Understanding the Impact of an HIV Intervention Package for Adolescents

by

Faikah Bruce

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Department of Mathematics,
University of Stellenbosch,
Private Bag X1, Matieland 7602, South Africa.

Supervisors:

Dr. L. F. Johnson
Prof. A. Welte

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Declaration

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Abstract

Adolescents are regarded as a high risk group in South Africa with the highest human immunodeficiency virus (HIV) incidence occurring in this group. Prevention among adolescents is therefore a key in decreasing the HIV burden. This thesis aims to assist in the design of trials by simulating the potential outcomes of a combination prevention trial in adolescents. We develop a stochastic individual-based model stratified by sex and age. We then use this model to determine the impact of various prevention packages on HIV incidence among adolescents participating in a hypothetical trial over a three year period. The trial that is simulated involves an intervention arm, in which adolescents are offered a choice of a prevention methods (including medical male circumcision (MMC), oral pre-exposure prophylaxis (PrEP) and antiretroviral-based vaginal microbicides (ARV-VM)), and a control arm. We predict that the impact of a full prevention package on HIV incidence would be a 46% per person-year(PPY) (95% CI 45–47%) risk reduction. The combination of MMC and PrEP has a substantial impact on HIV incidence in males, with a 51% PPY (95% CI 49–53%) relative risk of HIV infection. Offering women the choice of PrEP, a microbicide gel or a microbicide in the form of a vaginal ring would be less effective, with a 57% PPY (95% CI 56–58%) relative risk of HIV acquisition. This is not substantially different from the relative risk estimated when the vaginal ring alone is offered, as the ring is assumed to be the most accept-

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able of the three prevention methods. We determine a sample size requirement of approximately 1013 in each arm of a trial would achieve 80% power to detect a statistically significant reduction in HIV risk. We find that the relative risk is sensitive to the assumed degree of correlation between condom use and the acceptability of the prevention method. We also find that the most efficient trial design may be to offer both MMC and PrEP to males but to offer only a microbicide ring to females. Further work is required to better understand the processes by which adolescent prevention method choices are made.

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Uittreksel

Adolessente word beskou as ‘n hoe risiko groep in Suid Afrika, met die hoogste menslike immuniteitsgebrekvirus (MIV) insidensie in hierdie groep. Voorkoming van MIV onder adolessente is daarom noodsaaklik om die MIV las te verminder. Die doel van hierdie tesis is om te help met die ontwerp van studies deur die moontlike uitkomste van ‘n kombinasie-voorkoming studie in adolessente te simuleer. Ons het ‘n stogastiese individu-gebaseerde model, gestratifiseer met betrekking tot seks en ouderdom, ontwikkel. Ons het toe die model gebruik om die impak van ‘n verskeinheid van voorkomingspakette op MIV insidensie onder adolessente wat deelneem aan ‘n hipotetiese proef oor ‘n drie jaar periode, te bepaal. Die proef wat gesimuleer word behels a intervensie groep, waarin die jong volwassenes ‘n keuse van voorbehoedings metodes (insluitende mediese manlike besnydenis (MMB), pre-blootstelling profilakse (PrBP) en anti-retrovirale vaginale mikrobisiedes (ARV-VM)) aangebied word, en ‘n kontrole groep. Ons voorspel dat die impak van ‘n volle voorkomingspaket op MIV insidensie ‘n 46% per persoon-jaar (PPJ) (95% VI 47–47%) risiko vermindering sal wees. Die kombinasie van MMB en PrBP het ‘n substansiele impak op MIV insidensie onder mans, met ‘n relatiewe risiko van MIV infeksie van 51% PPJ (95% VI 49–53%). Om die keuse van PrBP, ‘n mikrobisiede gel of ‘n mikrobisiede in die vorm van ‘n vaginale ring aan vrouens te bied, is minder effektief, met ‘n relatiewe risiko van MIV infeksie van 57% PPJ (95% VI

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56%–58%). Hierdie verskil nie substansieel van die beraamde relatiewe risiko in die geval waar slegs die vaginale ring gebied word nie, aangesien daar aanvaar word dat die ring die mees aanvaarde van die drie voorkomingsmetodes is. Ons het bepaal dat ‘n steekproef van ongeveer 1013 individue in elke arm van die proef nodig is om ‘n 80% kans te he om ‘n statisties betekenisvolle afname in MIV-risiko te bespeur. Ons vind dat die relatiewe risiko sensitief is tot die aanvaarde graad van die korrelasies tussen kondoom-gebruik en die aanvaarding van die voorkomings metodes. Ons het ook gevind dat dit mag wees dat die mees doeltreffende proef ontwerp is om beide MMB en PrBP vir mans en slegs ‘n mikrobisiede ring vir vrouens te bied. Verdere werk word benodig om die prosesse waarby jong volwassenes keuses maak oor voorkomingsmetodes te verstaan.

