the first time that differential condom use behavior between men and women has been incorporated into a model of HIV disease transmission. While Western models of HIV transmission have specified that condom use between two partners with differing practices is the greater of the two (e.g. if one person uses condoms 70% of the time and another person uses condoms 30% of the time, then condom use in that partnership will be 70%)[24], we believe that this does not accurately reflect condom use negotiation in the African setting. We assumed exclusive male-negotiation of condom use in our model to reflect the decreased ability of South African women to negotiate condom use in heterosexual partnerships[59-62], a disadvantage which is found in many countries throughout sub-Saharan Africa and in part explains the shift towards a female-dominated epidemic[38]. Therefore, in our model, the

likelihood of condom use in a given sexual partnership was exclusively linked to the condom usage rate of the male partner; as a result, changes in risk behavior were linked to male-determined changes in condom use.

We only varied post-vaccination condom use, despite other changes in risk behavior that could occur such as changes in the type or frequency of sex acts and changes in the number of sexual partners. Similar to previous studies[24], we used changes in condom use behavior to capture all potential for risk behavior change in this analysis. As such, decreasing condom use, for example, would have been similar (although not identical) to increasing the number of sex acts or the number of sex partners. However, other studies investigating risk behavior effects have instead used changes in the number of sex partners[18,48] or risk behavior summary measures including both sexual partnerships and condom use[20,22] to capture the potential for risk behavior change. We felt that in the African setting, particularly when modeling closed populations, gender differences in risk behavior were easier to capture with condom use behavior than with other behaviors.

Our current analyses have assumed an ARV-naïve population, as very few people in South Africa presently have access to ARV therapy. In addition to prolonging life, ARV therapy decreases viral loads in HIV-infected individuals, and decreased viral loads have been shown to result in decreased sexual transmission of HIV[18,50,52,55]. The effects of the national plan for widespread public sector distribution of antiretroviral medications to South Africans infected with HIV[64] will need to be included in future analyses of the impact of HIV vaccination programs once significant coverage of ARV therapy for HIV-positive individuals is achieved.

We have at present modeled the effects of a preventive HIV vaccine in a South

African population because (1) preventive vaccines have a larger potential to control the epidemic than disease-modifying vaccines[25], (2) novel design approaches for preventive vaccines and clinical trials are still underway[2,65], and (3) preventive HIV vaccines have been previously modeled in a heterosexual African population only in Uganda[18]. Because of scientific challenges in developing preventive vaccines that stimulate broadly-neutralizing antibody responses, disease-modifying vaccines that stimulate cellular immunity via specific cytotoxic T lymphocyte-based responses are also currently under development[3,66]. Similar to ARV therapy, these disease-modifying vaccines might be able to decrease viral load (and therefore infectivity) and disease progression in those already infected. While they may not prevent HIV infection at the individual level, disease-modifying vaccines might decrease HIV transmission, and thus HIV prevalence, at the population level over time[67]. Other models have investigated the impact of disease-modifying vaccines[15,19-21,24-26,48,68,69], and further exploration of the impact of disease-modifying vaccines on heterosexual HIV transmission in Africa in particular is merited.

Despite the uncertainty about the efficacy of a vaccine, we have been able to make general conclusions for communities such as the township of Soweto regarding the use of partially effective vaccines and the implications of risk behavior change. In addition to the consideration of potential disease-modifying vaccines and widespread access to ARV therapy, future analyses would benefit from the incorporation of migration and heterogeneous risk behavior groups into the model. Vaccination scenarios varying other parameters such as vaccination coverage levels, vaccine take, and duration of protection as well as the timing, length, costs and benefits of vaccination campaigns should also be

considered when a potential vaccine candidate has been identified for use and decisions must be made regarding its implementation. And, because so little is currently known about the potential for risk behavior change in the African setting, studies to evaluate whether risk behavior changes might occur in future vaccination campaigns [e.g. Dissertation Paper 2] are greatly needed.

Due to the significant effects of changes in risk behavior on the potential benefits of mass vaccination campaigns, programs to reduce risk behavior will be important components of successful vaccination campaigns for South Africa and other countries with similar epidemic profiles, particularly when lower-efficacy vaccines are used. Programs to reduce risk behavior such as those used during the rollout of ARV therapy or other HIV prevention campaigns in African countries may serve as templates for risk behavior reduction strategies[56,70]. Because of the decreased ability of women to negotiate condom use in their relationships and the higher risk behaviors found in men throughout sub-Saharan Africa[38], programs specifically targeting men should also be considered.

More immediately, risk behavior assessment [e.g. Dissertation Paper 1] must remain an important component of HIV vaccine clinical trials as it will provide one of the only means of predicting changes in risk behavior that might occur at the population level in an actual mass vaccination campaign. However, the reductions in HIV prevalence and new HIV infections that can result from using partially-effective vaccines are substantial, even in the presence of increased risk behavior; therefore development of preventive vaccines should remain a high priority despite concerns that these vaccines will have only moderate efficacy.

REFERENCES

1. Anonymous. Press release. VaxGen, Inc., February 24, 2003. Available at: www.vaxgen.com.

2. IAVI database of AIDS vaccines in human trial [database online]. New York, NY: International AIDS Vaccine Initiative, 2006. Updated June 13, 2006.

3. Garber DA, Silvestri G and Feinberg MB. Prospects for an AIDS vaccine: three big questions, no easy answers. *Lancet Infect Dis* 2004; **4**:397-413.

4. Self S. Vaccine efficacy trial design: role of Phase IIb vs. Phase III trials [56]. Paper presented at: AIDS Vaccine International Conference; 2005; Montreal.

5. Anonymous. Future access to HIV vaccines. Report from a WHO-UNAIDS Consultation, Geneva, 2-3 October 2000. *AIDS* 2001; **15**:W27-44.

6. Bishai D, Pariyo G, Ainsworth M and Hill K. Determinants of personal demand for an AIDS vaccine in Uganda: contingent valuation survey. *Bull World Health Organ* 2004; **82**:652-660.

7. Newman PA, Duan N, Rudy ET and Anton PA. Challenges for HIV vaccine dissemination and clinical trial recruitment: if we build it, will they come? *AIDS Patient Care STDS* 2004; **18**:691-701.

8. Newman PA, Duan N, Rudy ET, Roberts KJ and Swendeman D. Posttrial HIV vaccine adoption: concerns, motivators, and intentions among persons at risk for HIV. *J Acquir Immune Defic Syndr* 2004; **37**:1393-1403.

9. Lurie P, Bishaw M, Chesney MA, Cooke M, Fernandes ME, Hearst N, Katongole-Mbidde E, Koetsawang S, Lindan CP and Mandel J. Ethical, behavioral, and social aspects of HIV vaccine trials in developing countries. *JAMA* 1994; **271**:295-301.

10. Cohen J. The HIV vaccine paradox. *Science* 1994; **264**:1072-1074.

11. Halloran ME, Longini IM, Jr., Haber MJ, Struchiner CJ and Brunet RC. Exposure efficacy and change in contact rates in evaluating prophylactic HIV vaccines in the field. *Stat Med* 1994; **13**:357-377.

12. Schaper C, Fleming TR, Self SG and Rida WN. Statistical issues in the design of HIV vaccine trials. *Annu Rev Public Health* 1995; **16**:1-22.

13. Frey SE. Unique risks to volunteers in HIV vaccine trials. *J Investig Med* 2003; **51(Suppl 1)**:S18-20.

14. Blower S, Schwartz EJ and Mills J. Forecasting the future of HIV epidemics: the impact of antiretroviral therapies & imperfect vaccines. *AIDS Rev* 2003; **5**:113-125.

15. Anderson RM and Garnett GP. Low-efficacy HIV vaccines: potential for community-based intervention programmes. *Lancet* 1996; **348**:1010-1013.

16. Anderson RM, Swinton J and Garnett GP. Potential impact of low efficacy HIV-1 vaccines in populations with high rates of infection. *Proc Biol Sci* 1995; **261**:147-151.

17. Stover J, Garnett GP, Seitz S and Forsythe S. The epidemiological impact of an HIV/AIDS vaccine in developing countries [World Bank Policy Research Working Paper No. 2811]. The World Bank Development Research Group, March 2002. Available at: http://papers.ssrn.com/sol3/papers.cfm?abstract_id=636094.

18. Gray RH, Li X, Wawer MJ, Gange SJ, Serwadda D, Sewankambo NK, Moore R, Wabwire-Mangen F, Lutalo T, Quinn TC and the Rakai Project Group. Stochastic simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission; Rakai, Uganda. *AIDS* 2003; **17**:1941-1951.

19. Owens DK, Edwards DM and Shachter RD. Population effects of preventive and therapeutic HIV vaccines in early- and late-stage epidemics. *AIDS* 1998; **12**:1057-1066.

20. Anderson R and Hanson M. Potential public health impact of imperfect HIV type 1 vaccines. *J Infect Dis* 2005; **191(Suppl 1)**:S85-96.

21. Blower SM, Koelle K, Kirschner DE and Mills J. Live attenuated HIV vaccines: predicting the tradeoff between efficacy and safety. *Proc Natl Acad Sci U S A* 2001; **98**:3618-3623.

22. Blower SM and McLean AR. Prophylactic vaccines, risk behavior change, and the probability of eradicating HIV in San Francisco. *Science* 1994; **265**:1451-1454.

23. Bogard E and Kuntz KM. The impact of a partially effective HIV vaccine on a population of intravenous drug users in Bangkok, Thailand: a dynamic model. *J Acquir Immune Defic Syndr* 2002; **29**:132-141.

24. Edwards DM, Shachter RD and Owens DK. A dynamic HIV-transmission model for evaluating the costs and benefits of vaccine programs. *Interfaces* 1998; **28**:144-166.

25. Smith RJ and Blower SM. Could disease-modifying HIV vaccines cause population-level perversity? *Lancet Infect Dis* 2004; **4**:636-639.

26. Davenport MP, Ribeiro RM, Chao DL and Perelson AS. Predicting the impact of a nonsterilizing vaccine against human immunodeficiency virus. *J Virol* 2004; **78**:11340-11351.

27. Francis DP, Heyward WL, Popovic V, Orozco-Cronin P, Orelind K, Gee C, Hirsch A, Ippolito T, Luck A, Longhi M, Gulati V, Winslow N, Gurwith M, Sinangil F and Berman PW. Candidate HIV/AIDS vaccines: lessons learned from the world's first phase III efficacy trials. *AIDS* 2003; **17**:147-156.

28. Bartholow BN, Buchbinder S, Celum C, Goli V, Koblin B, Para M, Marmor M, Novak RM, Mayer K, Creticos C, Orozco-Cronin P, Popovic V, Mastro TD and the Vision Vax Study Team. HIV sexual risk behavior over 36 months of follow-up in the world's first HIV vaccine efficacy trial. *J Acquir Immune Defic Syndr* 2005; **39**:90-101.

29. van Griensvan F, Keawkungwal J, Tappero JW, Sangkum U, Pitisuttithum P, Vanichseni S, Suntharasamai P, Orelind K, Gee C, Choopanya K and the Bangkok Vaccine Evaluation Group. Lack of increased HIV risk behavior among injection drug

users participating in the AIDSVAX B/E HIV vaccine trial in Bangkok, Thailand. *AIDS* 2004; **18**:295-301.

30. Rerks-Ngam S, Pitisuttithum P, Nitayaphan S, Kaewkungwan J, Kim J, Benenson M, Gurunathan S, Gurwith M, Brown AE and Birx D. An update of progress in the Thai HIV prime boost vaccine trial: VCP1521 (ALVAC-HIV) + GP120 B/E (AIDSVAX B/E) [31]. Paper presented at: AIDS Vaccine International Conference; 2005; Montreal.

31. Lampinen TM, Chan K, Remis RS, Merid MF, Rusch M, Vincelette J, Logue K, Popovic V, Alary M, Schechter MT and Hogg RS. Sexual risk behaviour of Canadian participants in the first efficacy trial of a preventive HIV-1 vaccine. *Can Med Assoc J* 2005; **172**:479-483.

32. Chesney MA, Chambers DB and Kahn JO. Risk behavior for HIV infection in participants in preventive HIV vaccine trials: a cautionary note. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; **16**:266-271.

33. HIV Vaccine Trials Network current vaccine trials [database online]. Seattle, WA: HIV Vaccine Trials Network, 2006. Updated September 2006.

34. Sandstrom E and Birx D. HIV vaccine trials in Africa. *AIDS* 2002; **16(Suppl 4)**:S89-95.

35. Jackson DJ, Martin HL, Jr., Bwayo JJ, Nyange PM, Rakwar JP, Kashonga F, Mandaliya K, Ndinya-Achola JO and Kreiss JK. Acceptability of HIV vaccine trials in high-risk heterosexual cohorts in Mombasa, Kenya. *AIDS* 1995; **9**:1279-1283.

36. Dorrington R, Bradshaw D and Budlender D. *HIV/AIDS profile in the provinces of South Africa: indicators for 2002.* Cape Town: University of Cape Town Centre for Actuarial Research, South African Medical Research Council Burden of Disease Research Unit, & Actuarial Society of South Africa; 2002.

37. Dorrington R, Bradshaw D, Johnson L and Budlender D. *The demographic impact of HIV/AIDS in South Africa: national indicators for 2004.* Cape Town: University of Cape

Town Centre for Actuarial Research, South African Medical Research Council Burden of Disease Research Unit, & Actuarial Society of South Africa; 2004.

38. UNAIDS. 2006 report on the global AIDS epidemic. Joint United Programme on HIV/AIDS, May 2006. Available at: http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp.

39. Mesesan K, Owens DK and Paltiel AD. Predicting the impact of a partially effective HIV vaccine and subsequent risk behavior change on the HIV epidemic in developing countries: a South African example [Opening Plenary Session]. Paper presented at: 26th Annual Meeting of the Society for Medical Decision Making; 2004.

40. Mesesan K, Owens DK, Vardas E, Gray GE, McIntryre JA and Paltiel AD. Predicting the impact of a partially effective HIV vaccine and subsequent risk behavior change on the heterosexual HIV epidemic in developing countries: a South African example [479]. Paper presented at: 13th Conference on Retroviruses & Opportunistic Infections; 2006; Denver, Colorado.

41. Anonymous. 2001 South African Census. Statistics South Africa, 2004. Available at: www.statssa.gov.za.

42. Anonymous. *Mid-year population estimates, South Africa: 2004.* Pretoria: Statistics South Africa; July 27 2004.

43. Anonymous. ASSA2000 Model. Actuarial Society of South Africa, 2004. Available at: http://www.assa.org.za/.

44. Simbayi LC, Chauveau J and Shisana O. Behavioural responses of South African youth to the HIV/AIDS epidemic: a nationwide survey. *AIDS Care* 2004; **16**:605-618.

45. Pettifor AE, Rees HV, Steffenson A, Hlonga-Madikizela L, MacPhail C, Vermaak K and Kleinschmidt I. *HIV and sexual behavior among young South Africans: a national survey of 15-24 year olds.* Johannesburg: Reproductive Health Research Unit, University of the Witwatersrand; April 6 2004.

46. Pettifor AE, Rees HV, Kleinschmidt I, Steffenson AE, MacPhail C, Hlongwa-Madikizela L, Vermaak K and Padian NS. Young people's sexual health in South Africa: HIV prevalence and sexual behaviors from a nationally representative household survey. *AIDS* 2005; **19**:1525-1534.

47. Shisana O, Rehle T, Simbayi LC, Parker W, Zuma K, Bhana A, Connolly C, Jooste S and Pillay V. *South African national HIV prevalence, HIV incidence, behaviour and communication survey, 2005.* Cape Town: HSRC Press; 2005.

48. Anderson RM, Gupta S and May RM. Potential of community-wide chemotherapy or immunotherapy to control the spread of HIV-1. *Nature* 1991; **350**:356-359.

49. McLean AR and Blower SM. Imperfect vaccines and herd immunity to HIV. *Proc Biol Sci* 1993; **253**:9-13.

50. Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, Wabwire-Mangen F, Lutalo T, Li X, vanCott T, Quinn TC and the Rakai Project Team. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet* 2001; **357**:1149-1153.

51. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, Kiwanuka N, Kigozi G, Kiddugavu M, Lutalo T, Nalugoda F, Wabwire-Mangen F, Meehan MP and Quinn TC. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis* 2005; **191**:1403-1409.

52. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, Meehan MO, Lutalo T, Gray RH and the Rakai Study Group. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000; **342**:921-929.

53. Baeten JM, Richardson BA, Lavreys L, Rakwar JP, Mandaliya K, Bwayo JJ and Kreiss JK. Female-to-male infectivity of HIV-1 among circumcised and uncircumcised Kenyan men. *J Infect Dis* 2005; **191**:546-553.

54. Gray RH, Li X, Kigozi G, Serwadda D, Brahmbhatt H, Wabwire-Mangen F, Nalugoda F, Kiddugavu M, Sewankambo N, Quinn TC, Reynolds SJ and Wawer MJ.

Increased risk of incident HIV during pregnancy in Rakai, Uganda: a prospective study. *Lancet* 2005; **366**:1182-1188.

55. Fideli US, Allen SA, Musonda R, Trask S, Hahn BH, Weiss H, Mulenga J, Kasolo F, Vermund SH and Aldrovandi GM. Virologic and immunologic determinants of heterosexual transmission of human immunodeficiency virus type 1 in Africa. *AIDS Res Hum Retroviruses* 2001; **17**:901-910.

56. Bunnell R, Ekwaru JP, Solberg P, Wamai N, Bikaako-Kajura W, Were W, Coutinho A, Liechty C, Madraa E, Rutherford G and Mermin J. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. *AIDS* 2006; **20**:85-92.

57. Morgan D, Mahe C, Mayanja B, Okongo JM, Lubega R and Whitworth JA. HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? *AIDS* 2002; **16**:597-603.

58. Anonymous. *Workshop summary: scientific evidence of condom effectiveness for sexually transmitted disease (STD) prevention.* Herndon, Virginia: National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services; June 12-13 2000.

59. Simbayi L, Strebel A, Wilson T, Andipatin M, Msomi N, Potgieter C, Ratele K and Shefer T. *Sexually transmitted diseases in the South African public sector*: National Department of Health's Directorate of Health Systems Research and Epidemiology in conjunction with the Directorate of HIV/AIDS and STDs; August 1999.

60. Williams BG, Taljaard D, Campbell CM, Gouws E, Ndhlovu L, Van Dam J, Carael M and Auvert B. Changing patterns of knowledge, reported behaviour and sexually transmitted infections in a South African gold mining community. *AIDS* 2003; **17**:2099-2107.

61. Pettifor AE, Measham DM, Rees HV and Padian NS. Sexual power and HIV risk, South Africa. *Emerg Infect Dis* 2004; **10**:1996-2004.

62. Ackermann L and de Klerk GW. Social factors that make South African women vulnerable to HIV infection. *Health Care Women Int* 2002; **23**:163-172.

63. Anonymous. ASSA2003 Model. Actuarial Society of South Africa, 2005. Available at: http://www.assa.org.za/.

64. Anonymous. *Monitoring review: Progress report on the implementation of the comprehensive HIV and AIDS care, management and treatment programme*: Department of Health, South Africa; September 2004.

65. Anonymous. AIDS Vaccine Blueprint 2006. International AIDS Vaccine Initiative, Available at: http://www.iavi.org/blueprint.

66. Wasserheit JN. Clinical trials: State of the field in the era of efficacy trials of CTL-mediated HIV vaccines [55]. Paper presented at: AIDS Vaccine International Conference; 2005; Montreal.

67. Levy JA. What can be achieved with an HIV vaccine? *Lancet* 2001; **357**:223-224.

68. Walensky RP, Paltiel AD, Goldie SJ, Gandhi RT, Weinstein MC, Seage GR, 3rd, Smith HE, Zhang H and Freedberg KA. A therapeutic HIV vaccine: how good is good enough? *Vaccine* 2004; **22**:4044-4053.

69. Blower SM, Bodine EN and Grovit-Ferbas K. Predicting the potential public health impact of disease-modifying HIV vaccines in South Africa: the problem of subtypes. *Curr Drug Targets Infect Disord* 2005; **5**:179-192.

70. Kaul R, Kimani J, Nagelkerke NJ, Fonck K, Keli F, MacDonald KS, Ronald AR, Plummer FA, Bwayo JJ, Ngugi EN, Temmerman M and Moses S. Reduced HIV risk-taking and low HIV incidence after enrollment and risk-reduction counseling in a sexually transmitted disease prevention trial in Nairobi, Kenya. *J Acquir Immune Defic Syndr* 2002; **30**:69-72.

71. Brandeau ML, Owens DK, Sox CH and Wachter RM. Screening women of childbearing age for human immunodeficiency virus. A cost-benefit analysis. *Arch Intern Med* 1992; **152**:2229-2237.

72. Kaplan EH and Lee YS. How bad can it get? Bounding worst case endemic heterogeneous mixing models of HIV/AIDS. *Math Biosci* 1990; **99**:157-180.

73. Pequegnat W, Fishbein M, Celentano D, Ehrhardt A, Garnett G, Holtgrave D, Jaccard J, Schachter J and Zenilman J. NIMH/APPC workgroup on behavioral and biological outcomes in HIV/STD prevention studies: a position statement. *Sex Transm Dis* 2000; **27**:127-132.

74. Kaplan EH. Modeling HIV infectivity: must sex acts be counted? *J Acquir Immune Defic Syndr* 1990; **3**:55-61.

75. Anonymous. HIV Prevalence, Incidence, Behavior and Communication Survey 2005. Centre for AIDS Development, Research and Evaluation, 2006. Available at: www.cadre.org.za.

TABLE 1. Parameter values[a]

Parameter name	Symbol	Value[b]
Preventive vaccine parameters		
Percentage of uninfected or asymptomatic HIV+ males and females vaccinated annually	$\nu(t)$	0.75 (0.50-0.75)
Vaccine take (proportion of those vaccinated in whom vaccine stimulates an immune response)	ψ	1
Vaccine efficacy (percent of partnerships protected from infection)	ε	0.40 (0-1.0)
Change in (male-negotiated) condom use after vaccination[c]	Δ	1.0 (0.5-1.5)
Mean duration (in years) of vaccine protection	$1/\omega$	50
HIV transmission parameters		
Male infectivity (per-partner probability of transmission to a female)		
Asymptomatic period of HIV infection	$\beta_{M1,j}$	0.0684 (0.06-0.11)
Symptomatic period of HIV infection	$\beta_{M2,j}$	0.1657 (0.16-0.27)
Female infectivity (per-partner probability of transmission to a male)		
Asymptomatic period of HIV infection	$\beta_{W1,j}$	0.1112 (0.06-0.11)
Symptomatic period of HIV infection	$\beta_{W2,j}$	0.2697 (0.03-0.27)
Contact rate (number of new partners per year) of males or females		
Uninfected	ρ_0	3
HIV infected, asymptomatic period	ρ_1	3
HIV infected, symptomatic period	ρ_2	1
HIV infected, AIDS	ρ_3	0
Baseline (male-negotiated) condom use for all partnerships (no vaccination program)	$h_{i,0}$	0.5
Condom failure rate for all partnerships	f	0.14
HIV disease duration parameters		
Asymptomatic HIV infection (years)	$1/\mu_{1,j}$	6.8
Symptomatic HIV infection (years)	$1/\mu_{2,j}$	2.6
AIDS (years)	$1/\mu_{3,j}$	0.8
Initial population parameters, heterosexual men/women > 16 years		
Total population size		823,000
Initial HIV prevalence, male population (%)		11.6
Initial HIV prevalence, female population (%)		20.0
Mean age (years)		25.1
Non-AIDS life expectancy (years)		60.8
Non-AIDS-related annual mortality rate	μ	0.028[d]

[a] Model variable terminology adapted from Owens *et al.* and Edwards *et al.*, 1998

[b] See text for parameter value references and assumptions; values in parentheses are ranges used in sensitivity analyses

[c] e.g. for $\Delta = 1.0$, no change in condom use; for $\Delta = 1.25$, 25% increase in condom use; for $\Delta = 0.75$, 25% decrease in condom use

[d] Non-AIDS mortality rate calculated as follows: $1/\mu +$ (population mean age) = (non-AIDS population life expectancy)

Figure 1.