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Dedications

To my husband, Basheer Ah Shene, and my family.

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Chapter 1

Introduction

South Africa has one of the highest HIV prevalence levels in the world, with the highest HIV incidence rates occurring in young people (UNAIDS, 2010). Adolescents therefore must be key targets in preventing the spread of HIV at a population level. During adolescence, many biological, physical and behavioural changes take place. These factors, together with peer pressure and socio-economic challenges, can result in poor decision making regarding sex. Lack of condom usage, multiple partners and intergenerational sex, are a few of these choices that account for the increased risk of acquiring HIV.

The range of possible biomedical HIV prevention methods has advanced considerably over the last decade. HIV prevention methods now include medical male circumcision (MMC), pre-exposure prophylaxis (PrEP) and antiretroviral-based vaginal microbicides (ARV-VM). Randomized controlled trials (RCTs) have already shown MMC to be effective in reducing the risk of acquiring HIV (Mills *et al.*, 2008). Both PrEP and ARV-VM are currently undergoing evaluation to determine levels of efficacy as HIV prevention methods (Abdool Karim *et al.*, 2010; Thigpen *et al.*, 2012; Baeten *et al.*, 2012). Although RCTs are the so-called gold standard for demonstrating the efficacy/effectiveness of

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a prevention method, not all trials produce conclusive or positive results, and trials are costly to conduct and require numerous resources. To minimize the risk that a trial produces inconclusive or negative results, the careful design of the trial is essential. Mathematical modelling is often important in helping to inform the design of a trial.

Mathematical modelling plays a vital role in understanding HIV/AIDS epidemiology (Garnett, 2002; Auvert *et al.*, 2000). Modelling the population level impact and cost-effectiveness of an HIV prevention method helps to inform policy (Pretorius *et al.*, 2010; Hankins *et al.*, 2009; Cremin *et al.*, 2011). Modelling is particularly useful in evaluating the likely impact of a combination of prevention methods, showing how results might vary depending on levels of acceptability, product adherence and whether there would be synergy or antagonism between prevention methods. Modelling is also important in the context of trial designs for multi-component prevention methods, identifying the intervention components that are most critical to maximizing effectiveness and assisting in determining a sample size that is needed to achieve an adequately powered trial.

Most previous HIV prevention trials and studies have focused on adults, and it is unclear how far conclusions can be extended to adolescents as adolescents are behaviourally and biologically different from adults. More than one adolescent-tailored prevention method option is required to address the diverse needs and unique challenges of HIV prevention in adolescents. The National Institutes of Health (NIH) in the U.S. is funding exploratory work in South Africa to evaluate multi-component prevention programmes in adolescents, with a view to possibly conducting a randomized trial of such a multi-component prevention package. This thesis will assist in the consideration of

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this trial.

The aim of this thesis is to determine the potential impact of an HIV intervention package on HIV incidence for adolescents in a trial setting, based on a mathematical model. Prevention methods that are considered for inclusion in the package are MMC, ARV-VM for females and PrEP. Comparisons of the impact of different permutations of these prevention methods will assist in identifying which prevention methods should be included in the ideal package.

The thesis is structured as follows. Chapter 2 reviews the literature on adolescent sexual behaviour and the HIV prevention methods considered in this thesis, including MMC, ARV-VM and PrEP. In Chapter 3 we explain the mathematical model we developed. We demonstrate how the characteristics of each individual, as well as the partner's characteristics, are simulated. With HIV incidence being one of the main outputs of the model, we show the calibration of the model by comparing the simulated HIV incidence to South African HIV incidence data. The impact of the prevention package on HIV incidence is presented in Chapter 4. We present the relative risk of HIV infection for different prevention packages and evaluate the sample size requirements. We conclude the thesis with a discussion in Chapter 5 of the findings, as well as the strengths and limitations of the model.