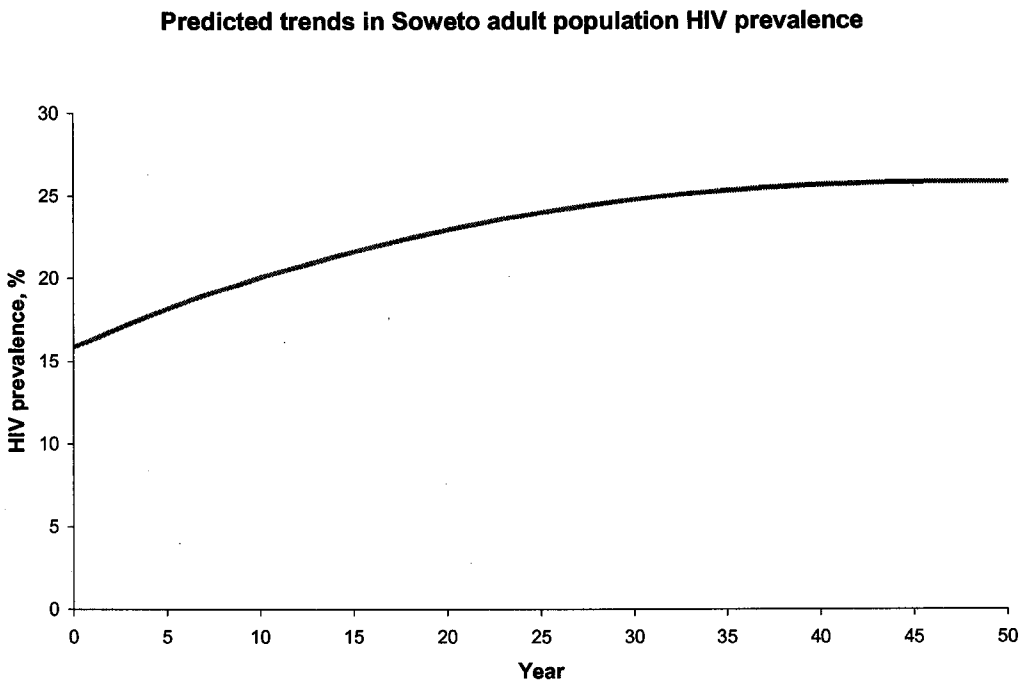
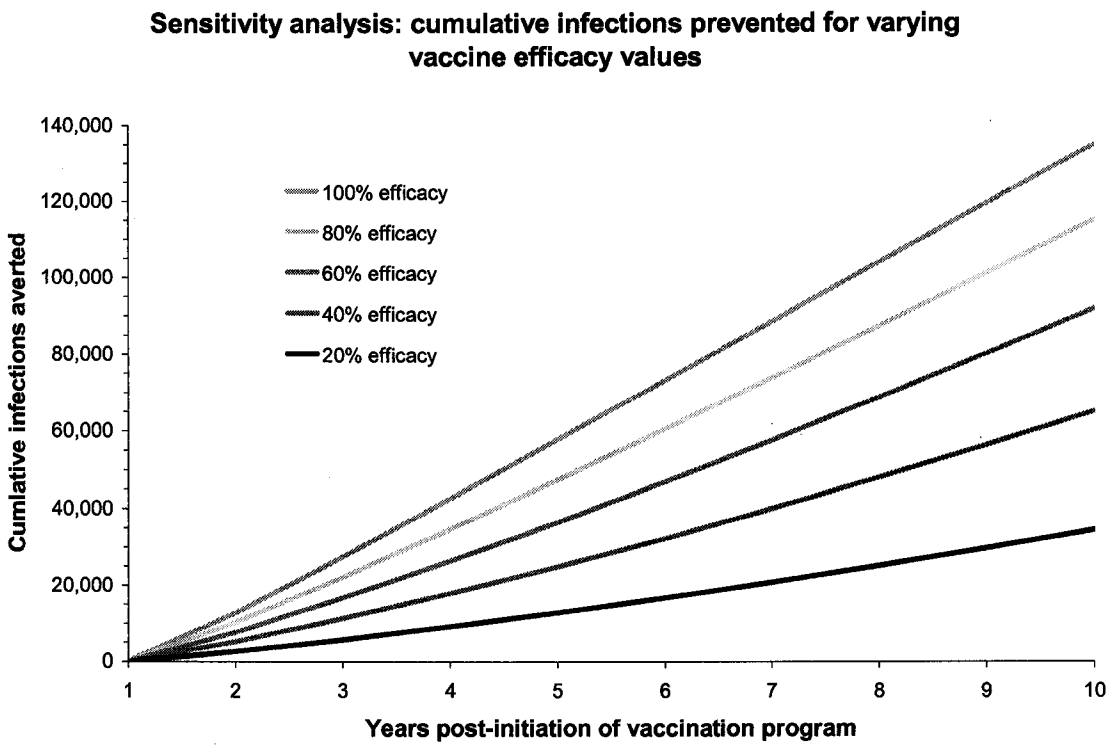


Figure 2.



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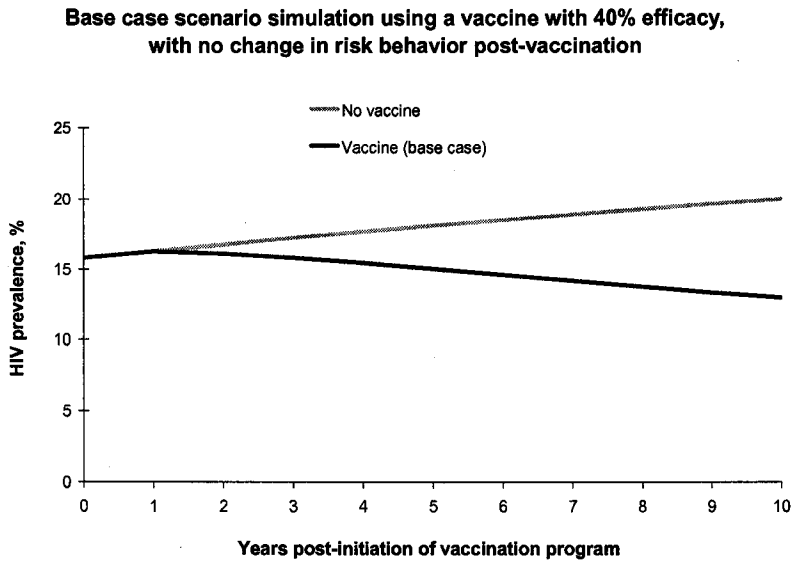

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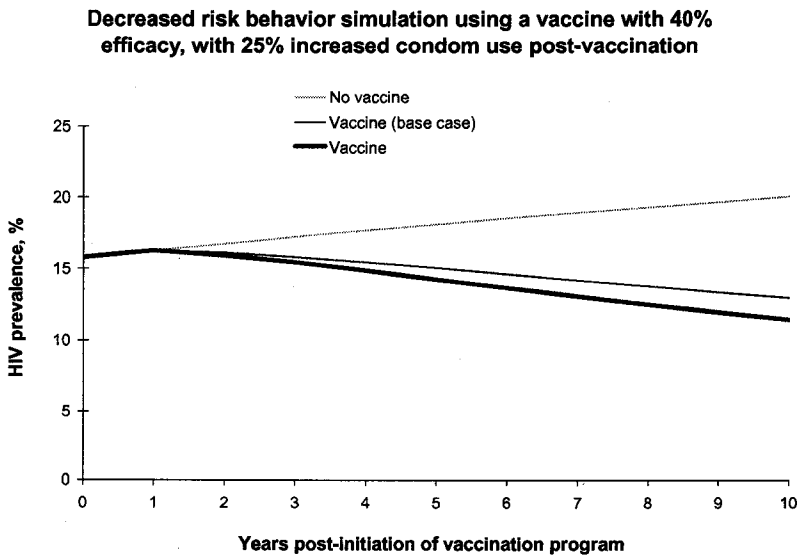

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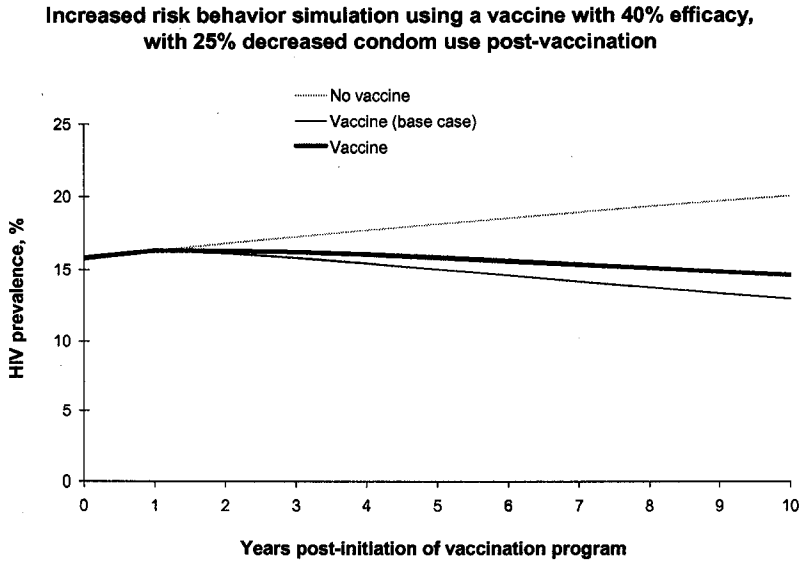

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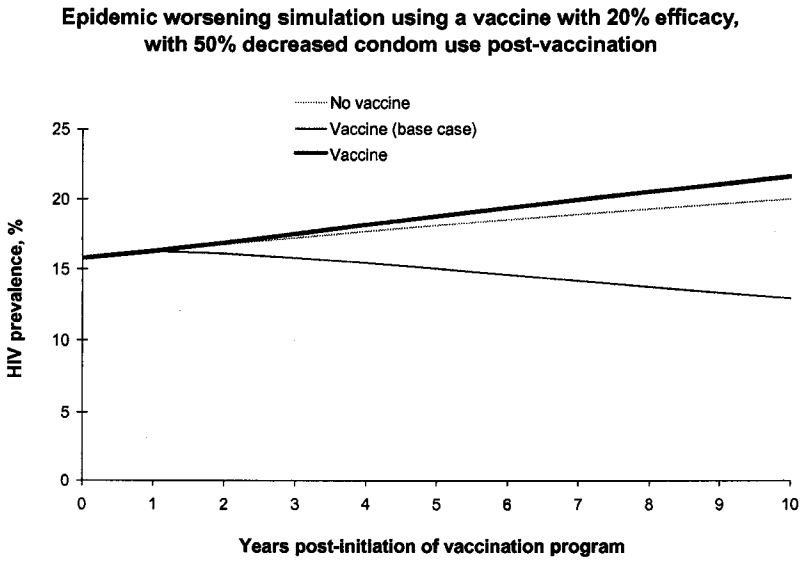


Figure 4A.

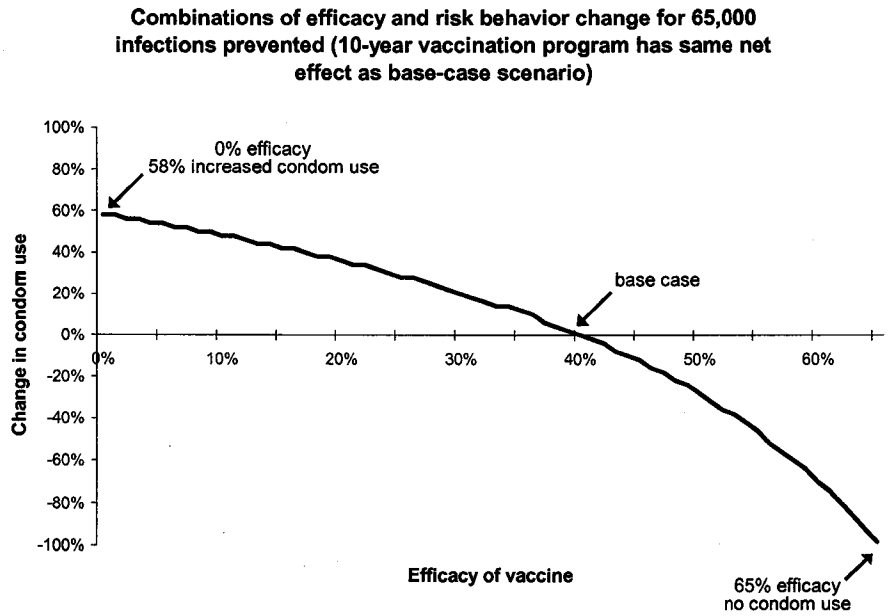


Figure 4B.

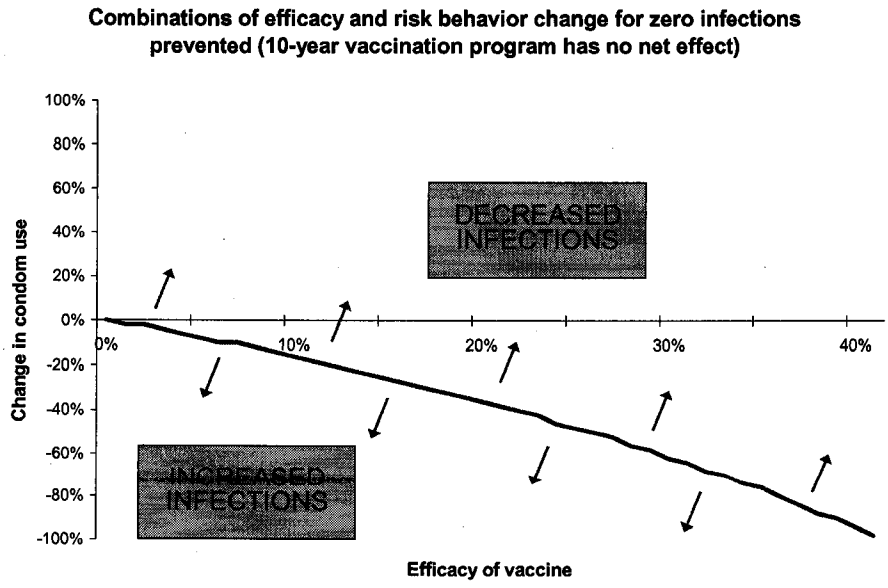


FIGURE CAPTIONS

Figure 1. Model-predicted trends in Soweto population HIV prevalence over 50 years for sexually active adult population.

Figure 2. Sensitivity analysis showing cumulative HIV infections averted over 10 years for vaccination programs using vaccines with varying efficacy values (20%, 40%, 60%, 80%, and 100%).

Figure 3. Changes in population HIV prevalence compared to a no-vaccine simulation over 10 years for various vaccination program scenarios: base-case scenario using a 40% effective vaccine with no post-vaccination change in risk behavior (panel A); decreased risk behavior scenario using a 40% effective vaccine with a 25% increase in post-vaccination condom use (panel B); increased risk behavior scenario using a 40% effective vaccine with a 25% decrease in post-vaccination condom use (panel C); and, a scenario to demonstrate the potential for epidemic worsening, using a 30% effective vaccine with a 75% decrease in post-vaccination condom use (panel D).

Figure 4. Equivalence graph showing various combinations of vaccine efficacy and changes in post-vaccination condom use in vaccination scenarios that would result in the same number of cumulative infections averted: all combinations of programs preventing 65,000 new HIV infections, which is the number of infections prevented in the base-case scenario (panel A); and, all combinations of programs with no net effect, or zero

infections prevented, such that combinations of programs falling above the curve would prevent infections while those falling below the curve would lead to additional infections (panel B).

APPENDIX

Detailed information on the mathematical model used for the evaluation of various HIV vaccination program scenarios is provided in this Appendix.

We based the model design on a mathematical model for homosexual HIV transmission and disease progression simulating the effects of HIV vaccination programs in men who have sex with men in San Francisco[19,24], which had incorporated characteristics of previously published models of HIV disease[48,49,71]. We developed the current epidemic model for the heterosexual transmission of HIV that occurs in African populations. We adapted the model in the following ways: (1) to account for two different populations (male and female) linked by heterosexual HIV transmission; (2) to account for HIV transmission conditions in sub-Saharan Africa, including male-driven negotiation of condom use and lack of knowledge of one's HIV status; and, (3) to assess the impact of a preventive vaccine only. Model input parameters and assumptions were also chosen to reflect the African setting.

The model defines six health states, which differ for males and females, for a total of twelve states overall. Movement of individuals from the unvaccinated HIV-negative (state 1) to the vaccinated HIV-negative (state 2) compartment and from the unvaccinated asymptomatic HIV-positive (state 3) to the vaccinated asymptomatic HIV-positive (state 4) compartment is determined by effective vaccination with an HIV vaccine, whereas movements in the reverse direction are determined by vaccine protection waning over time. Movement of individuals from the unvaccinated HIV-negative (state 1) to the unvaccinated asymptomatic HIV-positive (state 3) compartment and from the vaccinated HIV-negative (state 2) to the vaccinated asymptomatic HIV-positive compartment (state

4) is determined by acquisition of HIV infection from a heterosexual partner. Movement of individuals from the unvaccinated and vaccinated asymptomatic HIV-positive (states 3 and 4) compartments to the symptomatic HIV-positive (state 5) compartment and subsequently to the AIDS (state 6) compartment is determined by disease progression in those that become infected with HIV. Other movements between compartments in the model are not allowed. For model simulations, transitions between the twelve population subgroups were calculated annually to determine the number of men and women in each compartment.

Table 2 lists a description of the variables used in the model equations. Table 3 lists the twelve differential equations that define transitions between various health states in the model. For example, equation (1) describes the rate of change of the male $[M_{i,j}]$ unvaccinated $[j=0]$, HIV-negative $[i=0]$ sexually active population at time t:

$$(1)\quad \frac{dM_{0,0}(t)}{dt} = I_{M0,0} - \psi\nu(t)M_{0,0}(t) - \mu M_{0,0}(t) - p_0\lambda_M(t)M_{0,0}(t) + \omega M_{0,1}(t)$$

This rate depends on the following factors, which are each terms in equation (1): (a) $I_{M0,0}$, the number of unvaccinated, HIV-negative males who arrive into the sexually active population each year upon reaching the age of 17 years; (b) $\psi\nu(t)M_{0,0}(t)$, the number of unvaccinated, HIV-negative males $[M_{0,0}(t)]$ who are vaccinated each year [proportion of the population vaccinated, $\nu(t)$] and in whom the vaccine has an effect [take, ψ]; (c) $\mu M_{0,0}(t)$, the number of unvaccinated, HIV-negative males $[M_{0,0}(t)]$ who die each year due to non-AIDS related causes [non-AIDS mortality rate, μ]; (d) $p_0\lambda_M(t)M_{0,0}(t)$, the number of unvaccinated HIV-negative males $[M_{0,0}(t)]$ who

become infected with HIV [per-partnership probability of an unvaccinated male acquiring HIV from any female at time $t, \lambda_M(t)$] each year from a female partner [number of female partners per year for an uninfected male, p_0]; and, (e) $\omega M_{0,1}(t)$, the number of vaccinated [$j=1$], HIV-negative males [$M_{0,1}(t)$] for whom protection from the vaccine wanes each year [rate of vaccine waning, ω], returning them to the immunologic and behavioral 'unvaccinated' state. Rates of change for other population subgroups are determined in a similar fashion.

We modeled a heterogeneous population with respect to gender and disease stage and a homogeneous population with respect to risk behavior and vaccination coverage (e.g. except for changes in behavior based on vaccination or disease progression, sexual risk behavior was uniform throughout population subgroups, mixing of sexual partnerships was random, and vaccination was not targeted to individuals at higher risk of HIV infection). Models with greater complexity generally confirm the insights gained from those assuming homogeneous populations[20] and random mixing[72].

We assumed, in accordance with the theoretical framework of McLean and Blower, that a vaccine could fail to protect an individual from HIV infection in three different ways[49]. The vaccine might not produce an immunological response in the individual (imperfect, or less than 100%, take ψ); in those who produce an immunological response, the vaccine might provide only partial protection to individuals (imperfect, or less than 100%, degree, or efficacy ε); and, the duration of protection (mean duration in years, $1/\omega$) afforded by the vaccine may not last for the entire sexually-active life of the vaccine recipient. However, because this analysis considered a vaccine with 100% take and 50 years duration of protection, only imperfect vaccine efficacy is examined as a

significant source of vaccine failure in the current study. As different combinations of vaccine imperfections produce different outcomes[49], our model allows for future analyses varying vaccine take and duration, in addition to efficacy.

We assumed that an HIV vaccine protected an uninfected individual from acquiring HIV infection when exposed to an HIV-positive heterosexual partner and that vaccines with less than 100% efficacy did not provide complete protection from HIV infection. We modeled this incomplete protection as partial protection on an individual level, e.g. a 40% effective vaccine ($\varepsilon = 0.4$) would only provide protection from 40% of sexual partnerships with an HIV-positive partner. As shown in equations (3) and (4) in Table 3, a partially-effective vaccine reduces the rate of HIV infection by a factor of $(1-\varepsilon)$. Therefore, a 40% effective vaccine will reduce the probability of HIV infection from sexual partnerships with HIV-positive individuals to 60%.

As detailed in the model equations, the rate of HIV infection for individuals in the model depends on the following factors: an individual's vaccination status, the efficacy of the vaccine used, the number of sexual partners per year, the probability of choosing an HIV-positive partner from the population at any point in time, the probability that HIV is transmitted (infectivity) in a particular partnership, the condom use in a particular partnership, and the change in male-negotiated condom use behavior that occurs post-vaccination. Table 3 also lists the three equations [for $\lambda_M(t)$, $\lambda_{Mv}(t)$ and $\lambda_W(t)$] that define the 'force of infection', or probability of acquiring HIV from any partner at a given point in time, to which an uninfected man or woman is exposed.

The force of infection partially depends on the probability of transmission of HIV from a particular sexual partnership. The probability of HIV transmission per sex act

varies both within and between sexual partnerships[73]. Rather than using infectivity parameters for the probability of HIV transmission per sex act, we use infectivity parameters for the probability of HIV transmission over the course of a sexual partnership. The probability of HIV transmission from a given sexual partnership (for example, from a female to a male partner) is determined by the likelihood of choosing an HIV-infected partner $[\sum_{i=1}^{i=3}\sum_{j=0}^{j=1} p_i W_{i,j}(t) \Big/ \sum_{i=0}^{i=3}\sum_{j=0}^{j=1} p_i W_{i,j}(t)]$ and the likelihood of HIV being transmitted during the course of that partnership $[\sum_{i=1}^{i=3}\sum_{j=0}^{j=1} \beta_{Wi,j}]$ if an HIV-infected partner is chosen, both of which depend on the disease stage of the HIV-infected partner, given all possible potential heterosexual partnerships that exist.

The force of infection also depends on condom use. Condom use is captured by the term $n_{Mi,j}$, which is the probability that a particular sexual partnership between a male with disease stage i and vaccination stage j and a female (with any disease stage and vaccination status) is *not* protected by condoms. This is determined by the baseline condom use $h_{i,0}$, the change in condom use as a result of a vaccination program Δ, and the likelihood of condom failure f (see Table 2 for equations). Because we assume that condom use is negotiated by the male in the partnership, only changes in male post-vaccination risk behavior affected condom use in heterosexual partnerships. Therefore, the force of infection which an unvaccinated, uninfected male experiences includes a condom use term based only on his own condom use behavior, $n_{M0,0}$. Similarly, the force of infection which a vaccinated, uninfected male experiences includes a condom use term based on his own condom use behavior, which may have changed post-vaccination, $n_{M0,1}$.

However, the force of infection to be applied to an uninfected female (regardless of vaccination status) includes a condom use term based on the male condom use behaviors for all of her potential partnerships, $\sum_{i=1}^{i=3}\sum_{j=0}^{j=1} n_{Mi,j}$.

HIV transmission was modeled to occur only via heterosexual contact; transmission from mother-to-child and transmission through blood transfusions, intravenous drug use, or homosexual contact was not included in the model equations. Epidemics driven by other routes of transmission, such as injection drug use or men who have sex with men, would be better addressed with models specifying the particular transmission and risks of HIV in those populations. Of these alternate infection routes, mother-to-child transmission is a significant contributor to the HIV epidemic in South Africa. However, we have allowed for early HIV infection in the model by specifying that a proportion of arriving 17-year olds are already HIV-positive. Adolescents who were infected through mother-to-child transmission at birth and who have not yet succumbed to AIDS, as well as adolescents who acquired HIV through early sexual activity, are included in this group.

HIV transmission was modeled on a per-partnership basis; thus, rates of HIV transmission were used for the probability of transmission over the entire duration of a partnership between a male and a female, rather than on a per-contact or per-sex act basis. We assumed uniform HIV transmission risk across different partnerships, such that having very risky sex in a partnership (because of chosen partner, type of sex act, or use of condoms) just a few times might be equivalent to having less risky sex many times in a different sexual partnership[74]. For the per-partnership probability of HIV transmission calculations, we used MTF and FTM transmission data from serodiscordant

monogamous couples in rural Uganda[18,50], calculated person-years of follow-up time, and assumed that transmissions per person per year in a serodiscordant monogamous sexual relationship would accurately estimate transmissions per partnership per year.

Although European and North American data have indicated that HIV infectivity from MTF is greater than from FTM, African studies have shown that infectivity either is equal from MTF and FTM, is greater from FTM than MTF, and/or is instead dependent on other factors such as age, viral load, genital ulceration, pregnancy, circumcision, and type of sexual partnership (monogamous vs. casual partner)[18,50,52-56]. Because of these other factors, the apparent geographic differences in infectivity data can be partially resolved (1) by the observation that viral loads in females are significantly lower than in males for similar disease stages, (2) by the high rate of circumcision in Western populations, which decreases FTM HIV transmission, and (3) by the varying degrees of condom use between studies. Due to the discrepancies in the literature, we performed additional sensitivity analyses in which the MTF and FTM infectivity parameters were exchanged. We also assumed that males in the model were not circumcised, an issue which we have addressed elsewhere [Dissertation Paper 4].

We used an HIV viral load of 38,500 copies/mL to distinguish asymptomatic HIV infection from symptomatic infection, and derived an asymptomatic infectivity parameter which is 41% of the symptomatic infectivity parameter using this assumption. While viral load does not directly correlate with clinical HIV symptoms—the same viral load can result in various ranges of clinical symptoms for different individuals—the viral load point we used as a cutoff value resulted in an infectivity ratio between asymptomatic and symptomatic infection which closely approximates ratios from other studies of 39-45%

using different methodology[51,52,71].

Using the Ugandan data and the calculations described above, we derived an infectivity parameter for asymptomatic and symptomatic MTF transmission probabilities of 0.07 and 0.17 per sexual partnership per year, respectively. While these values appear relatively high, a smaller study of MTF transmission in the same Ugandan population showing that pregnant women were at a two-fold increased risk for HIV infection revealed that married pregnant women in serodiscordant relationships with HIV-positive partners became infected with an overall probability of 0.15 per person per year[54]. Because 96% of the women in the study reported never using condoms and couples who were married reported few extra-marital partners, the transmission data were fairly reliable and agree with the magnitude of transmission parameters we calculated. We derived infectivity parameters for asymptomatic and symptomatic FTM transmission of 0.11 and 0.27 per sexual partnership per year, respectively. Although a study on FTM HIV transmission in a high risk cohort of Kenyan truck drivers reported FTM HIV infectivity of 0.0128 per coital act for uncircumcised men[53], transmission probabilities for individual sex acts can not be correlated with transmission probabilities over the course of a sexual partnership. We performed sensitivity analyses on the symptomatic FTM infectivity parameter due to its relatively high value and the lack of additional African transmission studies.

We modeled a stable population size over time except for deaths due to AIDS. In the simulation, men and women join the sexually active, heterosexual population upon reaching the age of 17 years, defined as the age by which all individuals are sexually active[44-47]. These new arrivals enter the model at a constant rate (determined by the

number of men and women who die due to non-AIDS-related causes) into the uninfected or HIV-infected asymptomatic compartment populations. We assumed that no one was vaccinated prior to the age of 17 years. Some individuals will have already been infected with HIV; we estimated that 3% of 17-year-old males and 10% of 17-year-old females would be HIV-positive[45-47,75]. Acquisition of HIV infection prior to the age of 17 years (and therefore prior to entry into the model's compartment populations) may have occurred through mother-to-child transmission or other means such as early sexual activity, as described above. We assumed that all of the arriving HIV-positive 17-year-olds would still be in the asymptomatic stage of the disease, because they either acquired the infection recently or because individuals infected at birth through mother-to-child transmission that have developed AIDS would no longer be alive, and that disease progression to symptomatic HIV and further to AIDS would not occur until after entry into the model. Individuals can leave the model from any population subgroup due to non-AIDS mortality, or from the AIDS subgroup population due to AIDS-related death.

We assumed equal numbers of men and women in the initial population. We assumed that the percentage of people initially in each HIV disease stage was proportional to the time spent in that stage. We assumed that the vaccine would provide equal protection against all HIV subtypes. Because we assumed that the vaccine impacted only on initial HIV transmission, but had no effect on disease progression or infectivity (such as through a reduction in viral load) in those that became HIV infected either before or after vaccination, we have not described the vaccinated symptomatic HIV-positive and AIDS states as separate from the unvaccinated symptomatic HIV-

positive and AIDS states, respectively, or their respective infectivity values, despite the model allowing for such differentiation.

TABLE 2 (APPENDIX). Definition of model variables

Description of variable	Symbol
Disease stage (*i*)	
Uninfected (HIV-negative)	$i=0$
Infected (HIV-positive) asymptomatic	$i=1$
Infected (HIV-positive) symptomatic	$i=2$
AIDS	$i=3$
Vaccination status (*j*)	
Unvaccinated	$j=0$
Vaccinated	$j=1$
Disease-stage specific variables	
Number of men in disease stage *i* with vaccination status *j* at time *t*	$M_{i,j}(t)$
Number of women in disease stage *i* with vaccination status *j* at time *t*	$W_{i,j}(t)$
Probability of a male acquiring the infection at time *t* from any one female partner	$\lambda_M(t)$
Probability of a male acquiring the infection at time *t* from any one female partner, under behavior modifications due to male vaccination	$\lambda_{Mv}(t)$
Probability of a female acquiring the infection at time *t* from any one male partner, regardless of female vaccination status	$\lambda_W(t)$
Per-partner infectivity (chance of transmitting HIV) of a male in disease stage *i* with vaccination status *j*	$\beta_{Mi,j}$
Per-partner infectivity (chance of transmitting HIV) of a female in disease stage *i* with vaccination status *j*	$\beta_{Wi,j}$
Contact rate (number of new partners/year) of males, females in disease stage *i*	ρ_i
Mean duration (in years) of disease stage *i* under vaccination status *j*	$1/\mu_{i,j}$
Annual immigration of males in disease stage *i* with vaccination status *j*	$I_{Mi,j}$
Annual immigration of females in disease stage *i* with vaccination status *j*	$I_{Wi,j}$
Probability a partnership between an uninfected, unvaccinated male and a female with disease stage *i*, vaccination status *j* is not protected by condoms[a]	$n_{M0,0}$
Probability a partnership between an uninfected, vaccinated male and a female with disease stage *i*, vaccination status *j* is not protected by condoms[a]	$n_{M0,1}$
Probability a partnership between an uninfected female (regardless of vaccination status) and a male with disease stage *i*, vaccination status *j* is not protected by condoms[a]	$n_{Mi,j}$
Population variables	
Non-AIDS-related annual death rate	μ
Preventive-vaccine variables	
Annual percent of uninfected or asymptomatic HIV+ males or females who receive preventive vaccine	$\nu(t)$
Vaccine take (proportion of vaccinated in whom immune response stimulated)	ψ
Vaccine efficacy (percent of partnerships protected from infection)	ε
Mean duration (in years) of vaccine protection	$1/\omega$

[a] $n_{Mi,j} = fg_{i,j} + (1 - g_{i,j})$, where $g_{i,0} = h_{i,0}$ and $g_{i,1} = \Delta h_{i,0}$ [f = condom failure rate for all partnerships; $h_{i,0}$ = baseline condom use for all partnerships, with no vaccination program; Δ = change in condom use after vaccination; $g_{i,j}$ = condom use for all partnerships, following program implementation]

TABLE 3 (APPENDIX). Model equations[a]

State Equation

(1) $$\frac{dM_{0,0}(t)}{dt} = I_{M0,0} - \psi\nu(t)M_{0,0}(t) - \mu M_{0,0}(t) - p_0\lambda_M(t)M_{0,0}(t) + \omega M_{0,1}(t)$$

(2) $$\frac{dW_{0,0}(t)}{dt} = I_{W0,0} - \psi\nu(t)W_{0,0}(t) - \mu W_{0,0}(t) - p_0\lambda_W(t)W_{0,0}(t) + \omega W_{0,1}(t)$$

(3) $$\frac{dM_{0,1}(t)}{dt} = \psi\nu(t)M_{0,0}(t) - \mu M_{0,1}(t) - p_0(1-\varepsilon)\lambda_{M\nu}(t)M_{0,1}(t) - \omega M_{0,1}(t)$$

(4) $$\frac{dW_{0,1}(t)}{dt} = \psi\nu(t)W_{0,0}(t) - \mu W_{0,1}(t) - p_0(1-\varepsilon)\lambda_W(t)W_{0,1}(t) - \omega W_{0,1}(t)$$

(5) $$\frac{dM_{1,0}(t)}{dt} = I_{M1,0} - \psi\nu(t)M_{1,0}(t) - \mu M_{1,0}(t) + p_0\lambda_M(t)M_{0,0}(t) + \omega M_{1,1}(t) - \mu_{1,0}M_{1,0}(t)$$

(6) $$\frac{dW_{1,0}(t)}{dt} = I_{W1,0} - \psi\nu(t)W_{1,0}(t) - \mu W_{1,0}(t) + p_0\lambda_W(t)W_{0,0}(t) + \omega W_{1,1}(t) - \mu_{1,0}W_{1,0}(t)$$

(7) $$\frac{dM_{1,1}(t)}{dt} = \psi\nu(t)M_{1,0}(t) - \mu M_{1,1}(t) + p_0(1-\varepsilon)\lambda_{M\nu}(t)M_{0,1}(t) - \omega M_{1,1}(t) - \mu_{1,1}M_{1,1}(t)$$

(8) $$\frac{dW_{1,1}(t)}{dt} = \psi\nu(t)W_{1,0}(t) - \mu W_{1,1}(t) + p_0(1-\varepsilon)\lambda_W(t)W_{0,1}(t) - \omega W_{1,1}(t) - \mu_{1,1}W_{1,1}(t)$$

(9) $$\frac{dM_{2,0}(t)}{dt} = I_{M2,0} + \sum_{j=0}^{j=1}\mu_{1,j}M_{1,j}(t) - \mu M_{2,0}(t) - \mu_{2,0}M_{2,0}(t)$$

(10) $$\frac{dW_{2,0}(t)}{dt} = I_{W2,0} + \sum_{j=0}^{j=1}\mu_{1,j}W_{1,j}(t) - \mu W_{2,0}(t) - \mu_{2,0}W_{2,0}(t)$$

(11) $$\frac{dM_{3,0}(t)}{dt} = \mu_{2,0}M_{2,0}(t) - \mu M_{3,0}(t) - \mu_{3,0}M_{3,0}(t)$$

(12) $$\frac{dW_{3,0}(t)}{dt} = \mu_{2,0}W_{2,0}(t) - \mu W_{3,0}(t) - \mu_{3,0}W_{3,0}(t)$$

(13),(14) $$\lambda_M(t) = \frac{n_{M0,0}\sum_{i=1}^{i=3}\sum_{j=0}^{j=1}\rho_i\beta_{Wi,j}W_{i,j}(t)}{\sum_{i=0}^{i=3}\sum_{j=0}^{j=1}\rho_i W_{i,j}(t)} \quad , \quad \lambda_{M\nu}(t) = \frac{n_{M0,1}\sum_{i=1}^{i=3}\sum_{j=0}^{j=1}\rho_i\beta_{Wi,j}W_{i,j}(t)}{\sum_{i=0}^{i=3}\sum_{j=0}^{j=1}\rho_i W_{i,j}(t)}$$

(15) $$\lambda_W(t) = \frac{\sum_{i=1}^{i=3}\sum_{j=0}^{j=1}n_{Mi,j}\rho_i\beta_{Mi,j}M_{i,j}(t)}{\sum_{i=0}^{i=3}\sum_{j=0}^{j=1}\rho_i M_{i,j}(t)}$$

[a] Model equations adapted from Owens *et al.* and Edwards *et al.*, 1998

PAPER 4

The Potential Benefits of Expanded Adult Male Circumcision Programs in Africa: Predicting the Population-Level Impact on Heterosexual HIV Transmission in Soweto

INTRODUCTION

Twenty-five years into the HIV/AIDS epidemic, 11,000 new infections are still occurring globally every day[1]. Although research into preventive tools including vaccines and microbicides is promising, large-scale implementation of these technologies is years away. In addition to maximizing the impact of current HIV prevention and education campaigns, new effective HIV prevention technologies are needed to fight the epidemic. Recent studies have identified male circumcision, practiced for cultural and religious reasons in certain populations for centuries, as a novel potential HIV prevention strategy which could be implemented immediately.

The role of circumcision in reducing heterosexual HIV transmission was first proposed in the scientific literature 20 years ago[2]. Since that time, a number of ecological and cohort studies, largely in sub-Saharan Africa, have proposed a relationship between HIV prevalence or HIV transmission and male circumcision status[3-12]. These studies laid the foundation for a formal evaluation of the impact of circumcision on female-to-male (FTM) HIV transmission in three large randomized controlled trials of adult male circumcision conducted in Kenya, Uganda and South Africa. The first results came from the South African trial when interim analysis showed that circumcision decreased FTM transmission of HIV by 61% (95% CI 34%-77%); the trial was halted on ethical grounds, allowing all participants to undergo circumcision[13]. Recently[8], the other two trials were also halted when interim analyses showed a decrease in FTM HIV transmission of 53% in the Kenyan trial and 48% in the Ugandan trial[14].

[8] The announcement to halt the circumcision trials in Kenya and Uganda on December 13, 2006 had just been made at the time of writing. At that point no further trial results beyond estimates of efficacy were available. Both studies were subsequently published on February 24, 2007, during the final drafting of this dissertation, in the *Lancet*. In general, the discussion presented here remains the same, except for the observation that the trials in Kenya and Uganda found no evidence of increased risk-taking behavior.

In addition to being highly effective, adult male circumcision has been shown to be safe, affordable, and culturally acceptable to men in many African countries including South Africa, Malawi, Kenya, Zimbabwe, Uganda, Swaziland, and Botswana[13-22]. One modeling study has shown that male circumcision has the potential to prevent millions of infections across sub-Saharan Africa and decrease HIV prevalence in both men and women[23]. Another study has shown that male circumcision will be a very cost-effective intervention for HIV prevention in South Africa[24]. Yet the success of male circumcision programs is not guaranteed—as with any partially-effective HIV prevention program, it is possible that sexual risk behavior might change in response to the intervention, thus increasing or decreasing the potential benefits of that program[25]. Although no analyses of risk behavior have yet been reported for the Kenyan and Ugandan trials, there was a moderate increase in risk behavior during the South African trial[13], and we are unable to predict what might occur outside of clinical trial conditions in an expanded circumcision program[26]. One prospective study in Kenya found no behavioral disinhibition for the first year in men who underwent voluntary circumcision[27], but whether this represents permanent and widely applicable behavior patterns in light of the recent public awareness of male circumcision and HIV prevention remains to be seen.

Governments and international health policy makers are now considering the addition of large-scale expanded adult male circumcision programs to their current arsenal of HIV prevention packages[28-36]. However, because the field is fairly new and data on outcomes of large circumcision programs will not be available for many years, there is relatively little information upon which to base policy decisions regarding how best to implement expanded adult male circumcision programs. In the absence of such

information, further capacity for potential program evaluation is needed, in particular for the specific African HIV transmission dynamics within local populations where these programs will likely be implemented.

We developed a mathematical model[9] to examine the potential impact of expanded adult male circumcision programs in Africa[37]. We selected input parameters to simulate the late-stage, high-prevalence HIV epidemic in the township of Soweto, South Africa as an example. Soweto is located southwest of Johannesburg and close to the community of Orange Farm, where the first male circumcision trial was conducted. We performed simulations to explore the outcomes of various circumcision programs that could be implemented, and varied the effectiveness of circumcision in reducing transmission, program coverage levels, and post-circumcision changes in risk behavior. We assessed the impact of each of these programs on heterosexual transmission of HIV, and compared them in terms of HIV infections prevented and changes in population HIV prevalence.

[9] Partial data from this manuscript have been previously reported at the XVI International AIDS Conference (Toronto, 2006).

METHODS

We created an epidemic model to explore the effects of present circumcision levels on predicted trends in HIV prevalence and to simulate the impact of expanded adult male circumcision programs on the HIV epidemic in a population at high risk for heterosexually transmitted HIV in Soweto, South Africa.

Model description

We formulated the present model to examine the influence of male circumcision on HIV transmission. The design incorporates characteristics of prior models of HIV disease[38-42] and includes factors specific to modeling the HIV epidemic in Africa such as predominantly heterosexual HIV transmission, limited knowledge of HIV infection status, and gender differences in circumstances surrounding sexual risk, which we have previously described [Dissertation Paper 3].

The model specifies ten 'compartments' or 'states' to simulate the process of heterosexual HIV transmission and disease progression in a population of sexually active adults. These include HIV-negative females (1), uncircumcised males (2), and circumcised males (3); asymptomatic HIV-positive females (4), uncircumcised males (5), and circumcised males (6); symptomatic HIV-positive females (7) and males (8); and, females (9) and males (10) with AIDS. For this study, we combined the circumcised and uncircumcised male compartments for both the symptomatic HIV-positive and AIDS states (see Appendix for further details). Individuals join the model population by entering into one of the first six compartments, and can leave the model population as a result of either non-AIDS or AIDS-related mortality. Transitions between these compartments or population subgroups are defined by a set of ten deterministic

differential equations which specify the rates of movement for the individuals in the model. A detailed description of model assumptions, parameters, and equations can be found in the Appendix.

Effects of circumcision

We incorporated current levels of male circumcision in South Africa[43,44] into both the initial and arriving populations of sexually active males who were HIV-negative or asymptomatic HIV-positive. We also incorporated the biological effect of circumcision on heterosexual transmission of HIV in the model. HIV-negative men who are circumcised are protected from HIV infection in sexual partnerships with HIV-infected women a certain proportion of the time, which is the protective effect. Therefore, if the protective effect of male circumcision were 75% for example, circumcised HIV-negative men would then be protected from HIV infection in 75% of heterosexual partnerships with infected women.

We modeled only a reduction in HIV transmission for circumcised HIV-negative males who have HIV-positive female partners. Although in theory it is possible that male circumcision may also reduce HIV transmission from circumcised HIV-positive males to their HIV-negative female partners, we have not incorporated this potential reduction because a clinical trial to address this question is still under way in Uganda[45]. However, the model can be adapted to explore this question when the trial is completed[10] by incorporating any male-to-female (MTF) transmission effects of circumcision that are

[10] Although the trial in Uganda to assess whether circumcision protected males from infection due to decreased female-to-male (FTM) transmission has been completed, a separate trial to assess whether circumcision protects females from infection due to decreased male-to-female (MTF) transmission is still under way.

found and by adding additional compartments specifying the circumcised and uncircumcised HIV-positive symptomatic states.

For our simulations, we used a protective effect from circumcision based on results from the first randomized controlled trial of circumcision in Africa[13] and performed additional sensitivity analyses on several possible values for this effect, approximating the confidence intervals for the trial data. We modeled expanded circumcision programs which targeted asymptomatic uncircumcised males aged 17 or older without testing them for HIV, therefore both HIV-negative and asymptomatic HIV-positive males would be eligible for circumcision while males with symptomatic HIV or AIDS would be ineligible.

Effects of risk behavior

Individuals could change their sexual risk-taking behavior as a result of the implementation of a large-scale program for male circumcision. Men targeted in an expanded circumcision program might increase their risky behavior because they feel protected following circumcision or they might decrease their risky behavior as a response to the risk-reduction counseling that may be given in a mass campaign. Men previously circumcised as infants/youths or before the start of the program might also increase or decrease their risky behavior in a similar manner, even without participating in the program. Women, on the other hand, might increase or decrease their risky behavior because they feel that their male partners have a lower or higher probability of being HIV-infected, respectively, depending on their circumcision status. Uncircumcised men might also change their risk behavior due to the general notion that the risk for HIV infection is decreasing as a result of increased population circumcision prevalence, an

effect which could extend to all men and women irrespective of personal or partner circumcision status. Finally, all men and women might change their risk behavior as a result of the media and public health education outreach programs surrounding the implementation of an expanded program for adult male circumcision.

A change in risk behavior can be modeled as either a change in the number of sex partners, a change in the type or number of risky sex acts, or a change in the usage of protective measures, such as condoms. In our analyses, we modeled the potential effect of circumcision on behavior by exploring changes in levels of condom use. We examined changes in condom use for all circumcised men, irrespective of whether they were circumcised in the expanded program or elsewhere. While it is possible, as discussed above, that women and uncircumcised men might also change their behaviors, we assumed behavior change in circumcised males to be the primary influence on population changes in sexual risk behavior. We modeled exclusive male-negotiation of condom use in heterosexual partnerships in Soweto [Dissertation Paper 3], as studies have shown that there are significant imbalances in the ability of South African women to negotiate condom use with men in sexual partnerships[46-49]. By employing condom usage levels to explore changes in risk behavior, we were also able to capture this gender difference.

Simulations

Because most HIV models do not account for the transmission effect of circumcision, we first simulated the predicted trends for adult HIV prevalence in Soweto over the next 20 years with and without considering the reduction in HIV transmission due to current rates of male circumcision. Incorporating current rates of adult male

circumcision, we then conducted simulations for various expanded circumcision programs which were implemented for a period of 5 years. We evaluated the effects of these programs by examining the total number of HIV infections averted (estimated to the nearest 1,000) and the change in population HIV prevalence (estimated to the nearest 1%) over a 20-year period. To calculate these values, we compared model outputs from the circumcision program simulation with baseline outputs from a simulation without an expanded circumcision program. Because predicted infections without circumcision programs varied according to the population effects of reduced HIV transmission due to existing prevalent circumcision, baseline outputs for simulation comparisons were configured for each value of the reduction in HIV transmission due to circumcision used in the model.

We also simulated scenarios in which risk behavior changed following circumcision program implementation by varying condom use in circumcised males. Finally, we explored varying levels of program coverage levels and changes in male condom use for several values of circumcision efficacy to assess the tradeoff between the true impact on HIV transmission of male circumcision, the program coverage level achieved, and the potential for changes in risk behavior with implementation of circumcision programs. We used Excel® 2003 spreadsheet software (Microsoft Corporation, Redmond WA) for all model simulations and calculated transitions between various compartments in the model on an annual basis.