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Chapter 2

Literature Review

In this section, we outline and review previous studies and models that focus on adolescent sexual behaviour and the various prevention methods under consideration. The main objective of the review is to identify the data sources that are most relevant in estimating the parameters used in the model.

2.1 Sexual Behaviour of Adolescents

Development factors, such as neurobiological and biobehavioural, that occur during adolescence, result in an increase in risk behaviour, difficulties controlling behaviours and emotions, and the pressure to assert individuality (Rivers and Aggleton, 1998; Wilson *et al.*, 2010). Heterosexual transmission is the most common mode of HIV transmission among adolescents (Shisana *et al.*, 2009). Some key drivers of HIV transmission in adolescents are early age of sexual debut (McGrath *et al.*, 2009); inconsistent condom usage (Katz and Low-Beer, 2008; Pettifor *et al.*, 2004*a*); sex with multiple or concurrent partners (Ferry *et al.*, 2001; Johnson *et al.*, 2009); and intergenerational sex (Chapman *et al.*, 2010).

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Studies and models that help to inform model parameters, such as the rate of partnership formation, the propensity for concurrent partnerships, the duration of a partnership, the rate of partnership dissolution, sexual frequency and condom usage, are reviewed below.

2.1.1 Age of Sexual Debut

An early age of sexual debut means a larger probability of possible exposure to HIV. The percentage of adults who have had sex before the age of 15, reported by the HSRC National Household Survey of 2008, is 11.3% for males and 5.9% for females (Shisana *et al.*, 2009). Based on the Second National HIV Communication Survey (NCS) of 2009, Johnson *et al.* (2010) reports these percentages as 14% for males and 5% for females. Johnson *et al.* (2010) also reports the average age of sexual debut for 16–24 year olds as 16.3 and 17.2 for males and females, respectively. A 2003 national survey (Pettifor *et al.*, 2004*a*) reports similar ages for the mean age of sexual debut, 16.7 for males and 17 for females. The method to estimate these ages of sexual debut was based on face-to-face interviews which are subject to social desirability bias. The average age of sexual debut is likely to be exaggerated, especially in females (Mensch *et al.*, 2003).

The age of sexual debut is strongly associated with the level of risk behaviour in sexually experienced individuals. The younger the age of sexual debut, the higher the level of risk behaviour of the individual (Eaton *et al.*, 2003; Pettifor *et al.*, 2005, 2007; Wilson *et al.*, 2010).

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2.1.2 Sexual Frequency

In the National Survey of HIV and Sexual Behaviour Among 15–24 Year Olds, of the individuals who reported having had sex in the past year , 51% of the males and 50% of the females said they had had sex 1–5 times in the last month (Pettifor *et al.*, 2004*a*). In a study by Kelly (2000), the author collected data using a questionnaire from a sample of 618 individuals in the 15–30 year age group from various sites in South Africa. Results from this study showed that the average number of days an individual had sex in the last 4 weeks, was 3 in non-cohabiting relationships. These studies suggest a low frequency of sex in youth in the South African context.

2.1.3 Partnership Formation and Dissolution

Multiple partnerships contribute greatly to the transmission of HIV. All three surveys report on multiple partnerships (more than 1 partner) over the past year. These are listed in Table 2.1. Across these three surveys, males were 3–5 times more likely to report multiple partnerships than their female counterparts.

Although many studies report numbers of partners, few report rates of partnership formation and few address the problem of social desirability bias. The HIV/AIDS model by Johnson *et al.* (2009), calibrated to the reported numbers of current sexual partners in the 2005 HSRC national household survey, estimated the rates of non-marital relationship formation using a Bayesian approach that took into account social desirability bias in reporting of current partner numbers. The authors found that the social desirability bias in reporting of multiple partners was much greater for females than for males, so the differences in numbers of partners reported by young men and young women

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might be a poor reflection of the actual gender differences in rates of partner change.

A median relationship duration of 9 months (IQR 0.5–24 months) was reported by women in a study by (Jewkes *et al.*, 2001). Another study by Pettifor *et al.* (2005) reported somewhat shorter average partnership durations. There may be a bias in these studies because people will tend to report on the duration of their main relationship, not on that of their casual or secondary partnerships, which would typically be of shorter duration.

Marriage occurs at a relatively late age in SA, when compared with other African countries (Bongaarts, 2007). In this discussion (and in our model) of adolescent sexual behaviour, we therefore focus on non-marital relationships.