Input parameters and assumptions

We used published data sources for the majority of input parameters incorporated into the model (Table 1). We used a 61% reduction in FTM HIV transmission for

circumcised males[13] and assumed that the protection afforded by circumcision would last for the lifespan of that individual. We did not model a reduction in MTF HIV transmission for female partners of circumcised males. We performed sensitivity analyses incorporating circumcision-related reductions in FTM HIV transmission of 20%, 40%, 60%, and 80% to encompass the 95% confidence intervals (34%-77%) from the South African circumcision trial[13]; confidence intervals for the Kenyan and Ugandan trials have not yet been published. For some analyses, we also explored circumcision-related reductions in FTM HIV transmission of 0% to 100%. We incorporated baseline male circumcision levels of 35%[43,44] into the model, and performed additional sensitivity analyses for baseline circumcision levels of 0% and 100% to examine the influence of initial population circumcision prevalence on program outcomes. We explored the impact of expanded circumcision programs which targeted an additional 10-20% of uncircumcised males each year, with additional sensitivity analyses on all possible values for program coverage levels. Because circumcision would be done without testing for HIV, we used the same program coverage levels for uninfected and asymptomatic infected uncircumcised men. For simulations which considered changes in risk behavior, we also explored all values (0-100%) of post-circumcision program male-negotiated condom use.

We assumed an anti-retroviral (ARV)-naïve population because provision of ARV therapy in the population covered by the public-sector health system in South Africa is extremely low at present[50], and thus did not incorporate a reduction in transmission or increase in length of disease stage for members of the population receiving ARV therapy. We considered only heterosexual transmission of HIV in this analysis, as it is the

predominant mechanism for adult HIV transmission in South Africa. We varied the sexual risk behavior between population subgroups according to disease stage for the number of sex partners per year and according to gender and circumcision status for condom use, but did not incorporate further risk stratifications of sexual behavior. Details on the rationale used for estimates of input parameters which define other population characteristics, sexual risk behavior, HIV transmission, and disease progression have been reported elsewhere [Dissertation Paper 3]. Further details on the rationale and assumptions underlying the model specifications are provided in the Appendix.

RESULTS

We first simulated the predicted trends in adult HIV prevalence over the next 20 years in Soweto without considering the reduction in HIV transmission due to current rates of male circumcision (Figure 1A). The female population HIV prevalence would increase from 20% to 21% and the male population HIV prevalence would increase from 12% to 25%. The model predicted a total of 318,00 new infections (127,000 female infections and 191,000 male infections) would occur over this time period. We then incorporated the reduction in HIV transmission due to current rates of male circumcision and again simulated the predicted trends in adult HIV prevalence over the next 20 years (Figure 1B). Assuming current levels of male circumcision remain constant and a 61% reduction in FTM HIV transmission for circumcised males, the female population HIV prevalence would decrease from 20% to 17% and the male population HIV prevalence would increase from 12% to 17%. The model predicted 102,000 new female infections and 142,000 new male infections would occur over this time period. All subsequent analyses used this model incorporating the HIV transmission effects of circumcision and current rates of male circumcision as a baseline, although some analyses varied the reduction in FTM HIV transmission for circumcised males.

We then considered the impact of various 5-year expanded adult male circumcision programs which targeted an additional percentage of the uncircumcised male population each year. A program targeting 10% of the uncircumcised adult male population each year for five years would result in a decrease in predicted HIV prevalence in 20 years from 17% to 15% for the female population and from 17% to 14% for the male population (Figure 2A). If instead the program targeted an additional 20% of the

uncircumcised adult male population each year for five years, the decrease in predicted HIV prevalence would be more substantial. In 20 years, predicted HIV prevalence would decrease to 13% for females and 12% for males (Figure 2B). We next calculated the total number of new HIV infections prevented over a 20-year period by these programs. The circumcision program with a 10% coverage goal would avert 11,000 female infections and 22,000 male infections (Figure 3A), while the program with a 20% coverage goal would avert 18,000 female infections and 36,000 male infections (Figure 3B). For both program coverage goals, 33% of the total infections prevented over 20 years would be in females; and, looking at the long-term benefits of these programs, the proportion of female infections prevented increased to 40% over 50 years.

We also simulated scenarios in which sexual risk behavior changed following implementation of expanded circumcision programs for circumcised males. We examined behavior change only in circumcised males, including both those circumcised under the expanded program and those who had been circumcised previously. If sexual risk behavior decreased post-circumcision program implementation and condom use were to increase by 25% (corresponding to an absolute increase in condom use from 50% to 62.5% in circumcised males), then the benefits of the programs would be substantially greater. The 10% coverage program would avert 21,000 female infections and 33,000 male infections over 20 years (Figure 4A) and the 20% coverage program would avert 30,000 female infections and 49,000 male infections over 20 years (Figure 4B). If instead sexual risk behavior increased post-circumcision program implementation and condom use were to decrease by 25% (corresponding to an absolute decrease in condom use from 50% to 37.5% in circumcised males), then the benefits of the programs would

lessen substantially and would even cause additional HIV infections. Over 20 years, the 10% coverage program would prevent 9,000 male infections but result in a net additional 1,000 female infections (Figure 4C); the 20% coverage program would prevent 20,000 male infections and 4,000 female infections, despite an initial period of increased infections in the female population (Figure 4D).

We performed additional analyses for programs with 10% and 20% coverage goals and risk behavior changes of up to 100% in which the protective effect of male circumcision was varied from 20% to 80%. Infections prevented were calculated as compared to a situation in which no expanded circumcision program was implemented; however, the number of infections expected in the absence of circumcision programs varied due to the baseline population effects of circumcision on HIV transmission. Over 20 years, the number of infections expected if baseline population circumcision levels remain constant for circumcision protective effects of 20%, 40%, 60%, and 80% would be: 295,000 (20%), 271,000 (40%), 246,000 (60%), and 220,000 (80%). These numbers decrease with increasing ability of circumcision to reduce transmission of HIV in the population.

Our simulations to increase population circumcision levels with modest expanded adult male circumcision programs produced a wide variety of program outcomes, positive and negative (Table 2). As might be expected, both increasing condom use and increasing program coverage always increases the number of infections prevented for a given level of circumcision protective effect. However, as the magnitude of the circumcision protective effect increases, the number of infections prevented can increase or decrease depending on the magnitude of the change in condom use. While increases in

circumcision protective effect generally lead to increases in the number of infections prevented by a given program, increases in condom use of ~50% or greater over baseline levels can lead to fewer opportunities for additional prevention with increasing circumcision protective effect (Figure 5). This potentially counterintuitive result is due in large part to the baseline levels of circumcision in the population and the fact that we are reporting an incremental outcome measure. Unlike the results from vaccination simulations [Dissertation Paper 3], the results from circumcision program simulations differ because (1) there are baseline levels of circumcision (35%) in the population before adding on expanded circumcision programs, and (2) because of this, the model must be recalibrated to calculate infections prevented each time the efficacy of circumcision protective effect changes.

The outcome measure we report in Table 2 and Figure 5 is the number of infections prevented by a given circumcision program. It is the *difference*, or "delta value", between the number of infections expected given baseline levels of 35% circumcision prevalence (hereinafter referred to as Value A), and the number of infections expected under a policy of expanded circumcision (Value B). While both Values A and B decrease for increasing levels of condom use and for increasing protective effects of circumcision, as would be expected, the delta value behaves differently. For a given level of circumcision protective effect, increases in condom use always produce increases in the delta value. For a given level of condom use, though, the delta value rises with the circumcision protective effect at decreased and moderate increases in condom use, but falls with increasing circumcision protective effect at high increases in condom use. While it might appear that increasing circumcision efficacy makes matters worse in terms

of infections prevented, this is not the case. Rather, there are fewer infections to be prevented by an expanded circumcision program when circumcision efficacy increases, because an increase in circumcision efficacy lowers HIV transmission in the population already circumcised at baseline. Therefore the delta value might rise or fall as circumcision efficacy increases, depending on the interaction between the level of condom use and the baseline circumcision prevalence in the population.

To further our understanding of this somewhat counterintuitive effect, we performed additional simulations in which we varied the levels of baseline circumcision prevalence in the male population to extreme values (we used a 10% program coverage value for these simulations). We first considered the example of *no* males circumcised at baseline prior to program implementation (0% baseline circumcision prevalence): The number of infections expected without expanded programs [Value A] by efficacy was 318,000 (20%), 318,000 (40%), 318,000 (60%), 318,000 (80%). With an expanded program and no change in condom use, the number of infections prevented [delta value] by efficacy was 17,000 (20%), 35,000 (40%), 54,000 (60%), 74,000 (80%). With an expanded program and 100% increase in condom use, the number of infections prevented [delta value] by efficacy was 94,000 (20%), 97,000 (40%), 100,000 (60%), and 104,000 (80%). In this situation with no baseline circumcision, the number of infections expected without a program was a constant irrespective of efficacy (since no males were circumcised) and the number of infections prevented by a program always rose for increasing efficacy of circumcision (although the increase was not as dramatic at high levels of condom use).

We next considered the example of *all* males circumcised at baseline prior to program implementation (100% baseline circumcision prevalence): The number of infections expected without expanded programs [Value A] by efficacy was 263,000 (20%), 207,000 (40%), 153,000 (60%), 101,000 (80%). With an expanded program and no change in condom use, the number of infections prevented [delta value] by efficacy was 650 (20%), 1,200 (40%), 1,700 (60%), 2,000 (80%). With an expanded program and 100% increase in condom use, the number of infections prevented [delta value] by efficacy was 201,000 (20%), 153,000 (40%), 106,000 (60%), 61,000 (80%). In this situation with all men circumcised at baseline, the number of infections expected without a program declined rapidly with increasing circumcision efficacy. The number of infections prevented by a program with no change in condom use was almost zero, as all males were already circumcised. (The small numbers of infections prevented in this scenario were due to immigration of new sexually active uncircumcised males into the population.) Because all males were already circumcised at baseline, the number of infections prevented was dominated by condom use—but the number decreased with increasing circumcision efficacy because of the decreasing numbers of infections available to prevent. Given these two extreme examples, we have shown that there is a natural switch from increased infections prevented to decreased infections prevented for increasing circumcision efficacy at higher levels of condom use, as seen in Table 2 and Figure 5 in the original 35% baseline circumcision prevalence case. In summary, the benefits of expanded circumcision programs are reduced when the circumcision efficacy is high and baseline levels of circumcision are already successful at preventing infections.

Returning to the baseline population circumcision prevalence of 35% and to further explore these variations in program outcomes, we analyzed all possible combinations of different program coverage levels and post-program implementation changes in risk behavior for various levels of circumcision protective efficacy to determine which programs would be beneficial and which programs might be potentially harmful. While all circumcision programs in which condom use increased would be beneficial, many circumcision programs in which condom use decreased would still be beneficial, regardless of whether the program coverage level was moderate or high (Figure 6)[11]. This was particularly true for higher levels of circumcision protective effect.

We then explored the relationship between program coverage level and risk behavior change for specific levels of circumcision protective effects in greater detail (Figure 7). If the reduction in FTM HIV transmission due to male circumcision was only 20%, expanded adult male circumcision programs would have a minor impact if condom usage levels remain the same, regardless of the program coverage level (Figure 7A). However, these programs would be very sensitive to changes in condom use, with even small decreases in condom use leading to increased infections. If the reduction in FTM HIV transmission due to male circumcision was 40%, the program would be less sensitive to small changes in condom use and more sensitive to the lower values of program coverage (Figure 7B). If the reduction in FTM HIV transmission due to male circumcision was 60%, lower program coverage levels would be needed and further decreases in condom use could be tolerated while still providing a net program benefit

[11] While the graphs in Figures 6 and 7 demonstrate areas of program combinations resulting in increased versus decreased infections, they do not indicate the magnitude of these outcomes. Therefore, a program that prevented 1,000 infections and a program that prevented 100,000 infections would both be labeled 'decreased infections'.

(Figure 7C). Finally, if the reduction in FTM HIV transmission due to male circumcision was 80%, most programs would be beneficial irrespective of coverage level or decreases in condom use (Figure 7D).

Regardless of the true reduction in transmission due to male circumcision, all programs which generated an increase in condom use post-circumcision would be beneficial in terms of infections prevented. For programs which generated a decrease in condom use post-circumcision, whether a particular program was helpful or harmful was sensitive to the amount of decreased condom use, the program coverage level, and the true impact of circumcision on HIV transmission.

DISCUSSION

We designed a mathematical model to simulate the process of adult heterosexual HIV transmission which incorporates the effects of male circumcision on FTM HIV transmission. We chose model input parameters to simulate the HIV epidemic, including existing levels of male circumcision, in the population of Soweto, South Africa. To approximate HIV transmission conditions in the African setting, the model design also specified a gender difference in the ability of women to negotiate safe sex with their male partners [Dissertation Paper 3]. We simulated the potential impact of expanded adult male circumcision programs on the HIV epidemic in Soweto, considering different levels of program coverage goals, protective effects of male circumcision, and changes in risk behavior. In particular, we examined the dynamic interaction between reduced susceptibility to HIV infection and subsequent behavioral disinhibition following the implementation of expanded adult male circumcision programs.

We have shown that the reduction in HIV transmission due purely to current rates of male circumcision is significant, even without an active effort to expand circumcision programs, and that male circumcision is already having a tangible impact on the HIV epidemic. Because the effects of male circumcision substantially affect predicted outcomes, they should be routinely included in all HIV epidemic models for populations which practice circumcision and for which heterosexual transmission is the predominant mode of HIV spread. Additionally, epidemic models which simulate the potential benefits of expanded circumcision programs must take into account the existing benefits due to current male circumcision prevalence when estimating the additional impact of various program scenarios.

We estimated that modest 5-year expanded circumcision programs with only 10-20% coverage goals could produce substantial benefits in terms of infections prevented over a wide range of values for the effect of circumcision on HIV transmission. Even though circumcision was modeled to reduce only FTM HIV transmission, a substantial number of infections would be prevented in women nonetheless as a result of decreased HIV infections in men. Over twenty years, one-third of all infections prevented by programs with 10% and 20% coverage goals would occur in the female population. However, the magnitude of benefits from modest circumcision programs was sensitive to changes in sexual risk behavior, which we approximated with changes in condom use. Increased condom use would naturally lead to augmented program benefits but decreases in condom use would lead to decreased program benefits, while severe decreases in condom use could lead to a program being potentially harmful by resulting in increased HIV infections.

Still, the majority of potential program scenarios resulted in a positive net value for the number of infections prevented. Although more infections would be prevented in males, infections would also be prevented in females indirectly due to the decrease in male population HIV prevalence afforded by the circumcision programs and these discrepancies would diminish over time. However, the discrepancy between benefits to women versus men became potentially harmful when examining programs resulting in risk behavior change. For simulations in which risky sexual behavior increased following program implementation, women might experience a greater number of HIV infections over 20 years. This could occur despite a positive value for the total infections prevented because of the difference in magnitude between the outcomes of the program

for men and women. For this reason, programs must be evaluated on the basis of their individual benefits to both male and female populations. For the majority of potential changes in risk behavior, though, transmission of HIV to females was decreased for a wide variety of program scenarios—although the benefits to females were quantitatively less than the benefits to males.

Prior to the recent trials of circumcision, most observational studies suggested protective effects of circumcision clustering around 50%[4,5]. The reduction in FTM HIV transmission of 61% (95% CI: 34%, 77%) due to male circumcision used in our analyses for Soweto was based on the only published randomized controlled trial of adult male circumcision to date, which was a single site study conducted nearby in Orange Farm, a similar community in South Africa[13]. The other two trials in Kenya and Uganda have just been halted, with preliminary results reported as 53% and 48% reductions in FTM HIV transmission, respectively[14]. While circumcision likely reduces other sexually transmitted infections which in turn contribute to a reduction in HIV transmission, this effect is likely minimal compared to the effect of circumcision on HIV transmission itself[51]. The true effectiveness of circumcision in preventing HIV transmission likely lies within the range reported in these three trials, but might vary in other populations and non-trial conditions. For these reasons, we also explored values for the reduction in FTM HIV transmission from 20% to 80% which encompass the confidence intervals reported in the Orange Farm trial. We found that for very low reductions in transmission due to circumcision (e.g. 20%), the impact of expanded male circumcision programs would be minimal, regardless of coverage levels, and changes in condom use would ultimately determine whether the program will provide a net benefit. On the other hand, for high

reductions in transmission due to circumcision (e.g. 80%), the impact of expanded male circumcision programs was significant and changes in condom use would have much less influence on determining whether the program provides a net benefit. Further, high levels of reductions in transmission due to circumcision allowed programs with even minimal coverage levels to tolerate large decreases in condom use while still providing a net benefit.

Because of gender discrepancies in the protective effect of this intervention, circumcised males receive a direct benefit due to the protective effect of circumcision, while females receive only an indirect benefit from reduced population HIV prevalence. Further, because we modeled condom use in sexual partnerships to be determined by males, changes in sexual risk behavior for men receiving the intervention of circumcision directly correlated with changes in sexual risk behavior which place women at risk for HIV infection. In addition to highlighting the differences between potential benefits for male and female populations, our analyses also emphasize the idea that changes in risk behavior may be more or less influential in programs where an intervention can provide a direct benefit to only a fraction of the population (such as the case with male circumcision), than in programs where an intervention can provide a direct benefit to the entire population (such as the case with HIV vaccines [Dissertation Paper 3]).

To our knowledge, this analysis represents one of only three modeling simulations for the impact of male circumcision programs on the HIV epidemic in Africa. Williams and colleagues simulated the impact of achieving full coverage of male circumcision across sub-Saharan Africa within the next three to eight years and estimated that 6 million infections could be prevented in the region over a 20-year period[23]. Kahn and

colleagues estimated the costs of implementing various male circumcision programs in a South African setting and found them to be extremely cost-effective over a wide range of values[24]. We have furthered this research by examining the impact of modest expanded adult male circumcision programs using a detailed model for heterosexual HIV transmission with well-defined parameters for the population of Soweto and focused our simulations on exploring the dynamic effects of potential behavioral disinhibition in depth.

Now that a true protective effect for male circumcision has been shown by three randomized controlled trials, published estimates of FTM HIV transmission rates will need to take into consideration the circumcision status of males. For this modeling study, we calculated HIV infectivity parameters from studies of 170 monogamous serodiscordant couples in Uganda, which represented the only African transmission data currently available[52,53]. While the authors of the Ugandan studies noted that male circumcision status had no impact on MTF HIV transmission, they did not explore the impact of circumcision on FTM HIV transmission nor did they specify the baseline rates of male circumcision in their participants. These 170 couples were separated from a larger cohort of 415 serodiscordant couples based on their status of reporting monogamous relationships. Data from the larger cohort show that 19% of the men in the overall study population were circumcised; and, 27% of the men who were the HIV-negative partner were circumcised, of whom none became infected[12]. However, we do not know which of these participants were included in the sub-study and new analyses of those data according to circumcision status, in light of our current knowledge regarding protection from circumcision, would be beneficial to work such as that presented here.

For these reasons, we are unable to speculate on the true influence of circumcision on these HIV transmission data as it may be a confounding factor. Thus, if a substantial proportion of HIV-negative males were circumcised in those studies, FTM HIV transmission rates may actually be higher than described and should be reflected in future modeling studies.

We modeled only a decrease in FTM HIV transmission to circumcised HIV-negative males. Although the biologic and epidemiologic evidence is not as strong, it is also possible that there may be a decrease in MTF HIV transmission from circumcised HIV-positive males to their female partners[7,54,55]. This would be particularly important in South Africa where the prevalence of HIV in women is greater than in men[56,57]. A large randomized controlled trial is currently underway in Uganda to address this question[45], and further simulation studies should address this possibility when the data become available.

South Africa has a national plan for widespread distribution of antiretroviral medication to HIV-infected individuals[58], although progress on implementation has been slow. Only limited distribution has been accomplished to date within the public sector, with less than 100,000 HIV-infected individuals receiving ARV therapy[50] out of an estimated 5.5 million infected individuals in South Africa[1,59]. Antiretroviral therapy has been shown to decrease viral load and subsequent transmission of HIV[12,52,53,60] and therefore should be included, along with the concurrent increase in length of individual disease stages and overall lifespan for those treated, in future simulations when coverage levels begin to increase in South Africa.

We found that for any given level of circumcision protective effect, the impact of increasing condom use levels was greater than the impact of increasing program coverage beyond modest levels: for example, increasing condom use by 25% in circumcised men would be more effective than increasing program coverage levels for circumcision programs from 25% to 100%. Although it might appear that programs to increase condom use would be more beneficial than achieving high levels of circumcision coverage, these results do not take into account the fact that circumcision programs would involve a one-time intervention while programs to increase condom use require an intervention that must be exercised with every sex act over the life of the individual. Therefore, the best manner in which to allocate resources (e.g. between increasing circumcision program coverage and increasing condom distribution/education program coverage) can not be determined by our analyses.

Because there is no single intervention that is completely effective in preventing HIV transmission, interventions which are partially effective in reducing HIV transmission must be implemented. For heterosexual transmission in African populations, these currently include male circumcision, education programs, condom use campaigns, access to HIV volunteer counseling and testing, treatment of HIV-positive individuals to reduce viral load, stigma reduction, poverty alleviation, and empowerment of women. Eventually, chemoprophylaxis regimens, diaphragms, microbicides, and prophylactic or therapeutic vaccines may be added to this arsenal of programs[32]. While we have explored the impact of expanded adult male circumcision programs to address questions regarding their potential benefits and immediate implementation, further work on assessing the impact of multiple partially-effective prevention programs in a single

population is merited to allow for relative comparisons between different intervention package combinations.

Implementation of pilot male circumcision programs should begin immediately as male circumcision has been shown to be effective, safe, affordable, acceptable, and will likely confer lifelong benefits. Given the coverage of male circumcision in the media, uptake of programs should be successful—many clinics in Africa are already struggling to cope with the increased demand for circumcision[30]. However, programs must ensure that all male circumcision procedures are both safe and voluntary and must remain sensitive to the cultural practices of different populations. Nevertheless, even cultures and ethnic groups which do not currently encourage circumcision may find it acceptable, as was shown in the South African Zulu and Tswana populations[17,21]. Risk-reduction counseling must be provided by these circumcision programs, both to individuals as well as the community. This is particularly important in the South African context, where studies have revealed beliefs that circumcised men can increase their sexual risk behavior[15] and where risk behavior was already shown to increase slightly during the circumcision trial[13]. Finally, programs must be evaluated on their effectiveness, with particular emphasis on whether changes in sexual risk behavior have occurred.

In summary, even modest expanded male circumcision programs can confer substantial health benefits to males and females in South Africa and other populations with similar epidemic profiles and these programs should be implemented immediately. Although these findings were sensitive to the impact of circumcision on subsequent risk behavior, all programs resulting in decreased risk behavior and even most programs resulting in increased risk behavior would still be beneficial. Programs to reduce risk

behavior will remain an important component of successful prevention programs, including circumcision programs.

REFERENCES

1. UNAIDS. 2006 report on the global AIDS epidemic. Joint United Programme on HIV/AIDS, May 2006. Available at: http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp.

2. Fink AJ. A possible explanation for heterosexual male infection with AIDS. *N Engl J Med* 1986; **315**:1167.

3. Simonsen JN, Cameron DW, Gakinya MN, Ndinya-Achola JO, D'Costa LJ, Karasira P, Cheang M, Ronald AR, Piot P and Plummer FA. Human immunodeficiency virus infection among men with sexually transmitted diseases. Experience from a center in Africa. *N Engl J Med* 1988; **319**:274-278.

4. Weiss HA, Quigley MA and Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. *AIDS* 2000; **14**:2361-2370.

5. Siegfried N, Muller M, Deeks J, Volmink J, Egger M, Low N, Walker S and Williamson P. HIV and male circumcision--a systematic review with assessment of the quality of studies. *Lancet Infect Dis* 2005; **5**:165-173.

6. Baeten JM, Richardson BA, Lavreys L, Rakwar JP, Mandaliya K, Bwayo JJ and Kreiss JK. Female-to-male infectivity of HIV-1 among circumcised and uncircumcised Kenyan men. *J Infect Dis* 2005; **191**:546-553.

7. Gray RH, Kiwanuka N, Quinn TC, Sewankambo NK, Serwadda D, Mangen FW, Lutalo T, Nalugoda F, Kelly R, Meehan M, Chen MZ, Li C, Wawer MJ and the Rakai Project Team. Male circumcision and HIV acquisition and transmission: cohort studies in Rakai, Uganda. *AIDS* 2000; **14**:2371-2381.

8. Meier AS, Bukusi EA, Cohen CR and Holmes KK. Independent association of hygiene, socioeconomic status, and circumcision with reduced risk of HIV infection among Kenyan men. *J Acquir Immune Defic Syndr* 2006; **43**:117-118.

9. Gray R, Azire J, Serwadda D, Kiwanuka N, Kigozi G, Kiddugavu M, Nalugoda F, Li X and Wawer M. Male circumcision and the risk of sexually transmitted infections and HIV in Rakai, Uganda. *AIDS* 2004; **18**:2428-2430.

10. Auvert B, Buve A, Ferry B, Carael M, Morison L, Lagarde E, Robinson NJ, Kahindo M, Chege J, Rutenberg N, Musonda R, Laourou M, Akam E and the Study Group on the Heterogeneity of HIV Epidemics in African Cities. Ecological and individual level analysis of risk factors for HIV infection in four urban populations in sub-Saharan Africa with different levels of HIV infection. *AIDS* 2001; **15 Suppl 4**:S15-30.

11. Auvert B, Buve A, Lagarde E, Kahindo M, Chege J, Rutenberg N, Musonda R, Laourou M, Akam E, Weiss HA and the Study Group on the Heterogeneity of HIV Epidemics in African Cities. Male circumcision and HIV infection in four cities in sub-Saharan Africa. *AIDS* 2001; **15 Suppl 4**:S31-40.

12. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, Meehan MO, Lutalo T, Gray RH and the Rakai Study Group. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000; **342**:921-929.

13. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R and Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med* 2005; **2**:e298.

14. Anonymous. Adult male circumcision significantly reduces risk of acquiring HIV: Trials in Kenya and Uganda stopped early. National Institutes of Health News Release, December 13, 2006. Available at: http://www.nih.gov/news/pr/dec2006/niaid-13.htm.

15. Lagarde E, Dirk T, Puren A, Reathe R-T and Auvert B. Acceptability of male circumcision as a tool for preventing HIV infection in a highly infected community in South Africa. *AIDS* 2003; **17**:89-95.

16. Quinn TC. Circumcision and HIV transmission: the cutting edge [120]. Paper presented at: 13th Conference on Retroviruses & Opportunistic Infections; 2006; Denver, Colorado.

17. Scott BE, Weiss HA and Viljoen JI. The acceptability of male circumcision as an HIV intervention among a rural Zulu population, Kwazulu-Natal, South Africa. *AIDS Care* 2005; **17**:304-313.

18. Ngalande RC, Levy J, Kapondo CPN and Bailey RC. Acceptability of male circumcision for prevention of HIV infection in Malawi. *AIDS & Behavior* 2006; **10**:377-385.

19. Halperin DT, Fritz K, McFarland W and Woelk G. Acceptability of adult male circumcision for sexually transmitted disease and HIV prevention in Zimbabwe. *Sex Transm Dis* 2005; **32**:238-239.

20. Kebaabetswe P, Lockman S, Mogwe S, Mandevu R, Thior I, Essex M and Shapiro RL. Male circumcision: an acceptable strategy for HIV prevention in Botswana. *Sex Transm Infect* 2003; **79**:214-219.

21. Rain-Taljaard RC, Lagarde E, Taljaard DJ, Campbell C, MacPhail C, Williams B and Auvert B. Potential for an intervention based on male circumcision in a South African town with high levels of HIV infection. *AIDS Care* 2003; **15**:315-327.

22. Tsela S and Halperin D. Knowledge, attitudes and practices regarding male circumcision in the Manzini (central) region of Swaziland [CDC0611]. Paper presented at: XVI International AIDS Conference; 2006; Toronto.

23. Williams BG, Lloyd-Smith JO, Gouws E, Hankins C, Getz WM, Hargrove J, de Zoysa I, Dye C and Auvert B. The potential impact of male circumcision on HIV in sub-Saharan Africa. *PLoS Med* 2006; **3**:1032-1040.

24. Kahn JG, Marseille E and Auvert B. Cost-effectiveness of male circumcision for HIV prevention in a South African setting. *PLoS Med* 2006; **3**:2349-2358.

25. Cassell MM, Halperin DT, Shelton JD and Stanton D. Risk compensation: the Achilles' heel of innovations in HIV prevention? *BMJ* 2006; **332**:605-607.

26. Wegbreit J, Bertozzi S, DeMaria LM and Padian NS. Effectiveness of HIV prevention strategies in resource-poor countries: tailoring the intervention to the context. *AIDS* 2006; **20**:1217-1235.

27. Agot KE, Kiarie JN, Nguyen HQ, Odhiambo JO, Onyango TM and Weiss NS. Male circumcision in Siaya and Bondo Districts, Kenya: prospective cohort study to assess behavioral disinhibition following circumcision. *J Acquir Immune Defic Syndr* 2007; **44**:66-70.

28. Clark J. Male circumcision is not a panacea for HIV prevention. *BMJ* 2006; **333**:409.

29. Auerbach JD, Hayes RJ and Kandathil SM. Overview of effective and promising interventions to prevent HIV infection. *World Health Organ Tech Rep Ser* 2006; **938**:43-78; discussion 317-341.

30. Wise J. Demand for male circumcision rises in a bid to prevent HIV. *Bull World Health Organ* 2006; **84**:509-511.

31. Atashili J. Adult male circumcision to prevent HIV? *Int J Infect Dis* 2006; **10**:202-205.

32. Cohen J. Prevention cocktails: combining tools to stop HIV's spread. *Science* 2005; **309**:1002-1005.

33. Jones R, Gazzard B and Halima Y. Preventing HIV infection. *BMJ* 2005; **331**:1285-1286.

34. Beukes L. Caution on circumcision cuts South Africa's AIDS researchers. *Nat Med* 2005; **11**:1261.

35. Roehr B. Dramatic drop in HIV infections halts circumcision trials. *BMJ* 2007; **334**:11.

36. Hankins C, De Zoysa I, Alnwick D, Ntaganira I, Schmid G, Farley T, Collins L, Edouard L, Jackson H, Beger G, Mulenga D, O'Reilly K, Dick B, Kraus S, McDermott P

and Stirling M. Laying the policy and programming framework for decision making at country level on the potential role of male circumcision in comprehensive HIV prevention strategies [WEPE0893]. Paper presented at: XVI International AIDS Conference; 2006; Toronto.

37. Mesesan K, Owens DK and Paltiel AD. The potential benefits of expanded male circumcision programs in Africa: Predicting the population-level impact on heterosexual HIV transmission in Soweto [TUAC0203]. Paper presented at: XVI International AIDS Conference; 2006; Toronto.

38. Edwards DM, Shachter RD and Owens DK. A dynamic HIV-transmission model for evaluating the costs and benefits of vaccine programs. *Interfaces* 1998; **28**:144-166.

39. Owens DK, Edwards DM and Shachter RD. Population effects of preventive and therapeutic HIV vaccines in early- and late-stage epidemics. *AIDS* 1998; **12**:1057-1066.

40. Brandeau ML, Owens DK, Sox CH and Wachter RM. Screening women of childbearing age for human immunodeficiency virus. A cost-benefit analysis. *Arch Intern Med* 1992; **152**:2229-2237.

41. Anderson RM, Gupta S and May RM. Potential of community-wide chemotherapy or immunotherapy to control the spread of HIV-1. *Nature* 1991; **350**:356-359.

42. McLean AR and Blower SM. Imperfect vaccines and herd immunity to HIV. *Proc Biol Sci* 1993; **253**:9-13.

43. Shisana O and Simbayi L. *Nelson Mandela/HSRC study of HIV/AIDS: South African national HIV prevalence, behavioural risks and mass media: Household survey 2002.* Cape Town: Human Sciences Research Council Press; 2002.

44. Pettifor AE, Rees HV, Kleinschmidt I, Steffenson AE, MacPhail C, Hlongwa-Madikizela L, Vermaak K and Padian NS. Young people's sexual health in South Africa: HIV prevalence and sexual behaviors from a nationally representative household survey. *AIDS* 2005; **19**:1525-1534.

45. Anonymous. Male circumcision and HIV. UNAIDS & WHO Fact Sheet, December, 2006. Available at: http://data.unaids.org/pub/FactSheet/2007/20061229_mc_fs_en.pdf.

46. Simbayi L, Strebel A, Wilson T, Andipatin M, Msomi N, Potgieter C, Ratele K and Shefer T. *Sexually transmitted diseases in the South African public sector*: National Department of Health's Directorate of Health Systems Research and Epidemiology in conjunction with the Directorate of HIV/AIDS and STDs; August 1999.

47. Williams BG, Taljaard D, Campbell CM, Gouws E, Ndhlovu L, Van Dam J, Carael M and Auvert B. Changing patterns of knowledge, reported behaviour and sexually transmitted infections in a South African gold mining community. *AIDS* 2003; **17**:2099-2107.

48. Pettifor AE, Measham DM, Rees HV and Padian NS. Sexual power and HIV risk, South Africa. *Emerg Infect Dis* 2004; **10**:1996-2004.

49. Ackermann L and de Klerk GW. Social factors that make South African women vulnerable to HIV infection. *Health Care Women Int* 2002; **23**:163-172.

50. Anonymous. Progress on global access to HIV antiretroviral therapy: a report on "3 by 5" and beyond. WHO & UNAIDS, March, 2006. Available at: http://www.who.int/hiv/fullreport_en_highres.pdf.

51. Desai K, Boily MC, Garnett GP, Masse BR, Moses S and Bailey RC. The role of sexually transmitted infections in male circumcision effectiveness against HIV - insights from clinical trial simulation. *Emerg Them Epid* 2006; **3**:19.

52. Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, Wabwire-Mangen F, Lutalo T, Li X, vanCott T, Quinn TC and the Rakai Project Team. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet* 2001; **357**:1149-1153.

53. Gray RH, Li X, Wawer MJ, Gange SJ, Serwadda D, Sewankambo NK, Moore R, Wabwire-Mangen F, Lutalo T, Quinn TC and the Rakai Project Group. Stochastic

simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission; Rakai, Uganda. *AIDS* 2003; **17**:1941-1951.

54. Gray RH, Wawer MJ, Thoma M, Serwadda D, Nalugoda F, Li X, Kigozi G, Kiwanuka N, Laeyendecker O and Quinn TC. Male circumcision and the risks of female HIV and sexually transmitted infections acquisition in Rakai, Uganda [128]. Paper presented at: 13th Conference on Retroviruses & Opportunistic Infections; 2006; Denver, Colorado.

55. Norris Turner A, Morrison C, Padian N, Salata R and Miller W. Men's circumcision status and women's risk of HIV: a longitudinal analysis of Zimbabwean and Ugandan women [TUPE0457]. Paper presented at: XVI International AIDS Conference; 2006; Toronto.

56. Pettifor AE, Rees HV, Steffenson A, Hlonga-Madikizela L, MacPhail C, Vermaak K and Kleinschmidt I. *HIV and sexual behavior among young South Africans: a national survey of 15-24 year olds.* Johannesburg: Reproductive Health Research Unit, University of the Witwatersrand; April 6 2004.

57. Shisana O, Rehle T, Simbayi LC, Parker W, Zuma K, Bhana A, Connolly C, Jooste S and Pillay V. *South African national HIV prevalence, HIV incidence, behaviour and communication survey, 2005.* Cape Town: HSRC Press; 2005.

58. Anonymous. *Monitoring review: Progress report on the implementation of the comprehensive HIV and AIDS care, management and treatment programme*: Department of Health, South Africa; September 2004.

59. Dorrington R, Bradshaw D, Johnson L and Budlender D. *The demographic impact of HIV/AIDS in South Africa: national indicators for 2004.* Cape Town: University of Cape Town Centre for Actuarial Research, South African Medical Research Council Burden of Disease Research Unit, & Actuarial Society of South Africa; 2004.

60. Fideli US, Allen SA, Musonda R, Trask S, Hahn BH, Weiss H, Mulenga J, Kasolo F, Vermund SH and Aldrovandi GM. Virologic and immunologic determinants of

heterosexual transmission of human immunodeficiency virus type 1 in Africa. *AIDS Res Hum Retroviruses* 2001; **17**:901-910.

61. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, Kiwanuka N, Kigozi G, Kiddugavu M, Lutalo T, Nalugoda F, Wabwire-Mangen F, Meehan MP and Quinn TC. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis* 2005; **191**:1403-1409.

62. Mesesan K, Van Niekirk RM, Niccolai LM, Mlungwana ON, Holdsworth IM, Bogoshi M, McIntyre JA, Gray GE and Vardas E. Self-reported sexual risk behaviors of a cohort being prepared for multiple Phase I/II HIV vaccine trials in Soweto, South Africa [OA06-05]. Paper presented at: AIDS Vaccine International Conference; 2006; Amsterdam.

63. Simbayi LC, Chauveau J and Shisana O. Behavioural responses of South African youth to the HIV/AIDS epidemic: a nationwide survey. *AIDS Care* 2004; **16**:605-618.

64. Anonymous. *Workshop summary: scientific evidence of condom effectiveness for sexually transmitted disease (STD) prevention.* Herndon, Virginia: National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services; June 12-13 2000.

65. Morgan D, Mahe C, Mayanja B, Okongo JM, Lubega R and Whitworth JA. HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? *AIDS* 2002; **16**:597-603.

66. Anonymous. *Mid-year population estimates, South Africa: 2004.* Pretoria: Statistics South Africa; July 27 2004.

67. Anonymous. ASSA2000 Model. Actuarial Society of South Africa, 2004. Available at: http://www.assa.org.za/.

68. Anonymous. 2001 South African Census. Statistics South Africa, 2004. Available at: www.statssa.gov.za.

69. Anonymous. HIV Prevalence, Incidence, Behavior and Communication Survey 2005. Centre for AIDS Development, Research and Evaluation, 2006. Available at: www.cadre.org.za.

TABLE 1. Parameter values

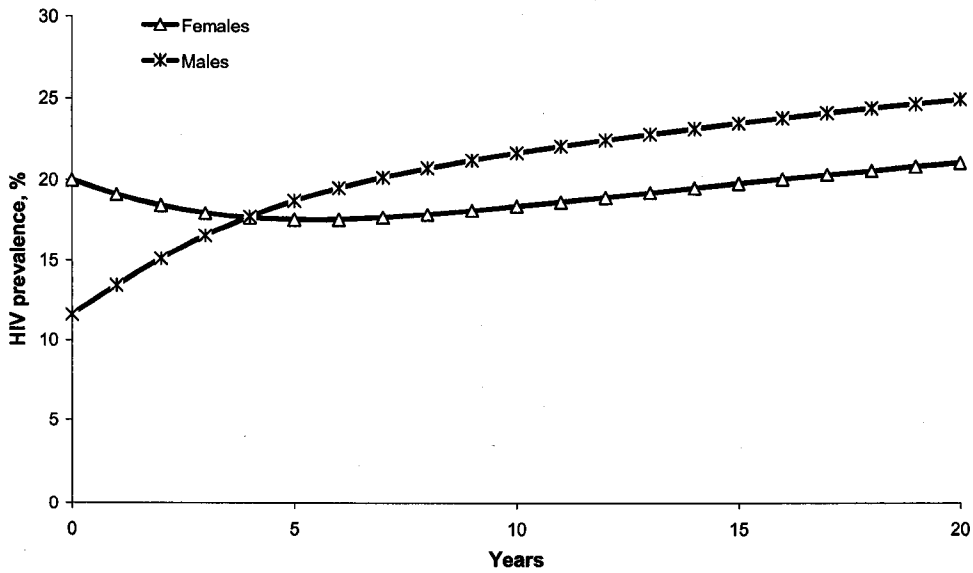
Parameter name	Symbol	Value[a]	Source
Preventive circumcision program parameters			
Percentage of uncircumcised uninfected or uncircumcised asymptomatic HIV+ males circumcised annually	$\kappa(t)$	0.10-0.20, t≤5 0, t>5	Assumption
Circumcision protective effect (percent of partnerships protected from infection)	ε	0.61 (0-1.0)	[13]
Change in (male-negotiated) condom use following circumcision, for males circumcised as adults, or following circumcision program implementation, for males previously circumcised in childhood[b]	Δ	1.0 (0-2.0)	Assumption
HIV transmission parameters			
Male infectivity (per-partner probability of transmission to a female)			
Asymptomatic period of HIV infection	$\beta_{M1,j}$	0.0684	[12,52,53,61]
Symptomatic period of HIV infection	$\beta_{M2,j}$	0.1657	[12,52,53,61]
Female infectivity (per-partner probability of transmission to a male)			
Asymptomatic period of HIV infection	β_{W1}	0.1112	[12,52,53,61]
Symptomatic period of HIV infection	β_{W2}	0.2697	[12,52,53,61]
Contact rate (number of new partners per year) of males or females			
Uninfected	ρ_0	3	[62]
HIV infected, asymptomatic period	ρ_1	3	[62]
HIV infected, symptomatic period	ρ_2	1	Assumption
HIV infected, AIDS	ρ_3	0	Assumption
Baseline (male-negotiated) condom use for all partnerships (without implementation of an adult male circumcision program)	$h_{i,j}$	0.5	[44,56,57,62,63]
Condom failure rate for all partnerships	f	0.14	[64]
HIV disease duration parameters			
Asymptomatic HIV infection (years)	$1/\mu_1$	6.8	[38,39,65]
Symptomatic HIV infection (years)	$1/\mu_2$	2.6	[38,39,65]
AIDS (years)	$1/\mu_3$	0.8	[65]
Population parameters, heterosexual men/women > 16 years			
Mean age (years)		25.1	[66]
Non-AIDS life expectancy (years)		60.8	[67]
Non-AIDS-related annual mortality rate	μ	0.028[c]	[66,67]
Initial population size		823,000	[44,56,57,63,68]
Initial HIV prevalence, male population (%)		11.6	[57]
Initial HIV prevalence, female population (%)		20.0	[57]
Initial circumcision rate, baseline male population (%)		0.35	[43]
Arriving male population HIV prevalence (%)		0.03	[44,56,57,69]
Arriving female population HIV prevalence (%)		0.10	[44,56,57,69]
Arriving male population circumcision rate (%)		0.35	[44]

[a] Values in parentheses are ranges used in sensitivity analyses

[b] e.g. for $\Delta = 1.0$, no change in condom use; for $\Delta = 1.30$, 30% increase in condom use; for $\Delta = 0.70$, 30% decrease in condom use

[c] Calculated [Dissertation Paper 3]

Figure 1A.



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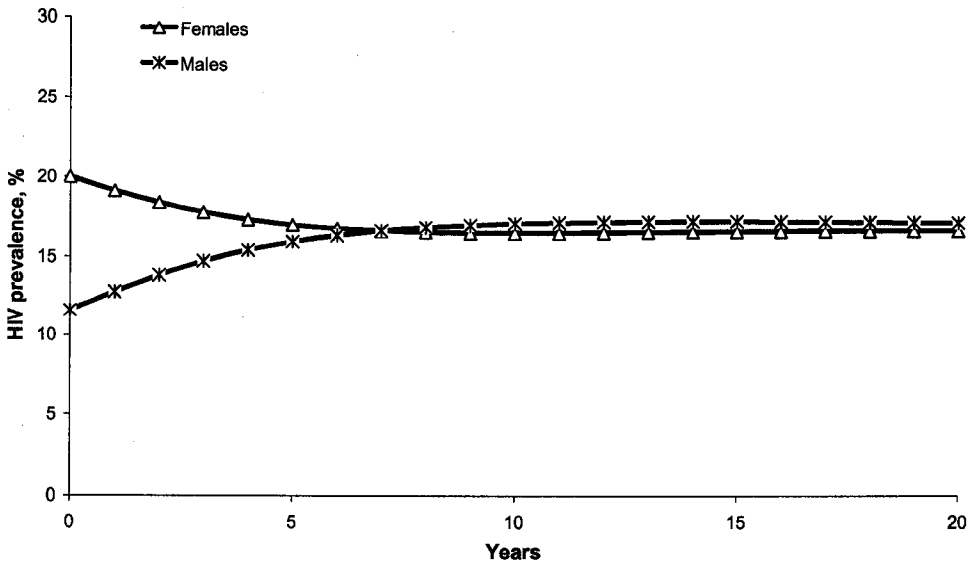

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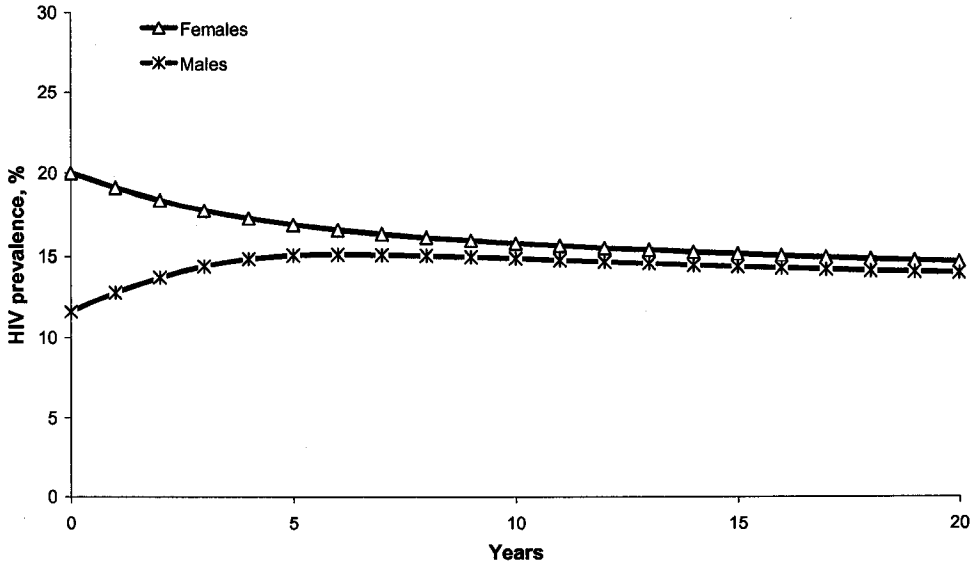