2.1.4 Age-mixing

A key driver of HIV transmission is age-disparate relationships (Chapman *et al.*, 2010). Data reported on sexual partnerships generally indicate that females tend to have older male partners and males tend to have younger female partners (Pettifor *et al.*, 2004*a*). Young women with older partners place themselves at higher risk as they are exposed to an HIV prevalence level that is higher than that of males of their own age group. Shisana *et al.* (2009) found that 15–19 year old males reported a partner age within 5 years of their own age, in 98.5% of cases. For females, this proportion was much lower, 72.4%, with a substantial percentage, 27.6%, of females having partners 5 or more years older than themselves. In the NCS survey of 2009, Johnson *et al.* (2010) reported that older males tended to have partners who were 5 or more years younger, when compared to the younger males. Females in the age group 16–24 years generally had partners 5 or more years older. Pettifor *et al.*

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(2004*a*) reported the average partner age difference for young females to be 4 years older.

Table 2.1: Multiple partnerships over the past year and condom use at last sex for different age groups, as reported by the various surveys.

Survey	Age group	Sex	More Than 1 Partner Over the Last Year (%)	Condom Use at Last Sex (%)
Pettifor *et al.* (2004*a*)	15–19	Male	43	57
		Female	15	55
	20–24	Male	45	57
		Female	10.0	44
Shisana *et al.* (2009)	15–24	Male	30.8	87.4
		Female	6	73.1
	25–49	Male	14.8	56.4
		Female	3.0	58.1
Johnson *et al.* (2010)	16–19	Male	29	75
		Female	9	63
	20–24	Male	16	68
		Female	2	49

2.1.5 Condom Use

Condoms are one of the most effective ways to prevent the spread of HIV (Pinkerton and Abramson, 1997). Their efficacy is dependant on the correct and consistent use of condoms.

The various surveys listed in Table 2.1 shows a generally high level of condom usage at last sex. These reported levels are subject to social desirability bias as the levels of condom usage are those reported by respondents in face-to-face interviews. There is a slight decrease in condom usage at last sex from the 15–24 year age group to the 25–49 year age group (Shisana *et al.*, 2009) and from the 16–19 year age group to the 20–24 year age group (Johnson

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et al., 2010) for both males and females. Although the proportion of youth who reported using condoms at last sex is high, there is a great variation in the consistency of condom use. For example, in the 2003 national survey (Pettifor *et al.*, 2004*a*), 33% reported always using a condom, while 31% reported never using condoms.

2.2 Male Circumcision

Male circumcision is a surgical procedure that involves the removal of the foreskin of the penis. It is one of the most commonly practised surgical procedures in the world and it is estimated that approximately 30% of the global male population is circumcised. This estimation is based on males aged 15 years and older (WHO/UNAIDS, 2008). There a two types of circumcisions, namely therapeutic and non-therapeutic circumcisions. Therapeutic circumcisions are performed to treat an underlying pathological process and non-therapeutic circumcisions are performed for social, cultural, religious, hygienic and prophylactic reasons (Perera *et al.*, 2010).

2.2.1 Patterns of Male Circumcision Adoption

Factors influencing the prevalence of male circumcision include religion, culture, tradition and hygiene. Muslims are the largest religious group to practice this procedure, followed by Jews. Circumcision among these groups takes place between birth and puberty. Most neonatal and pre-puberty circumcisions take place in a clinical setting which provides a safer environment and very few post-operative complications.

Connolly *et al.* (2008*b*) analysed the demographic and behavioural factors that are associated with male circumcision (based on a national survey in

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2002 in South Africa). The authors found that male circumcision was associated with increasing age, black race, religious affiliation, home language and province. Among black South Africans, the median age of male circumcision was 18 years of age. The ethnic groups that practice traditional male circumcision most frequently include the IsiXhosa-speaking, the Setswana-speaking, the Sepedi-speaking, the IsiNdebele-speaking and the Tshivenda-speaking people. These ethnic groups view the practice of male circumcision as a rite of passage to manhood and circumcision is thus performed mainly on the youth (Connolly *et al.*, 2008*b*). The IsiZulu-speaking people stopped the practise during the Zulu wars that took place in the early 19th century (WHO/UNAIDS, 2008). Traditional circumcisions are mainly performed in non-clinical settings where conditions may be unhygienic. The process is performed by medically untrained people who often work with unsterilised equipment. Safety is thus a major concern under these conditions as many serious complications have been reported, even death in some cases (WHO/UNAIDS, 2008). Circumcision is more common in the Gauteng, Limpopo, Mpumalanga and Eastern Cape provinces (Connolly *et al.*, 2008*b*).