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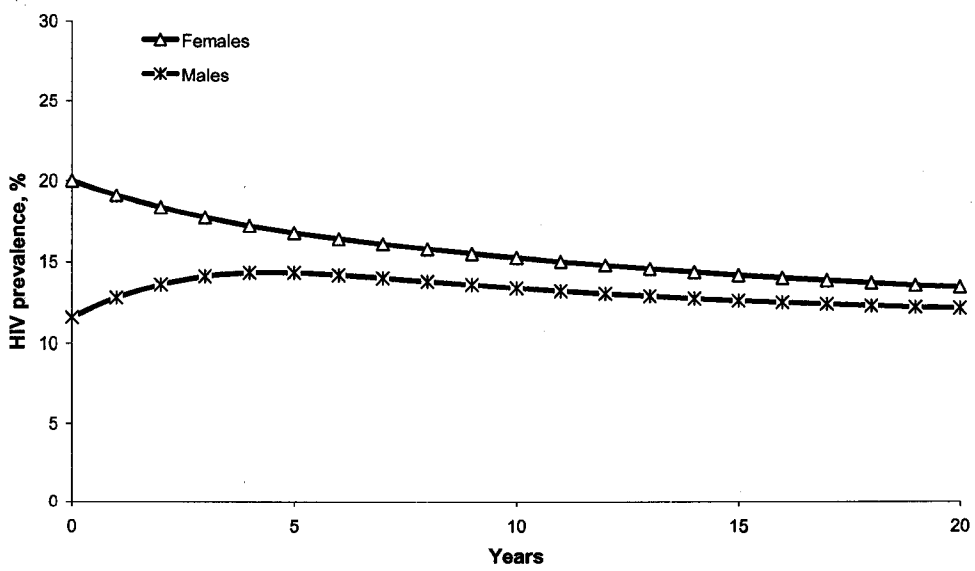

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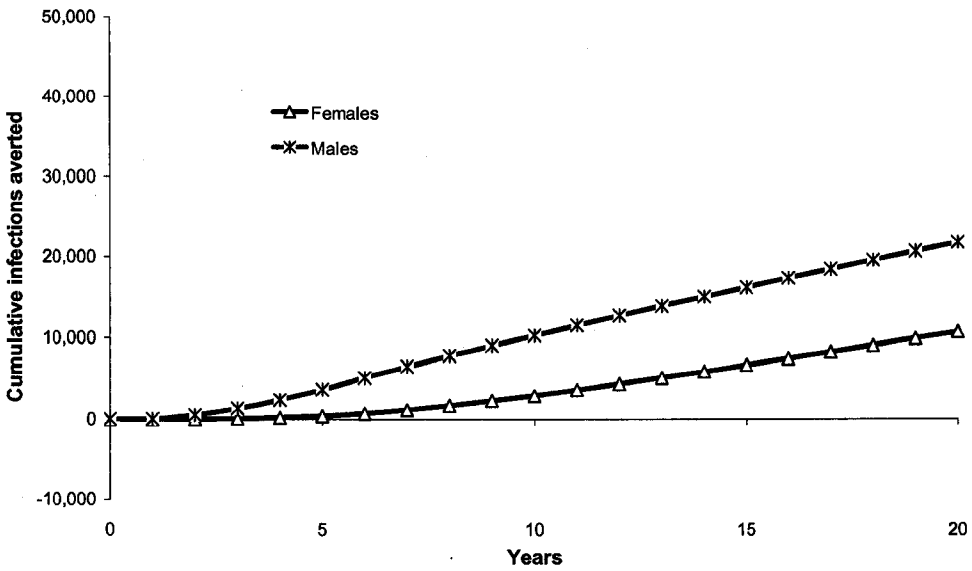
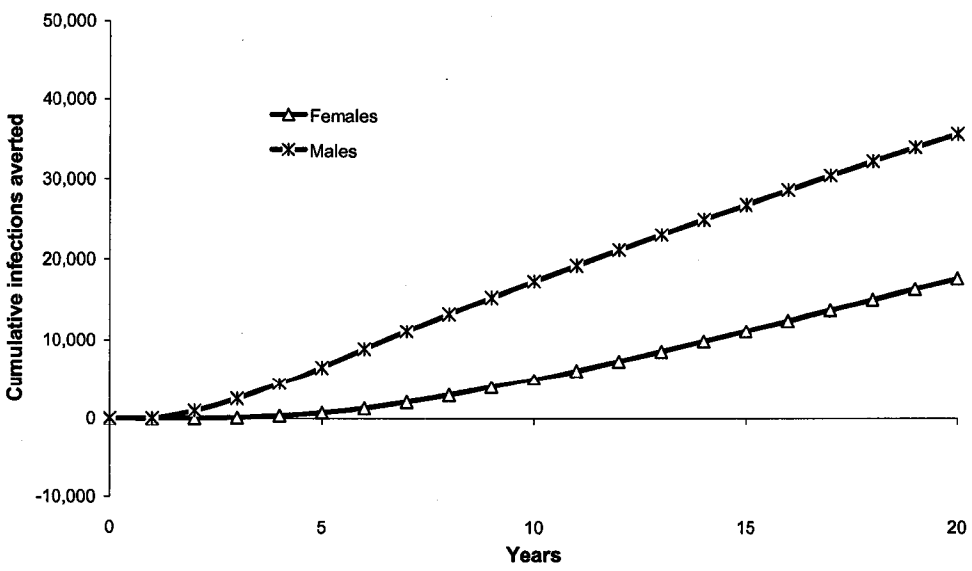


Figure 3B.



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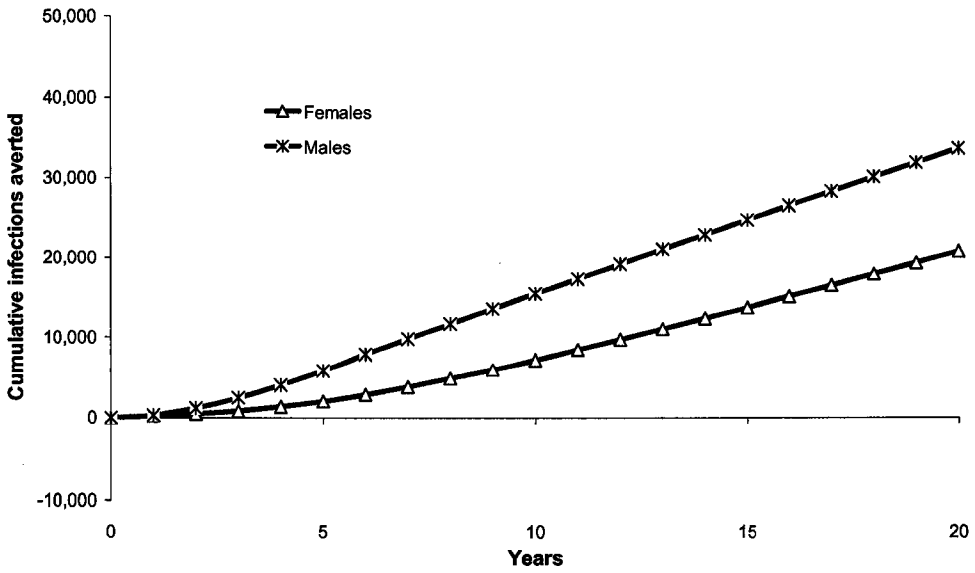

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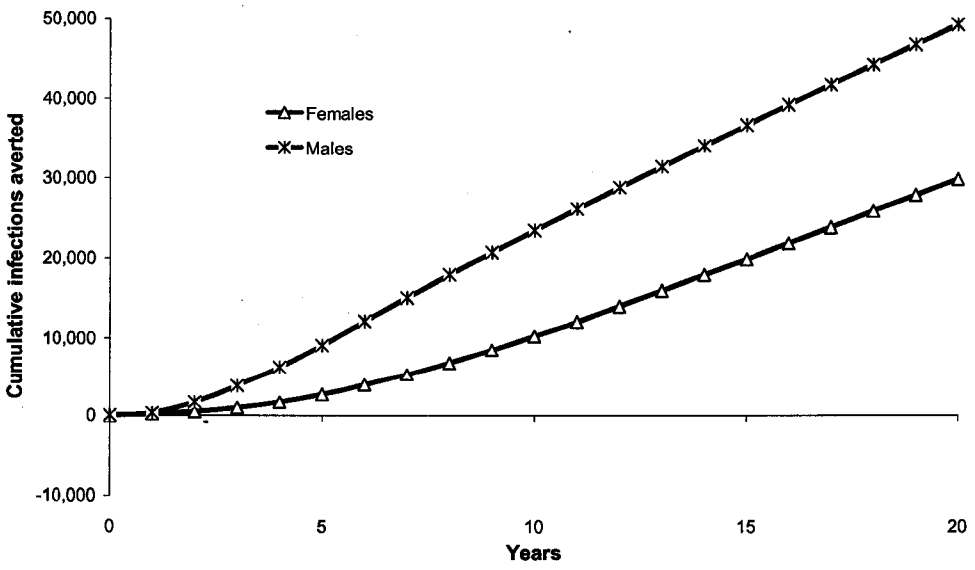

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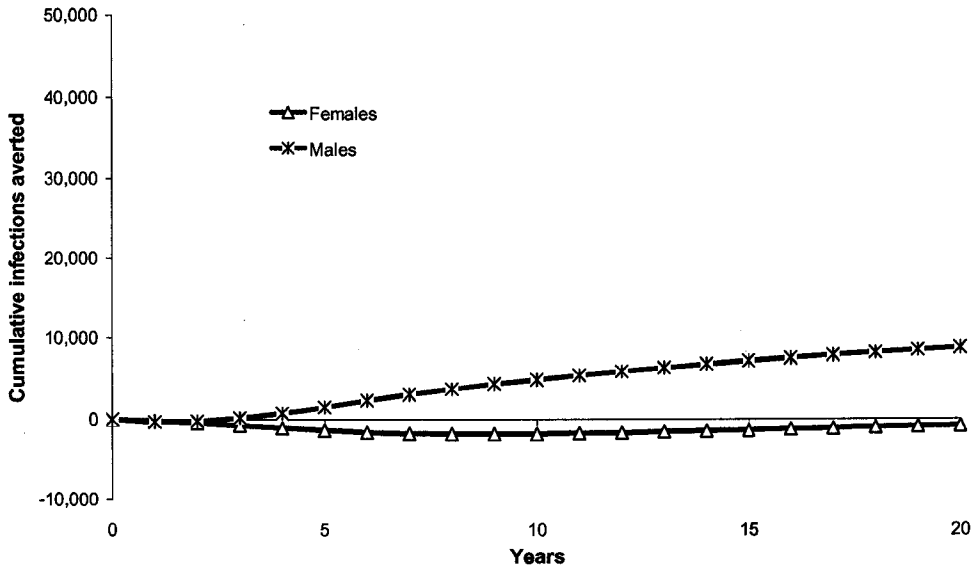

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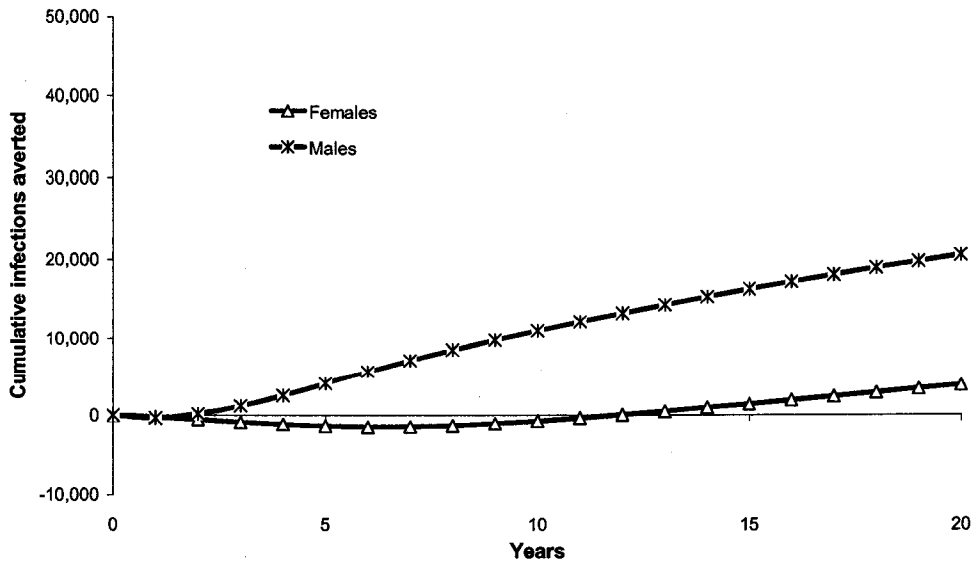
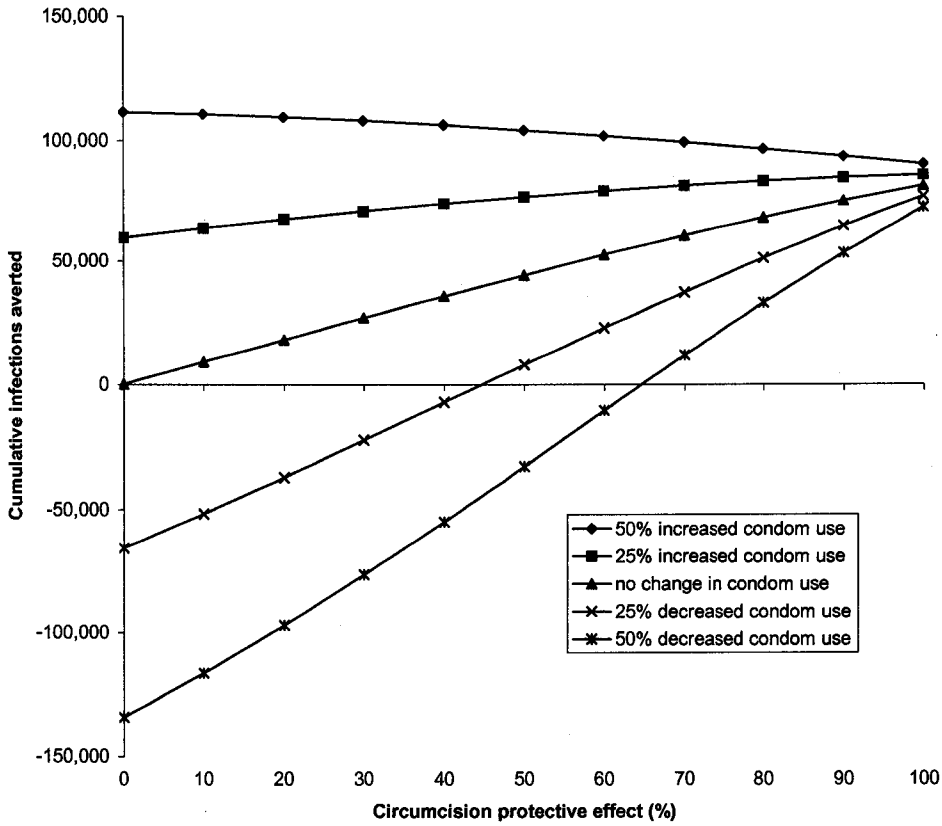


TABLE 2. Sensitivity analysis on potential risk behavior change and protective circumcision effect: total infections prevented after 20 years by various 5-year expanded circumcision programs[a]

Change in condom use post-circumcision[b]	Protective effect on HIV transmission due to circumcision			
	20%[c]	40%[c]	60%[c]	80%[c]
Programs with 10% coverage goals				
Condom use increases by 100%	145,000	126,000	107,000	87,000
Condom use increases by 50%	87,000	81,000	74,000	66,000
Condom use increases by 25%	51,000	53,000	54,000	54,000
No change in condom use	**11,000**	**21,000**	**32,000**	**41,000**
Condom use decreases by 25%	(34,000)	(14,000)	7,000	27,000
Condom use decreases by 50%	(83,000)	(53,000)	(21,000)	12,000
Condom use decreases by 100%	(186,000)	(139,000)	(84,000)	(23,000)
Programs with 20% coverage goals				
Condom use increases by 100%	175,000	158,000	139,000	119,000
Condom use increases by 50%	109,000	106,000	102,000	96,000
Condom use increases by 25%	67,000	73,000	79,000	83,000
No change in condom use	**18,000**	**36,000**	**52,000**	**68,000**
Condom use decreases by 25%	(37,000)	(7,000)	23,000	51,000
Condom use decreases by 50%	(97,000)	(55,000)	(10,000)	33,000
Condom use decreases by 100%	(222,000)	(161,000)	(87,000)	(9,000)

[a] Total infections prevented for male and female populations. Numbers in parentheses represent negative values, which indicate the number of *additional infections* caused by a particular program.
[b] *Considering an increase or decrease in baseline condom use levels of 50%.* A 25% difference implies an absolute increase to 62.5% or decrease to 37.5% in condom use levels. A 50% difference implies an absolute increase to 75% or decrease to 25% in condom use levels. A 100% difference implies an absolute increase to 100% or decrease to 0% in condom use levels.
[c] Total expected infections over 20 years for various circumcision protective effects in the *absence* of expanded circumcision programs: 295,000 (20%); 271,000 (40%); 246,000 (60%); and, 220,000 (80%)

Figure 5.



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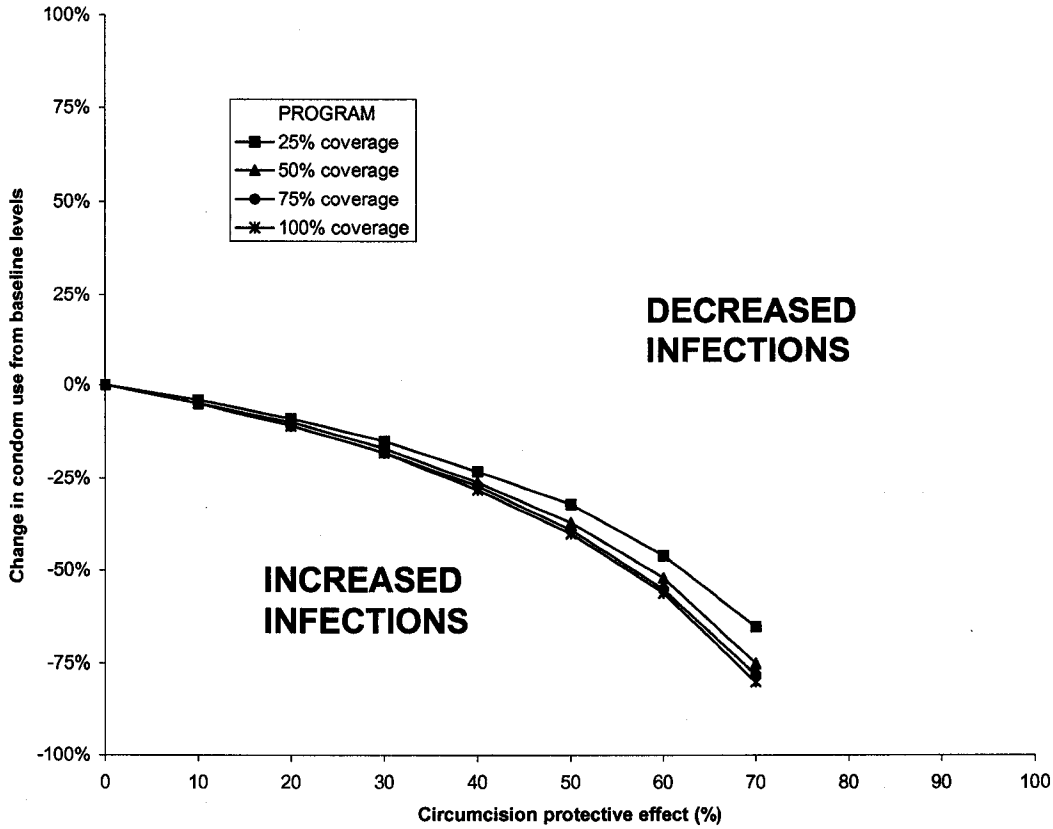
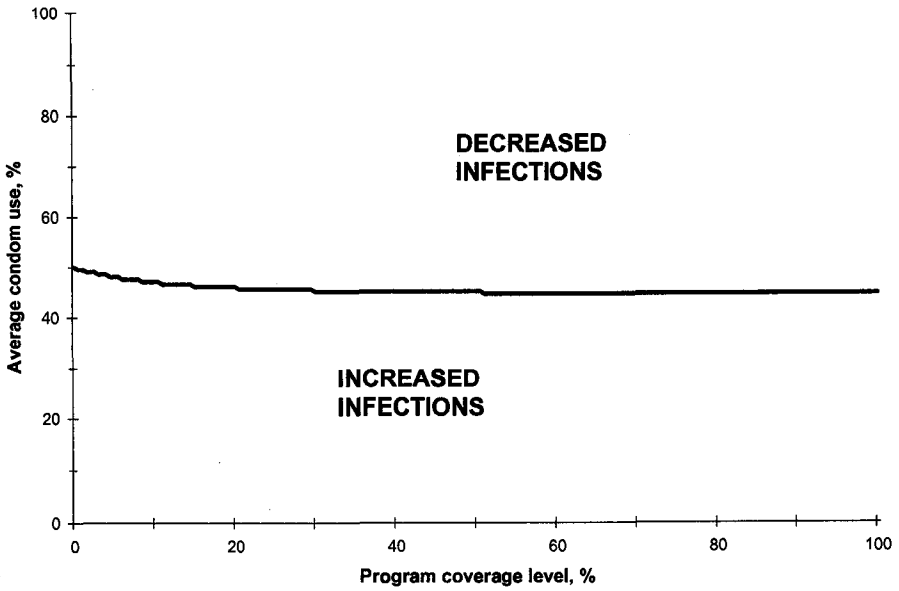


Figure 7A.



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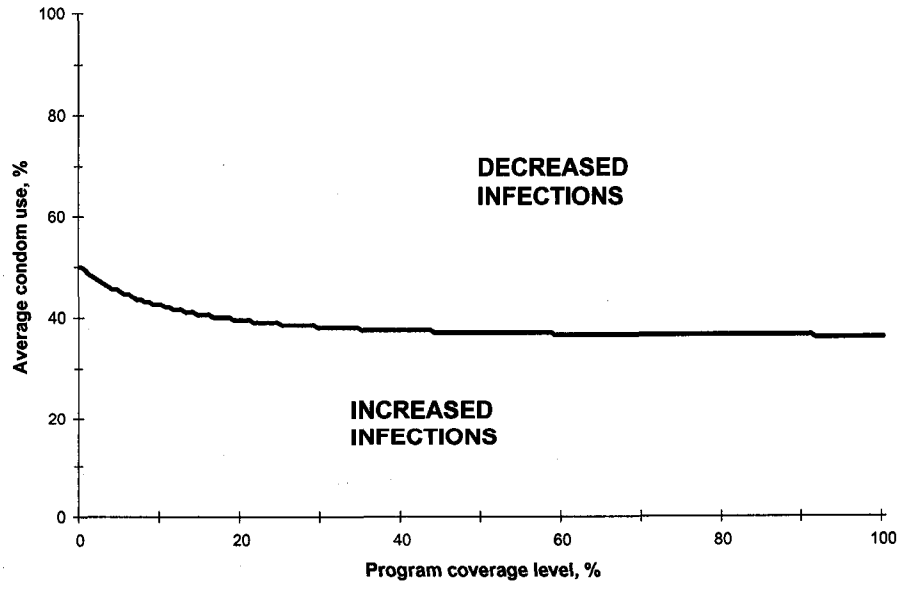

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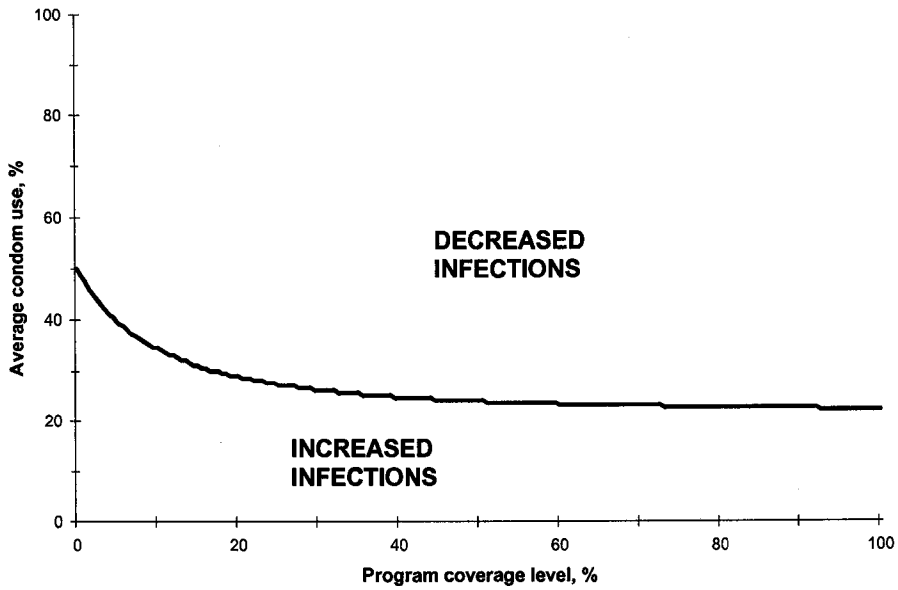

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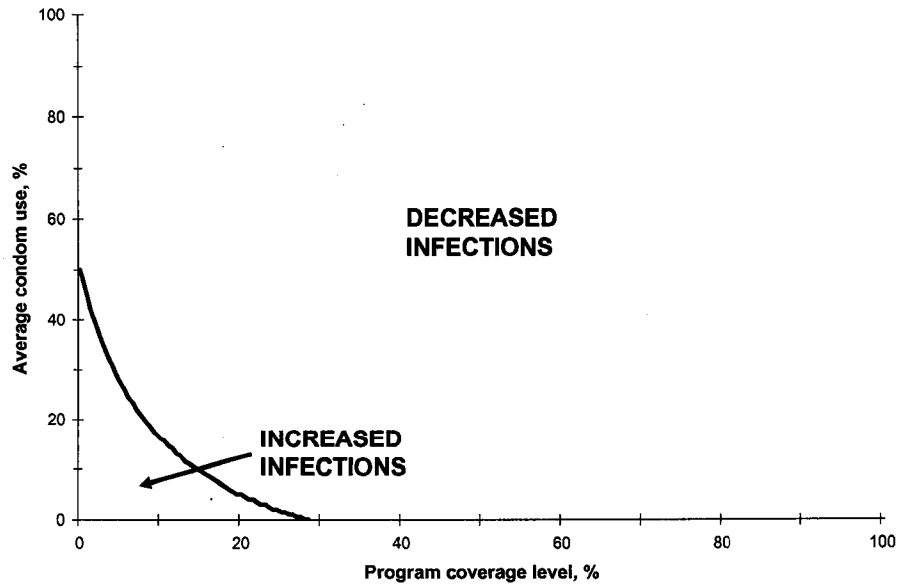

FIGURE CAPTIONS

Figure 1. Predicted trends in Soweto adult HIV prevalence over 20 years for male and female populations: model simulation *without considering* a reduction in HIV transmission due to current rates of male circumcision (panel A); model simulation *considering* a reduction in HIV transmission due to current rates of male circumcision (panel B)

Figure 2. Predicted trends in Soweto adult HIV prevalence over 20 years for male and female populations following implementation of expanded adult male circumcision HIV prevention programs: 5-year programs targeting an additional 10% (panel A) or 20% (panel B) of uncircumcised adult males each year.

Figure 3. Cumulative HIV infections prevented over 20 years for male and female populations following implementation of adult male circumcision HIV prevention programs: 5-year programs targeting an additional 10% (panel A) or 20% (panel B) of uncircumcised adult males each year.

Figure 4. Cumulative infections prevented over 20 years for male and female populations following implementation of adult male circumcision HIV prevention programs and subsequent risk behavior change: effects of a 25% *increase* in condom use on outcomes of 5-year programs targeting an additional 10% (panel A) or 20% (panel B) of uncircumcised adult males each year; effects of a 25% *decrease* in condom use on

outcomes of a 5-year programs targeting an additional 10% (panel C) or 20% (panel D) of uncircumcised adult males each year.

Figure 5. Cumulative number of infections averted after 20 years assuming a range of values for the protective effect of male circumcision on FTM HIV transmission: results for 5-year circumcision programs with 20% coverage goals and various levels of change in condom use behavior following program implementation (50% increased condom use, 25% increased condom use, no change in condom use, 25% decreased condom use, 50% decreased condom use).

Figure 6. Equivalence graph showing circumcision programs which would result in the program having no net effect (e.g. the total number of infections prevented 20 years following program implementation is zero) for combinations of circumcision protective effect (0% to 100%) and post-circumcision condom use (from a baseline condom use of 50%): results for 5-year circumcision programs with various levels of coverage levels (25%, 50%, 75%, and 100%) after 20 years.

Figure 7. Equivalence graphs showing all combinations of 5-year program coverage levels (targeting an additional proportion of uncircumcised males each year) and post-circumcision condom use (from a baseline condom use of 50%) which would result in the program having no net effect, e.g. the total number of infections prevented 20 years following program implementation is zero. Results are shown for reductions in FTM HIV transmission due to male circumcision of 20% (panel A), 40% (panel B), 60%

(panel C), and 80% (panel D). All programs for adult male circumcision with various coverage levels and changes in risk behavior values placing them above the curve will prevent infections, while all programs with various coverage levels and changes in risk behavior values placing them below the curve will cause additional infections.

APPENDIX

Further information on the mathematical model used for predicting the impact of expanded adult male circumcision programs is detailed in this Appendix.

The model defines ten health states, and only certain movements between these health states are allowed: Women can move from the HIV-negative compartment (state 1) to the asymptomatic HIV-positive compartment (state 4) by acquiring HIV infection from an infected male partner, and can move to the symptomatic HIV-positive (state 7) and AIDS (state 9) compartments as a result of subsequent disease progression. Men can move from the uncircumcised HIV-negative (state 2) and the asymptomatic HIV-positive (state 5) compartments to the circumcised HIV-negative (state 3) and asymptomatic HIV-positive (state 6) compartments by undergoing a circumcision procedure as a result of an expanded adult male circumcision program. Men can move from the uncircumcised (state 2) or circumcised (state 3) HIV-negative compartments to the uncircumcised (state 5) or circumcised (state 6) asymptomatic HIV-positive compartments, respectively, by acquiring HIV infection from an infected female partner, and can move to the symptomatic HIV-positive (state 8) and AIDS (state 10) compartments as a result of subsequent disease progression.

For the symptomatic HIV-positive and AIDS states, circumcised and uncircumcised males can be analyzed within the same compartment because they are already infected and thus circumcision does not afford them any further protection, nor does it influence their ability to transmit HIV to uninfected women. While we modeled risk behavior changes for men who are circumcised but HIV-negative or in the asymptomatic stage of HIV infection, we made the assumption that circumcised men in the symptomatic stage

of infection were aware of their HIV status and thus did not increase their risk behavior. Men in the AIDS state were modeled to have no sexual partners, but if this value were to change then this assumption would also be made for the AIDS state.

We define the model variables and the ten differential equations which govern transitions between the various compartments in the model in Tables 2 and 3. The equation number corresponds to the rate of change for individuals in the state or compartment of the same number, as indicated above. As an example, we explain how equation (2) describes the rate of change of the male [$M_{i,j}$] uncircumcised [$j = 0$], HIV-negative [$i = 0$] sexually active population at time t:

$$(2) \quad \frac{dM_{0,0}(t)}{dt} = I_{M0,0} - \kappa(t)M_{0,0}(t) - \mu M_{0,0}(t) - p_0\lambda_M(t)M_{0,0}(t)$$

This rate depends on the following terms: (a) $I_{M0,0}$, the number of uncircumcised, HIV-negative males who arrive into the sexually active population each year upon reaching the age of 17 years; (b) $\kappa(t)M_{0,0}(t)$, the number of uncircumcised, HIV-negative males [$M_{0,0}(t)$] who are circumcised each year [proportion $\kappa(t)$ of the uncircumcised HIV-negative or asymptomatic HIV-positive males who are circumcised each year under the expanded program]; (c) $\mu M_{0,0}(t)$, the number of uncircumcised, HIV-negative males [$M_{0,0}(t)$] who die each year due to non-AIDS related causes [non-AIDS mortality rate, μ]; and, (d) $p_0\lambda_M(t)M_{0,0}(t)$, the number of uncircumcised HIV-negative males [$M_{0,0}(t)$] who become infected with HIV [per-partnership probability of an unvaccinated male acquiring HIV from any female at time t, $\lambda_M(t)$] each year from a female partner [number of female partners per year for an uninfected male, p_0].

Additional equations define rates of change for the number of men and women in the nine other compartments in a similar manner.

We modeled HIV transmission on a per-partnership basis such that the HIV infectivity parameters simulated the total probability of transmission during the course of a sexual partnership rather than during a single sex act, as previously described [Dissertation Paper 3]. We modeled the protective effect of circumcision as partial protection for males on an individual level. Equation (3) in Table 3 shows that circumcised males experience a reduced rate of HIV infection by a factor of $(1-\varepsilon)$ when they are exposed to HIV-positive partners. Therefore, a circumcision protective effect of 61% ($\varepsilon = 0.61$) would provide protection from 61% of sexual partnerships between an uninfected circumcised male and an infected female partner Another way of saying this is that being circumcised would reduce the probability of HIV infection for males in that sexual partnership by 61%. Factors influencing the rate of HIV infection for uninfected men and women in the model, in addition to whether the male in a sexual partnership is circumcised, include the number of sexual partners they have per year, the condom use behaviors within each sexual partnership, and the 'force' of infection to which an uninfected individual is exposed.

The force of infection is the probability of acquiring HIV from any partner at a given point in time and is defined by equations (11), (12), and (13) in Table 3. As an example, we explain how equation (11) describes the force of infection which an uncircumcised uninfected male experiences at time t :

$$(11)\ \lambda_M(t) = \frac{n_{M0,0}\sum_{i=1}^{i=3}\rho_i\beta_{Wi}W_i(t)}{\sum_{i=0}^{i=3}\rho_i W_i(t)}$$

Given all of the potential heterosexual partnerships that are possible, the probability that this male becomes infected with HIV is determined by the likelihood that he chooses an HIV-infected female partner $[\sum_{i=1}^{i=3} p_i W_i(t) \Big/ \sum_{i=0}^{i=3} p_i W_i(t)]$ and the likelihood that HIV is transmitted during the course of that sexual partnership $[\sum_{i=1}^{i=3} \beta_{Wi}]$, both of which depend on the disease stage of the female partner. The probability that this male becomes infected with HIV also depends on the condom use within that partnership, which in this case is $n_{M0,0}$.

In general, the condom use term $n_{Mi,j}$ describes the probability that a particular sexual partnership between a male with disease stage i and circumcision status j and a female with disease stage i is *not* protected by condoms, and incorporates the idea that condom use is male-negotiated (see Table 2 for equations). In equation (11), condom use $n_{M0,0}$ within a partnership between an uncircumcised uninfected male and any female is based solely on his own condom use behavior. In equation (12), condom use $n_{M0,1}$ within a partnership between a circumcised uninfected male and any female is also based solely on his own condom use behavior, although his condom use behavior may have changed following the implementation of expanded circumcision programs. On the other hand, in equation (13), condom use $\sum_{i=1}^{i=3} \sum_{j=0}^{j=1} n_{Mi,j}$ in a partnership with an uninfected female, being male-negotiated, is based on all of the male partners she might encounter and their summed individual probabilities of condom use behaviors.

We assumed equal numbers of men and women in the population initially. For

HIV-infected individuals in the starting population, we assumed a distribution of men or women at various stages of HIV disease which was proportional to the relative length of each stage. We modeled a constant arriving population of 17-year-old sexually-active adults, of whom some were already infected with HIV, as previously described [Dissertation Paper 3]. Arriving females entered either the HIV-negative or asymptomatic HIV-positive populations, whereas arriving males entered the uncircumcised and circumcised HIV-negative or uncircumcised and circumcised asymptomatic HIV-negative populations. We assumed that the proportion of circumcised males in the arriving population was identical for both uninfected and infected individuals. While the true circumcision rate likely differs between uninfected and infected males due to the protective effect of circumcision, the HIV prevalence in arriving 17-year old males is only 3% and therefore this effect would be minimal. The model structure allows for this differentiation in the arriving population and thus this question could be further addressed either with assumptions on the difference in circumcision rate between these groups or with data collected on circumcision prevalence in adolescent boys by HIV status when they become available.

Only procedures performed as part of the expanded adult male circumcision programs described here have been modeled; we did not allow for adult males who might undergo circumcision independently of these programs. We assumed that the protection afforded to males by circumcision was uniform for various HIV virus subtypes.

TABLE 2 (APPENDIX). Definition of model variables

Description of variable	Symbol
Disease stage, males and females (*i*)	
Uninfected (HIV-negative)	$i=0$
Infected (HIV-positive) asymptomatic	$i=1$
Infected (HIV-positive) symptomatic	$i=2$
AIDS	$i=3$
Circumcision status, males only (*j*)	
Uncircumcised	$j=0$
Circumcised	$j=1$
Disease-stage specific variables	
Number of men in disease stage *i* with circumcision status *j* at time *t*	$M_{i,j}(t)$
Number of women in disease stage *i* at time *t*	$W_i(t)$
Probability of a male acquiring the infection at time *t* from any one female partner	$\lambda_M(t)$
Probability of a male acquiring the infection at time *t* from any one female partner, under behavior modifications due to male circumcision	$\lambda_{M\kappa}(t)$
Probability of a female acquiring the infection at time *t* from any one male partner	$\lambda_W(t)$
Per-partner infectivity (chance of transmitting HIV) of a male in disease stage *I* with circumcision status *j*	$\beta_{Mi,j}$
Per-partner infectivity (chance of transmitting HIV) of a female in disease stage *i*	β_{Wi}
Contact rate (number of new partners per year) of males or females in disease stage *i*	ρ_i
Mean duration (in years) of disease stage *i*	$1/\mu_i$
Annual immigration of males in disease stage *i* with circumcision status *j*	$I_{Mi,j}$
Annual immigration of females in disease stage *i*	I_{Wi}
Probability a partnership between an uninfected, uncircumcised male and a female with disease stage *i* is not protected by condoms[a]	$n_{M0,0}$
Probability a partnership between an uninfected, circumcised male and a female with disease stage *i* is not protected by condoms[a]	$n_{M0,1}$
Probability a partnership between an uninfected female and a male with disease stage *i* and circumcision status *j* is not protected by condoms[a]	$n_{Mi,j}$
Population variables	
Non-AIDS-related annual mortality rate	μ
Condom failure rate for all partnerships	f
Preventive circumcision program variables	
Annual percent of uncircumcised uninfected or uncircumcised asymptomatic HIV+ males who undergo adult circumcision procedure	$\kappa(t)$
Circumcision protective effect (percent of partnerships protected from infection)	ε

[a] $n_{Mi,j} = fg_{i,j} + (1-g_{i,j})$, where $g_{i,0} = h_{i,0}$ and $g_{i,1} = \Delta h_{i,1}$; [$h_{i,j}$ = baseline condom use for all partnerships; Δ = change in condom use following circumcision, for males circumcised as adults, or following circumcision program implementation, for males previously circumcised in childhood; $g_{i,j}$ = post-intervention condom use for all partnerships, following implementation of an adult male circumcision program]

TABLE 3 (APPENDIX). Model equations

State Equation

(1) $$\frac{dW_0(t)}{dt} = I_{W0} - \mu W_0(t) - p_0\lambda_W(t)W_0(t)$$

(2) $$\frac{dM_{0,0}(t)}{dt} = I_{M0,0} - \kappa(t)M_{0,0}(t) - \mu M_{0,0}(t) - p_0\lambda_M(t)M_{0,0}(t)$$

(3) $$\frac{dM_{0,1}(t)}{dt} = \kappa(t)M_{0,0}(t) - \mu M_{0,1}(t) - p_0(1-\varepsilon)\lambda_{M\kappa}(t)M_{0,1}(t) + I_{M0,1}$$

(4) $$\frac{dW_1(t)}{dt} = I_{W1} - \mu W_1(t) + p_0\lambda_W(t)W_0(t) - \mu_1 W_1(t)$$

(5) $$\frac{dM_{1,0}(t)}{dt} = I_{M1,0} - \kappa(t)M_{1,0}(t) - \mu M_{1,0}(t) + p_0\lambda_M(t)M_{0,0}(t) - \mu_1 M_{1,0}(t)$$

(6) $$\frac{dM_{1,1}(t)}{dt} = \kappa(t)M_{1,0}(t) - \mu M_{1,1}(t) + p_0(1-\varepsilon)\lambda_{M\kappa}(t)M_{0,1}(t) - \mu_1 M_{1,1}(t) + I_{M1,1}$$

(7) $$\frac{dW_2(t)}{dt} = I_{W2} + \mu_1 W_1 - \mu W_2(t) - \mu_2 W_2(t)$$

(8) $$\frac{dM_{2,0}(t)}{dt} = I_{M2,0} + \mu_1 \sum_{j=0}^{j=1} M_{1,j}(t) - \mu M_{2,0}(t) - \mu_2 M_{2,0}(t)$$

(9) $$\frac{dW_3(t)}{dt} = \mu_2 W_2(t) - \mu W_3(t) - \mu_3 W_3(t)$$

(10) $$\frac{dM_{3,0}(t)}{dt} = \mu_2 M_{2,0}(t) - \mu M_{3,0}(t) - \mu_3 M_{3,0}(t)$$

(11) $$\lambda_M(t) = \frac{n_{M0,0}\sum_{i=1}^{i=3}\rho_i\beta_{Wi}W_i(t)}{\sum_{i=0}^{i=3}\rho_i W_i(t)}$$

(12) $$\lambda_{M\kappa}(t) = \frac{n_{M0,1}\sum_{i=1}^{i=3}\rho_i\beta_{Wi}W_i(t)}{\sum_{i=0}^{i=3}\rho_i W_i(t)}$$

(13) $$\lambda_W(t) = \frac{\sum_{i=1}^{i=3}\sum_{j=0}^{j=1} n_{Mi,j}\rho_i\beta_{Mi,j}M_{i,j}(t)}{\sum_{i=0}^{i=3}\sum_{j=0}^{j=1}\rho_i M_{i,j}(t)}$$

DISCUSSION

My dissertation research contributes to the scientific literature, both in the novel survey procedures and modeling techniques I developed, as well as my application of these methods to the population studied. In addition, my research on risk behavior in HIV vaccine trial participants contributes to the practical and ethical conduct of current clinical trials for HIV vaccines; my studies of hypothetical behavior and vaccine modeling contribute to policy decisions that will eventually be made regarding the use of partially effective vaccines in mass vaccination programs; and, the circumcision modeling I did contributes in a timely manner to the international debate currently underway regarding the immediate and worldwide implementation of expanded adult male circumcision programs in populations at high risk of heterosexual HIV infection.

The data collected in the first paper on the current sexual risk behavior of individuals volunteering for HIV vaccine trials represent the first description of this cohort in Soweto, as well as the first characterization to date of a cohort participating in HIV vaccine trials in sub-Saharan Africa. Soweto is a large, predominantly black urban township with a mixture of various tribal ethnicities, on which little behavioral and sociological research has been done. The 2002 Soweto Household Survey[1], conducted by the Perinatal HIV Research Unit (PHRU), is the only large survey of Soweto residents to date[12]: 12,000 households were surveyed and detailed socioeconomic data were collected, but no information on HIV risk behaviors or HIV prevalence was obtained. My research can not be generalized to the greater community because individuals were not randomly selected for participation; a study elsewhere in South Africa found the risk behavior of participants in a cohort recruited for future vaccine trials had higher levels of risk behavior than individuals in the greater community[2]. However, in addition to the

[12] Results from this household survey have not yet been published.

substantial geographic and cultural variation in HIV risk behaviors that exist in South Africa[3-8], the behaviors of individuals enrolling in prevention trials have not been assessed[9-11]. Numerous HIV prevention technologies are being tested in clinical trials in Soweto, and my study provides a detailed sociodemographic and risk description of the population that is volunteering for these trials.

The risk behavior assessment survey I developed for use in the first paper has been permanently incorporated into the Pre-Screening Protocol at the PHRU HIV/AIDS Vaccine Division, in the Chris Hani Baragwanath Hospital in Soweto[12,13]. The PHRU is using it as a risk assessment screening tool to determine if participants are at relatively low risk for HIV infection and should be referred for screening for Phase I (safety) and Phase II (immunogenicity) HIV vaccine trials. In addition, the PHRU is preparing for much larger Phase III (efficacy) HIV vaccine trial capacity in Soweto and in Agincourt, a rural field site[14,15], which will require participants who are at relatively high risk for HIV infection when recruitment for these clinical trials begins. The predictors of higher risk behaviors identified by my study could potentially be used as future screening tools for different trials needing individuals at different risks of HIV infection.

Behavior assessment survey tools and the criteria used to measure risk can vary between different HIV vaccine trials, from qualitative interviews to more structured survey techniques. Individual vaccine trial protocols generally use a standardized risk assessment survey to monitor behavior at various trial sites worldwide, without adapting it to the specific cultural context of a particular trial site. Because many trial sites are conducting several vaccine trials simultaneously, risk assessment may be undertaken with several different survey instruments at a single trial site. These instruments have usually

been formulated by sponsors from high-income countries, where risks for HIV infection are very different. Further, these surveys have not been published to allow for comparisons in format and questioning techniques. I hope to publish or distribute the survey I developed for use in the first paper to allow other trial sites to adapt it for local needs.

Analysis of sexual risk behavior over time is necessary both for HIV vaccine trials to ensure that participants do not increase their risk of HIV infection and for the accurate assessment of vaccine candidate efficacy[16-23]. Standard vaccine trial risk assessment protocols, which take the time of vaccination as a baseline sexual risk level, are not able to detect changes in risk behavior that may occur before that time point. Participants can be monitored in 'screening' cohorts for months or even years prior to vaccine trial enrollment, during which time they can change their risk behavior dramatically[24]. Because of this, an increase or a decrease in self-reported risk behavior during a specific HIV vaccine trial, following participation in a screening cohort, may be relatively uninformative without knowing the baseline behaviors of participants prior to entering such a cohort.

The descriptive data presented in my first paper provide a baseline reference to assess for potential risk behavior change during the process of enrollment and follow-up for vaccine trials in Soweto. The PHRU will continue collecting data with this risk behavior survey every six months for participants enrolled into vaccine trials and longitudinal analyses can be conducted on these data when they become available. Future work will assess whether there are any changes in risk behavior changes during the course of pre-screening, subsequent enrollment into HIV vaccine trials, and follow-

up. Sexual practices related to HIV risk will be assessed at several time points in participants undergoing screening for enrollment into an HIV vaccine trial. Sexual risk behavior will continue to be assessed in participants after their enrollment into one of several HIV vaccine trials and their subsequent vaccination with a candidate HIV vaccine or placebo, with follow-up time generally in the range of several years. Eventually, sexual risk data collected using a standard risk assessment instrument (developed specifically for this trial site population and given to all participants, from the time of entry into the Pre-Screening Protocol through HIV vaccine trial enrollment and follow-up) can be compared with sexual risk data collected using vaccine trial-specific survey instruments (developed by sponsors of the trial protocols occurring at that site and given to participants in each trial, from the time of HIV vaccine trial enrollment).