Thomas *et al.* (2011) shows that self-reporting on male circumcision status could exaggerate the actual prevalence of male circumcision. Some men reported being circumcised, but when they were physically examined, it was found that they were either not circumcised or only partially circumcised. Partial male circumcision would not have the same efficacy as complete male circumcision. Ethnicity is a key determinant in the prevalence of male circumcision , with Isi-Xhosa speaking males having a prevalence of 64.3% and more than 89.1% of them being circumcised after the age of 17 (Connolly *et al.*, 2008*b*).

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2.2.2 Evidence of Efficacy of Male Circumcision

The foreskin of the male penis contains a large number of Langerhans cells. These cells are professional antigen presenting cells lining the mucosal tissue of the foreskin and form a protective barrier against infection by internalizing the virus into Birbeck granules where the virus is degraded. If the protective barrier is breached, the Langerhans cells become productively infected. These activated cells then migrate to the lymph nodes where they transmit the virus to the T-cells. The Langerhans cells are the main target of HIV, as they transmit the virus to the T-cells. Also, pre-existing co-infection of the Langerhans cells with other STIs changes the functionality of the Langerhans cells, thereby increasing the risk of the HIV infection (de Jong and Geijtenbeek, 2008).

For more than a decade, it has been suggested that male circumcision may be important in reducing the spread of HIV infection (Moses *et al.*, 1994, 1998; Seed *et al.*, 1995). Observational studies that include male circumcision as a risk factor for HIV infection support this premise and have provided substantial evidence that male circumcision may provide a degree of protection against HIV infection (Weiss *et al.*, 2007). Systematic reviews and meta-analyses of observational data in sub-Saharan Africa clearly indicate that there is a strong association between circumcision and a lower prevalence of HIV infection. Weiss *et al.* (2000) showed a significant reduction in HIV risk associated with male circumcision(RR = 0.52, 95% CI 0.40–0.68) with an adjusted risk ratio of 0.42 (95% CI 0.34–0.54). A multicentre study on the factors determining the rate of spread of HIV infection was conducted in four cities with contrasting levels of HIV prevalence in sub-Saharan Africa, namely Kisumu (Kenya), Ndola (Zambia), Cotonou (Benin) and Yaoundé (Cameroon) (Buvé *et al.*, 2001*a*). In this study it was concluded that male circumcision provided

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a protective effect against acquiring HIV infection and it was suggested that circumcision should be considered as an intervention strategy to help reduce the spread of HIV (Buvé *et al.*, 2001*b*). Confounding factors, such as sexual behaviour, social and economic circumstances and STIs, were taken into account and a multi-variate analysis of circumcision as a risk factor of HIV infection was conducted in Kisumu (Auvert *et al.*, 2001). This analysis found that there were two factors that significantly affected the probability of HIV transmission during sex: circumcision and co-infection with HSV-2 infection.

Randomized controlled trials provide the strongest evidence that male circumcision is effective. The ANRS1265 randomized controlled trial was carried out in Orange Farm, South Africa (Auvert *et al.*, 2005). Men aged 18-24 years were randomized to an intervention or a control group. The men in the intervention group were circumcised immediately. The relative risk of HIV acquisition in the intervention group was 0.40 (95% CI 0.24–0.68) corresponding to a protection of 60% (95% CI 0.32–0.76). In another randomized trial in Kisumu, Kenya, men aged 18–24 years were recruited (Bailey *et al.*, 2007). The trial was stopped 16 months after enrolment because of the significant reduction in HIV incidence in the circumcision group. In another randomized controlled trial in Rakai, Uganda, Gray *et al.* (2007*a*) studied men aged 15–49 years. This trial was also terminated early due to the reductions in HIV incidence in the intervention arm. The protective effect of male circumcision against HIV acquisition was estimated to be 51% (95% CI 16–72%). The adverse events that occurred in the 3 trials were all resolved with medical treatment. A meta-analysis of these randomized controlled trials showed an average relative risk of 0.44 (95% CI 0.33–0.60) (Mills *et al.*, 2008). Table 2.2 is a summary of the reduced risk associated with male circumcision found in

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the three randomized controlled trials.

Table 2.2: Relative risk of HIV infection in circumcised men compared to uncircumcised men, based on three randomized controlled trials.

Study	**Location**	**Relative Risk (95% CI)**	**Effectiveness (95% CI)**
Auvert *et al.* (2005)	Orange Farm, S.A.	0.40 (0.25-0.70)	60% (32%-76%)
Gray *et al.* (2007*a*)	Rakai, Uganda	0.49 (0.30-0.83)	51% (16%-72%)
Bailey *et al.* (2007)	Kisumu, Kenya	0.47 (0.28-0.78)	53% (32%-77%)

A concern regarding the introduction of male circumcision as an intervention strategy is that circumcised men may believe that circumcision protects against acquiring HIV (Lagarde *et al.*, 2003) and thus increase their sexual risk behaviour. This risk compensation could then offset the benefits of circumcision and is an important factor to consider when promoting circumcision as an intervention (Hallet *et al.*, 2008). There is also concern that male circumcision might increase the HIV infection risk if sexual intercourse is resumed before wound healing.

2.2.3 Acceptability of Male Circumcision

Acceptability of medical male circumcision is highly variable. Acceptability of medical male circumcision among Xhosa speakers, who traditionally practise male circumcision as a rite of passage into manhood, is very low (Rennie *et al.*, 2007; Mark *et al.*, 2012). A study by Rain-Taljaard *et al.* (2003) investigates the potential acceptability of male circumcision as an intervention against HIV in population with a high HIV prevalence in South Africa. In the analysis, of the males aged 13–24 years, 59.9% said they would get circumcised if it was

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shown to decrease the chance of getting HIV and STDs. A review done by Westercamp and Bailey (2007) on the acceptability of male circumcision in Africa found that the median proportion of uncircumcised men willing to be circumcised was 65% (range 29–87%). Over 50% of men participating in a community-based cross-sectional study conducted in the Westonaria District of South Africa showed willingness to be circumcised (Lagarde *et al.*, 2003). This percentage increased to 72.5% if male circumcision were to protect against acquiring HIV/STDs.

The previous studies evaluated stated acceptability, which may differ from actual uptake. As part of the HVTN503 vaccine efficacy trial, male circumcision was offered as an HIV prevention option (de Bruyn *et al.*, 2009). Of the uncircumcised males, aged 18–35 years, in the study, 33% accepted the offer to get circumcised. In another South African study of men aged 15–49 years conducted by Lissouba *et al.* (2011) in Orange Farm, the uptake of male circumcision was 58.8%.

The age at circumcision would greatly affect the impact of male circumcision on HIV incidence (Londish and Murray, 2008; White *et al.*, 2008). Westercamp and Bailey (2007) found the age of circumcision preferred by parents to be either at birth or around puberty and adolescence, and that acceptability among youth was more positive than in older adults. Women appear to have considerable influence on male circumcision, whether it is to circumcise their sons at birth or to influence their partner's decision to circumcise. Westercamp and Bailey (2007) found that 69% (range 47–79%) of women favoured circumcision for their partners and 71% (range 50–90%) of women were willing to circumcise their sons. Lagarde *et al.* (2003) found that 13% of men reported they were circumcised because their partner requested it.

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2.2.4 Mathematical Models of Male Circumcision

Various mathematical models have been developed to evaluate the impact of male circumcision on HIV incidence and prevalence. Increased coverage of male circumcision results in a greater reduction in HIV incidence (Hallet *et al.*, 2008; Nagelkerke *et al.*, 2007; White *et al.*, 2008; Williams *et al.*, 2006), but it would take more than ten years to observe the full effect. When investigating targeting male circumcision at adolescents or youth, Londish and Murray (2008) found that targeting 10–15 year old males would not have a massive impact on HIV incidence in the short term, as most in this age group are not sexually active. Targeting either 15–20 or 20–25 year old males would have much more of an impact (Londish and Murray, 2008; White *et al.*, 2008). These are the only studies that have considered the effect of targeting MMC promotion to adolescent or young age groups.