Except for studies which hypothesize risk behavior change scenarios using modeling simulations, the literature on anticipated changes in risk behavior following implementation of proposed HIV prevention programs is almost nonexistent—particularly for sub-Saharan Africa[25]. The survey I developed for use in the second paper attempts to address this gap as it relates to the future use of low-efficacy vaccines, with a focus on examining the potential for increases in sexual risk behaviors. This is particularly relevant given the high likelihood that the first licensed vaccine will have only minimal efficacy[19,26,27]. Based on self-reported anticipated changes in sexual behaviors which participants predicted for themselves, I found that the potential for individuals to change their risk behavior following vaccination with a low-efficacy HIV vaccine exists, even when participants understood that a low-efficacy vaccine would not provide complete protection against HIV transmission. Further, because my survey was

administered to participants volunteering for HIV vaccine trials, which are operated under idealized conditions with careful attention to HIV education, the anticipated increases in sexual risk behavior for the general population may be greater than I have described[28]. Although a majority of participants in my study actually reported that they might decrease their risk behaviors following vaccination, I believe these data are less reliable due to the social desirability bias inherent in my study design: participants were interviewed in a face-to-face format and were receiving education associated with screening and enrollment into HIV vaccine trials. Therefore, the anticipated decreases in sexual risk behavior for the general population may be less than I have described, and further studies in HIV vaccine trial-naïve populations is merited. Additional work might involve adapting this survey for a variety of other populations and proposed HIV prevention programs. While my initial study was small, further data collection of this genre is needed by governments and policymakers for the various HIV prevention technologies which are under consideration. Moreover, studies of this nature are needed for the mathematical modeling of epidemic impact (such as that demonstrated in this dissertation research), which is frequently used to inform policy decisions.

While an HIV vaccine may not be available for at least a decade, countries are already making resource allocation decisions regarding HIV prevention technologies which are available now. South Africa, for example, is implementing a package of various national programs for the prevention of sexual transmission of HIV, including social mobilization, improvement of nutrition, school-based HIV education, treatment of other sexually transmitted infections, and condom distribution[29,30]. South Africa is also attempting to scale up the provision of antiretroviral treatment to those who are

infected[31]. To effectively tackle the HIV epidemic, resource allocation decisions will need to be made regarding the implementation of both current and future HIV prevention programs.

Epidemic modeling can provide useful insights for program policy-making and is particularly helpful in assessing the impact of HIV prevention programs in low-income countries with a heavy burden of HIV/AIDS yet limited health care resources. Further, an analysis of potential changes in behavior is especially pertinent when examining the impacts of a disease such as HIV in which behavior plays such a significant role in its transmission. The epidemic model I developed for use in the third and fourth papers is one of only a handful of models in the vaccine literature and the only model in the circumcision literature which has considered heterosexual transmission of HIV in African populations[32-38], where there is the greatest need for HIV prevention interventions.

My methodology is also unique for several additional reasons: (1) The model I developed is the first to address gender differences in the ability of individuals to negotiate safe sex practices, which is an important consideration when addressing heterosexual partnerships in which females are affected by cultural and economic barriers to successfully negotiate condom use with their male partners, as shown by research in South Africa[3,39-41]. (2) The simulations I conducted with my model explore the dynamics of behavior change in greater detail than have been previously reported for heterosexual HIV transmission. (3) The detailed input data I used was collected for a specific population in South Africa, thus minimizing the assumptions that had to be made. By using different input parameters and assumptions, my model could be initialized for other populations in which the mode of HIV transmission is also primarily

heterosexual and in which gender differences in safe sex negotiation also exist. Analysis of program impacts in other regions would require adequate data for input values, which many low-income countries lack, but the framework described here could assist in guiding empirical data collection efforts by exploring which of the parameters might be central to policy decision-making.

At the time that the first partially effective vaccine does become available, government and health officials will have to make complex national policy decisions regarding the use of these vaccines in their own populations[19]. In particular, models can assist in answering many of the 'what if' scenarios of vaccine program implementation, such as whether or not to use a first-generation vaccine, whether to target only particular geographic areas or high risk groups, and, for this study in particular, what might happen if the vaccination program causes increased HIV transmission through a decrease in 'safe, preventive' behavior. In the third paper, I developed a model to address this last issue, and specifically showed that programs with high coverage using low-efficacy vaccines would provide substantial benefits in terms of infections prevented at the population level, even if sexual risk taking behavior were to increase significantly.

The decisions regarding implementation of expanded programs for adult male circumcision, however, must be made immediately[42-50]. Good estimates of the efficacy of circumcision in decreasing transmission of HIV are already available[51,52], and the surgical procedure has been shown to be safe, acceptable, and affordable for many populations in sub-Saharan Africa[51-60]. I created the model described in the fourth paper to assist in informing the urgent choices that now need to be made regarding program implementation. A simplified model of expanded circumcision programs has already

been developed and used to examine the impact and cost-effectiveness of these programs[37,38]; I developed my model to examine the impact of expanded circumcision programs in greater detail and to focus in particular on the dynamic interactions of reduced HIV transmission and changes in behavior. Using efficacy data from the circumcision trials which have recently been completed, my simulations predicted that short programs with even very low coverage goals would provide substantial benefits in terms of infections prevented at the population level over time for a wide range of potential changes in condom use following male circumcision. My model for circumcision programs also emphasized that the benefits to men versus women can be different and must not be ignored when evaluating potential program outcomes.

Both of the models I developed show that adequate education and risk-reduction campaigns must be considered when implementing HIV prevention programs with partial efficacy, as changes in sexual risk behavior can have significant effects on program outcomes. However, a comparison of the two models shows that a change in risk behavior was more influential in the implementation of circumcision programs than in the implementation of vaccination programs, e.g. higher levels of circumcision efficacy compared to vaccine efficacy were needed to overcome large decreases in condom use. These differences are due to the interaction between two factors: (1) the direct protection of vaccination for both men and women compared with the direct protection of circumcision solely for men, while women receive only indirect protection due to decreases in population HIV prevalence; and, (2) the male-negotiated condom use which I have modeled to simulate the inability of many women to negotiate safe sex practices in the African setting. Circumcision protects men from infection and an increase or

decrease in risk behavior for circumcised HIV-negative males will directly influence their likelihood of infection from an infected female partner. However, for an HIV-negative female, sex with a circumcised man will not decrease her chances of HIV infection if he is HIV-positive; further, if he increases his risk behavior in response to circumcision, she will be at greater risk of HIV infection than she would be if her partner were uncircumcised.

By comparing the outcomes between vaccination programs and circumcision programs, my findings suggest that risk-reduction counseling may be an even more critical component of partially effective prevention interventions where a certain fraction of the population at risk for HIV infection receives nothing more than an indirect benefit from the intervention. Further, the gender discrepancies in negotiation of safe sexual practices modeled here, combined with analyses of prevention programs providing both direct and indirect transmission benefits, have shown that changes in risk behavior do not affect prevention programs uniformly. This interaction is influenced by differences in power to negotiate safe sex and differences in benefits of reduction in HIV transmission which, in my analyses, were both gender-based. These results specifically emphasize the need for more detailed examinations of potential gender differences in outcomes expected from HIV prevention programs.

More generally, though, these results highlight the need for analyses of the tradeoff between allocating resources for increased coverage of a specific prevention technology (such as providing male circumcision) after modest coverage levels have been achieved, versus using those resources for increased coverage of a behavior-based prevention program (such as increasing condom use). Because many prevention technologies may

require only a one-time intervention to confer lifelong protective benefits, while behavioral prevention programs usually necessitate an intervention which must be practiced repeatedly for the life of the individual, further research is needed on how best to allocate resources between various types of prevention programs. My future research may involve examining the costs and benefits of increasing coverage levels for prevention programs with inherent differences in the timing and length of the intervention.

Additionally, the ability to model multiple interventions within the same population will be needed as governments and policy makers are confronted with numerous HIV prevention technologies, all with partial efficacy[46,50,61]. Decisions will need to be made not only on whether to use a single prevention program, but also on what combination of prevention programs should be used and the additive effects of multiple programs with varying coverage and target goals. I hope to adapt this model to allow for the assessment of other HIV prevention technologies. For example, a large randomized controlled trial is currently underway in South Africa and Zimbabwe, with Soweto as the South African site, to assess whether diaphragm use has an impact on male-to-female and/or female-to-male heterosexual transmission of HIV[62]. I am currently working with the principal investigator for the South African trial to develop a model that accurately simulates the dynamics of HIV transmission surrounding diaphragm use. My future research may involve developing additional models which can compare multiple HIV prevention programs simultaneously.

In conclusion, I have used the township of Soweto as an example to describe the impact of partially effective HIV prevention programs and associated changes in risk

behavior; but, the implications of my results reach beyond South Africa. The severity of the HIV/AIDS epidemic in South Africa has been enhanced by a history of apartheid and migratory labor practices, a lack of political will for HIV education and treatment, significant poverty and unemployment, and the stigma attached to the disease[3,9,30,63-67]. Although the particular combination of factors contributing to the initial spread of HIV disease in South Africa was unique, many other populations worldwide are experiencing similar generalized epidemics, in which HIV transmission is predominantly heterosexual and gender discrepancies exist in the negotiation of safe sexual practices. This dissertation research has applications for other low- and middle-income countries with similar epidemic profiles considering the use of partially effective HIV prevention programs on a regional or national scale, as well as for high-income countries considering the implementation of programs in particular groups such as those at high risk for HIV infection.

REFERENCES

1. Anonymous. *Soweto Household Survey 2002: The effects of adult morbidity and mortality on household welfare and the well-being of children in Soweto*: Perinatal HIV Research Unit; 2002.

2. Smit J, Middelkoop K, Myer L, Seedat S, Wood R, Stein DJ and Bekker L-G. Sexual risk factors associated with volunteering for HIV vaccine research in South Africa. *AIDS Care* 2006; **18**:569-573.

3. Simbayi L, Strebel A, Wilson T, Andipatin M, Msomi N, Potgieter C, Ratele K and Shefer T. *Sexually transmitted diseases in the South African public sector*: National Department of Health's Directorate of Health Systems Research and Epidemiology in conjunction with the Directorate of HIV/AIDS and STDs; August 1999.

4. Simbayi LC, Chauveau J and Shisana O. Behavioural responses of South African youth to the HIV/AIDS epidemic: a nationwide survey. *AIDS Care* 2004; **16**:605-618.

5. Pettifor AE, Rees HV, Steffenson A, Hlonga-Madikizela L, MacPhail C, Vermaak K and Kleinschmidt I. *HIV and sexual behavior among young South Africans: a national survey of 15-24 year olds.* Johannesburg: Reproductive Health Research Unit, University of the Witwatersrand; April 6 2004.

6. Pettifor AE, Rees HV, Kleinschmidt I, Steffenson AE, MacPhail C, Hlongwa-Madikizela L, Vermaak K and Padian NS. Young people's sexual health in South Africa: HIV prevalence and sexual behaviors from a nationally representative household survey. *AIDS* 2005; **19**:1525-1534.

7. Shisana O, Rehle T, Simbayi LC, Parker W, Zuma K, Bhana A, Connolly C, Jooste S and Pillay V. *South African national HIV prevalence, HIV incidence, behaviour and communication survey, 2005.* Cape Town: HSRC Press; 2005.

8. Anonymous. HIV Prevalence, Incidence, Behavior and Communication Survey 2005. Centre for AIDS Development, Research and Evaluation, 2006. Available at: www.cadre.org.za.

9. Shefer T, Strebel A, Wilson T, Shabalala N, Simbayi L, Ratele K, Potgieter C and Andipatin M. *The social construction of sexually transmitted infections (STIs) in South African communities* 2002.

10. Lindegger G, Slack C and Vardas E. HIV vaccine trials in South Africa--some ethical considerations. *S Afr Med J* 2000; **90**:769-772.

11. Slack C, Lindegger G, Vardas E, Richter L, Strode A and Wassenaar D. Ethical issues in HIV vaccine trials in South Africa. *S Afr J Sci* 2000; **96**:291-295.

12. Vardas E, Mlungwana ON, Van Niekerk RM, Mesesan K, Mogale M, Mayaphi S, McIntyre JA and Gray GE. Characteristics of a cohort of individuals screened for Phase I/II HIV vaccine trials in South Africa [344P]. Paper presented at: AIDS Vaccine International Conference; 2005; Montreal.

13. Vardas E, Gray GE, Van Niekerk R, Schwarz R, McIntyre J, Mlungwana O, Mogale M and the HIV Vaccine Trial Network. Recruiting into phase I/II HIV vaccine trials in Soweto, South Africa: a model for developing countries [OA06-04]. Paper presented at: AIDS Vaccine International Conference; 2006; Amsterdam.

14. Vardas E. *Second annual progress report: January 2002-August 2002.* Soweto: HIV AIDS Vaccine Division, Perinatal HIV Research Unit; 2002.

15. Vardas E, Tollman S, Gray G, McIntyre J, Kahn K and Garenne M. *Proposal to develop a rural phase III HIV vaccine testing site based on Agincourt Health and Demographic Surveillance System of the Agincourt Health and Population Unit (AHPU) of the University of Witwatersrand*: Perinatal HIV Research Unit; 2003.

16. Frey SE. Unique risks to volunteers in HIV vaccine trials. *J Investig Med* 2003; **51(Suppl 1)**:S18-20.

17. Lurie P, Bishaw M, Chesney MA, Cooke M, Fernandes ME, Hearst N, Katongole-Mbidde E, Koetsawang S, Lindan CP and Mandel J. Ethical, behavioral, and social aspects of HIV vaccine trials in developing countries. *JAMA* 1994; **271**:295-301.

18. Cohen J. The HIV vaccine paradox. *Science* 1994; **264**:1072-1074.

19. Anonymous. Future access to HIV vaccines. Report from a WHO-UNAIDS Consultation, Geneva, 2-3 October 2000. *AIDS* 2001; **15**:W27-44.

20. Halloran ME, Longini IM, Jr., Haber MJ, Struchiner CJ and Brunet RC. Exposure efficacy and change in contact rates in evaluating prophylactic HIV vaccines in the field. *Stat Med* 1994; **13**:357-377.

21. Blower SM, van Griensven GJ and Kaplan EH. An analysis of the process of human immunodeficiency virus sexual risk behavior change. *Epidemiology* 1995; **6**:238-242.

22. Schaper C, Fleming TR, Self SG and Rida WN. Statistical issues in the design of HIV vaccine trials. *Annu Rev Public Health* 1995; **16**:1-22.

23. Turner CF and Sheon AR. Behavioral studies relevant to vaccine trial preparation: an introduction. *AIDS Res Hum Retroviruses* 1994; **10(Suppl 2)**:S273-276.

24. Baeten JM, Richardson BA, Martin HL, Jr., Nyange PM, Lavreys L, Ngugi EN, Mandaliya K, Ndinya-Achola JO, Bwayo JJ and Kreiss JK. Trends in HIV-1 incidence in a cohort of prostitutes in Kenya: implications for HIV-1 vaccine efficacy trials. *J Acquir Immune Defic Syndr* 2000; **24**:458-464.

25. Bishai D, Pariyo G, Ainsworth M and Hill K. Determinants of personal demand for an AIDS vaccine in Uganda: contingent valuation survey. *Bull World Health Organ* 2004; **82**:652-660.

26. Garber DA, Silvestri G and Feinberg MB. Prospects for an AIDS vaccine: three big questions, no easy answers. *Lancet Infect Dis* 2004; **4**:397-413.

27. Self S. Vaccine efficacy trial design: role of Phase IIb vs. Phase III trials [56]. Paper presented at: AIDS Vaccine International Conference; 2005; Montreal.

28. Newman PA, Duan N, Rudy ET and Anton PA. Challenges for HIV vaccine dissemination and clinical trial recruitment: if we build it, will they come? *AIDS Patient Care STDS* 2004; **18**:691-701.

29. Anonymous. Strategic priorities for the national health system, 2004-2009. South African Department of Health, Available at: http://www.doh.gov.za/docs/policy-f.html.

30. Anonymous. Republic of South Africa: progress report on declaration of commitment on HIV and AIDS. South African Department of Health, Available at: http://www.doh.gov.za/docs/reports-f.html.

31. Anonymous. *Monitoring review: Progress report on the implementation of the comprehensive HIV and AIDS care, management and treatment programme*: Department of Health, South Africa; September 2004.

32. Gray RH, Li X, Wawer MJ, Gange SJ, Serwadda D, Sewankambo NK, Moore R, Wabwire-Mangen F, Lutalo T, Quinn TC and the Rakai Project Group. Stochastic simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission; Rakai, Uganda. *AIDS* 2003; **17**:1941-1951.

33. Anderson R and Hanson M. Potential public health impact of imperfect HIV type 1 vaccines. *J Infect Dis* 2005; **191(Suppl 1)**:S85-96.

34. Anderson RM, Swinton J and Garnett GP. Potential impact of low efficacy HIV-1 vaccines in populations with high rates of infection. *Proc Biol Sci* 1995; **261**:147-151.

35. Anderson RM and Garnett GP. Low-efficacy HIV vaccines: potential for community-based intervention programmes. *Lancet* 1996; **348**:1010-1013.

36. Stover J, Garnett GP, Seitz S and Forsythe S. The epidemiological impact of an HIV/AIDS vaccine in developing countries [World Bank Policy Research Working Paper No. 2811]. The World Bank Development Research Group, March 2002. Available at: http://papers.ssrn.com/sol3/papers.cfm?abstract_id=636094.

37. Kahn JG, Marseille E and Auvert B. Cost-effectiveness of male circumcision for HIV prevention in a South African setting. *PLoS Med* 2006; **3**:2349-2358.

38. Williams BG, Lloyd-Smith JO, Gouws E, Hankins C, Getz WM, Hargrove J, de Zoysa I, Dye C and Auvert B. The potential impact of male circumcision on HIV in sub-Saharan Africa. *PLoS Med* 2006; **3**:1032-1040.

39. Ackermann L and de Klerk GW. Social factors that make South African women vulnerable to HIV infection. *Health Care Women Int* 2002; **23**:163-172.

40. Pettifor AE, Measham DM, Rees HV and Padian NS. Sexual power and HIV risk, South Africa. *Emerg Infect Dis* 2004; **10**:1996-2004.

41. Williams BG, Taljaard D, Campbell CM, Gouws E, Ndhlovu L, Van Dam J, Carael M and Auvert B. Changing patterns of knowledge, reported behaviour and sexually transmitted infections in a South African gold mining community. *AIDS* 2003; **17**:2099-2107.

42. Clark J. Male circumcision is not a panacea for HIV prevention. *BMJ* 2006; **333**:409.

43. Auerbach JD, Hayes RJ and Kandathil SM. Overview of effective and promising interventions to prevent HIV infection. *World Health Organ Tech Rep Ser* 2006; **938**:43-78; discussion 317-341.

44. Wise J. Demand for male circumcision rises in a bid to prevent HIV. *Bull World Health Organ* 2006; **84**:509-511.

45. Atashili J. Adult male circumcision to prevent HIV? *Int J Infect Dis* 2006; **10**:202-205.

46. Cohen J. Prevention cocktails: combining tools to stop HIV's spread. *Science* 2005; **309**:1002-1005.

47. Jones R, Gazzard B and Halima Y. Preventing HIV infection. *BMJ* 2005; **331**:1285-1286.

48. Beukes L. Caution on circumcision cuts South Africa's AIDS researchers. *Nat Med* 2005; **11**:1261.

49. Roehr B. Dramatic drop in HIV infections halts circumcision trials. *BMJ* 2007; **334**:11.

50. Hankins C, De Zoysa I, Alnwick D, Ntaganira I, Schmid G, Farley T, Collins L, Edouard L, Jackson H, Beger G, Mulenga D, O'Reilly K, Dick B, Kraus S, McDermott P and Stirling M. Laying the policy and programming framework for decision making at country level on the potential role of male circumcision in comprehensive HIV prevention strategies [WEPE0893]. Paper presented at: XVI International AIDS Conference; 2006; Toronto.

51. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R and Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med* 2005; **2**:e298.

52. Anonymous. Adult male circumcision significantly reduces risk of acquiring HIV: Trials in Kenya and Uganda stopped early. National Institutes of Health News Release, December 13, 2006. Available at: http://www.nih.gov/news/pr/dec2006/niaid-13.htm.

53. Lagarde E, Dirk T, Puren A, Reathe R-T and Auvert B. Acceptability of male circumcision as a tool for preventing HIV infection in a highly infected community in South Africa. *AIDS* 2003; **17**:89-95.

54. Quinn TC. Circumcision and HIV transmission: the cutting edge [120]. Paper presented at: 13th Conference on Retroviruses & Opportunistic Infections; 2006; Denver, Colorado.

55. Scott BE, Weiss HA and Viljoen JI. The acceptability of male circumcision as an HIV intervention among a rural Zulu population, Kwazulu-Natal, South Africa. *AIDS Care* 2005; **17**:304-313.

56. Ngalande RC, Levy J, Kapondo CPN and Bailey RC. Acceptability of male circumcision for prevention of HIV infection in Malawi. *AIDS & Behavior* 2006; **10**:377-385.

57. Halperin DT, Fritz K, McFarland W and Woelk G. Acceptability of adult male circumcision for sexually transmitted disease and HIV prevention in Zimbabwe. *Sex Transm Dis* 2005; **32**:238-239.

58. Kebaabetswe P, Lockman S, Mogwe S, Mandevu R, Thior I, Essex M and Shapiro RL. Male circumcision: an acceptable strategy for HIV prevention in Botswana. *Sex Transm Infect* 2003; **79**:214-219.

59. Rain-Taljaard RC, Lagarde E, Taljaard DJ, Campbell C, MacPhail C, Williams B and Auvert B. Potential for an intervention based on male circumcision in a South African town with high levels of HIV infection. *AIDS Care* 2003; **15**:315-327.

60. Tsela S and Halperin D. Knowledge, attitudes and practices regarding male circumcision in the Manzini (central) region of Swaziland [CDC0611]. Paper presented at: XVI International AIDS Conference; 2006; Toronto.

61. Cassell MM, Halperin DT, Shelton JD and Stanton D. Risk compensation: the Achilles' heel of innovations in HIV prevention? *BMJ* 2006; **332**:605-607.

62. Hillier S. Beyond condoms: chemical and physical barriers to protect women from HIV [55]. Paper presented at: 13th Conference on Retroviruses & Opportunistic Infections; 2006; Denver.

63. Nattrass N. *The moral economy of AIDS in South Africa.* Cambridge, UK ; New York, NY: Cambridge University Press; 2004.

64. Zuma K, Lurie MN, Williams BG, Mkaya-Mwamburi D, Garnett GP and Sturm AW. Risk factors of sexually transmitted infections among migrant and non-migrant sexual partnerships from rural South Africa. *Epidemiol Infect* 2005; **133**:421-428.

65. Crewe M. AIDS in Southern Africa. *Postgrad Med J* 2002; **78**:127-128.

66. Crewe M. How do we make sense of President Mbeki? *AIDS Anal Afr* 2000; **11**:10-11.

67. Crewe M. Spectacular failure--a view from the epicenter. *Yale J Health Policy Law Ethics* 2004; **4**:157-163.

SOURCES OF FUNDING

Tuition and stipend support [Kyeen Mesesan]: National Institute of General Medical Sciences MD/PhD Medical Scientist Training Program (GM07205); National Institute on Drug Abuse (RO1DA015612)

Vaccine trial participant cohort and survey research-related expenses [Pre-Screening Protocol, Perinatal HIV Research Unit, South Africa]: National Institute of Allergy and Infectious Diseases HIV Vaccine Trials Network; International AIDS Vaccine Initiative; South African AIDS Vaccine Initiative

Research and travel expenses [Kyeen Mesesan]: Yale Center for International and Area Studies; Yale Center for the Study of Globalization; European Union AIDS Vaccine Integrated Project Consortium

Attendance of scientific conferences [Kyeen Mesesan]: Yale University Graduate Student Assembly Conference Travel Fund; Yale University Graduate and Professional Student Senate Conference Travel Fund; Yale University Department of Epidemiology and Public Health Conference Travel Fund; Secretariat, International AIDS Conference; Secretariat, AIDS Vaccine International Conference; Secretariat, Conference on Retroviruses and Opportunistic Infections; Perinatal HIV Research Unit; National

Institute of General Medical Sciences MD/PhD Medical Scientist Training Program (GM07205); National Institute on Drug Abuse (RO1DA015612)