Combining male circumcision with other prevention methods, like condoms, has been shown to have a greater impact on HIV incidence than male circumcision alone (Podder *et al.*, 2007). Behavioural change and male circumcision in combination, also yields a greater impact (Hallet *et al.*, 2008). Alsallaq *et al.* (2013) predicts a potential for synergies between three prevention methods (MMC, ART and home-based HIV counselling and testing). The authors report a combined reduction in HIV incidence in Kwazulu-Natal, South Africa, of about 50% over a 4 year period. In another model also focussing on the HIV incidence in KwaZulu-Natal, South Africa, Cremin *et al.* (2013) demonstrated a greater decline in HIV incidence when modelling the impact of a combination of MMC with PrEP and early ART (but at very high coverage levels), than what was expected from the individual prevention methods.

Several modelling studies have evaluated the potential effect of risk com-

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pensation in circumcised men. Risk compensation, behavioural disinhibition and a decrease in condom use could all negate the effect of male circumcision on HIV incidence (Gray *et al.*, 2007*b*; Hallet *et al.*, 2008; Nagelkerke *et al.*, 2007; White *et al.*, 2008). Behavioural disinhibition could also directly affect women and potentially result in an increase in HIV incidence in women (Hallet *et al.*, 2008; Dushoff *et al.*, 2011). However, in most simulations in which little or no risk compensation is assumed, the effect of male circumcision on HIV incidence rates in women is positive (Alsallaq *et al.*, 2009).

2.3 Pre-exposure Prophylaxis

Pre-exposure prophylaxis (PrEP) is the prophylactic use of antiretroviral drugs (ARVs) by HIV-uninfected individuals in an attempt to prevent HIV acquisition. The idea behind PrEP is to prevent HIV from replicating after an exposure to an HIV transmission event, thus decreasing the probability of HIV establishing permanent infection.

ARVs are currently being given to HIV-infected pregnant women before and during birth, as well as to neonates, in order to prevent mother to child transmission (PMTCT) of HIV. ARVs are also used as post-exposure prophylaxis (PEP) by health-care workers after percutaneous exposure to HIV, to reduce the risk of HIV transmission (Cardo *et al.*, 1997). Tenofovir Disoproxil Fumarate(TDF) and Emtricitabine (FTC), as well as combination of the two, FTC-TDF, are now being considered as possible PrEP. TDF and TDF-FTC have good safety profiles, as well as infrequent side-effects (Grant *et al.*, 2010; Thigpen *et al.*, 2012; Baeten *et al.*, 2012). Some side-effects include gastrointestinal discomfort, dizziness, headache, and rash. FTC-TDF also has occasional skin pigmentation as an adverse effect. Another concern

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is the loss of bone mineral density (Thigpen *et al.*, 2012). Different regimens, either TDF or FTC or FTC-TDF combinations, and different dosing regimens, either continuous, intermittent or coitally dependant, are being investigated. Microbicides are a form of pre-exposure prophylaxis, but generally the two terms are understood to refer to different routes of administration. Microbicides are administered vaginally and pre-exposure prophylaxis is administered orally.

2.3.1 Evidence of Efficacy of PrEP

Clinical trials have already been conducted in various settings. A randomized controlled trial conducted in Ghana, Cameroon and Nigeria could not show the effectiveness of TDF in preventing HIV infection (Peterson *et al.*, 2007*b*). A phase 3 trial involving MSM, referred to as the iPrEx study, has also been completed recently (Grant *et al.*, 2010). Participants from Peru, Ecuador, Brazil, the United States, Thailand and South Africa were randomly assigned to receive either a combination of FTC-TDF (Truvada) or a placebo once daily. The Truvada showed an efficacy of 44% (95% CI 15–63%). In a sub-analysis of the iPrEx data, individuals with adherence levels of 90% or more, experienced an HIV risk reduction of 72.8% (95% CI 40.7–87.5%) if they received Truvada. Another recent trial, the FEM-PrEP trial, evaluated oral Truvada, with a sample size of 3900 women (Van Damme *et al.*, 2012). The trial was stopped early due to a lack of evidence, indicating no conclusive reduction in the rate of HIV incidence among the trial participants. The lack of efficacy in the FEM-PrEP trial was likely due to low adherence as less than 40% of the participants had detectable levels of drugs in their blood. Another clinical trial among men and women aged 18–39 years in Botwsana investigated the

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impact of FTC-TDF (Thigpen *et al.*, 2012). The overall efficacy of the product was 62.2% (95% CI 21.5–83.4%) with high levels of acceptability and product adherence. In another trial, HIV serodiscordant couples in Kenya and Uganda were randomized in a trial to one of three study groups; receiving either only TDF, TDF-FTC or a placebo (Baeten *et al.*, 2012). The trial demonstrated an HIV risk reduction of 67% (95% CI 44–81%) in the TDF arm, and 75% (95% CI 55–87%) in the TDF-FTC arm. The efficacy was even higher in subjects who had the study drug detectable in their blood plasma. Results from the Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial demonstrated no effectiveness of the oral TDF and FTC-TDF against HIV acquisition (Marrazzo *et al.*, 2013) and this appeared to be due to low average levels of adherence. These results are a clear indication of the importance of adherence.

2.3.2 Acceptability of and Adherence to PrEP

In a study of high risk Ghanaian women aged 18–35 years, the acceptability of oral TDF was high (Guest *et al.*, 2010). In a cross-sectional study by Heffron *et al.* (2012), very high levels of acceptability of PrEP (92.7%) were reported by the HIV uninfected partners of HIV-positive individuals in Kenya. Most of the studies focus on self-reported acceptability. There does not seem to be any data on actual uptake. No relevant studies that focus on the acceptability of PrEP in adolescents were found, although the Eisingerich *et al.* (2012) study found that acceptability was highest in younger adults. This study found higher acceptability in individuals who had higher consistency of condom use.

Adherence may be related to age as Marrazzo *et al.* (2013) found drug concentrations were higher in older women than in younger women. Guest

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et al. (2010) reported that adherence levels were over 80%. Testing for drug in blood specimens may be a more accurate measure of adherence than pill counts, and self-reported adherence may be very unreliable (as the VOICE data show). Adherence levels measured in the different RCTs are in the Table 2.3.

Table 2.3: Adherence levels to PrEP as measured in four randomized control trials.

Trial Reference	Pill counts (%)	Detectable levels of drugs (%)
Grant *et al.* (2010)	95	51
Thigpen *et al.* (2012)	84.1	81
Baeten *et al.* (2012)	92.1	82
Van Damme *et al.* (2012)	86	38

2.3.3 Mathematical Models of Pre-exposure Prophylaxis

Prior to the effectiveness of PrEP being shown in trials (Grant *et al.*, 2010; Thigpen *et al.*, 2012; Baeten *et al.*, 2012), modellers assumed a wide range of values (30–90%) for the efficacy of PrEP to determine its impact on the HIV epidemic (Abbas *et al.*, 2007; Vissers *et al.*, 2008; Desai *et al.*, 2008; Paltiel *et al.*, 2009). The deterministic model by Abbas *et al.* (2007) predicts that with 90% effective PrEP and 75% coverage of the sexually active target population, a 74% decrease in HIV incidence can be achieved in 10 years. With the assumptions of an efficacy of 50% and adherence of 50%, Desai *et al.* (2008) predicts that PrEP would avert 8.7% of new infections over a 5 year period (the population was high risk MSM in New York City).

Some models predict that targeting the most-at-risk population and those with highest sexual activity, such as 15–35 year old women in South Africa

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(Pretorius *et al.*, 2010), and MSM in the United States (Desai *et al.*, 2008; Paltiel *et al.*, 2009), would have the greatest impact on HIV incidence and avert the most HIV infections in the overall population. Very few studies have considered the effect of targeting PrEP at adolescents/young adults.

A few models have evaluated the possible impact of risk compensation. A decrease in condom use (Vissers *et al.*, 2008; Van de Vijver *et al.*, 2009; Cremin *et al.*, 2013) and an increase in risk behaviour (Abbas *et al.*, 2007; Supervie *et al.*, 2010) could negate the impact of PrEP.

The impact of PrEP, as a method of decreasing susceptibility, in combination with ART, as a method of reducing infectiousness, has been modelled (Hallett *et al.*, 2011). This study considered the effect of PrEP and ART in serodiscordant couples and found that to achieve the most effective impact on reducing HIV transmission, the HIV uninfected partner should always use PrEP, or until the HIV infected partner dies, although this may not be the most cost effective strategy. The model by Cremin *et al.* (2013) predicts a huge decline in the level of HIV infection if PrEP is used in combination with ART and medical male circumcision, but these predictions are only valid at high coverage levels.

The possible increase in acquired drug resistance with the introduction of PrEP has become a major concern and has been considered in a number of modelling studies (Van de Vijver and Coucher, 2010; Supervie *et al.*, 2010; Baggaley *et al.*, 2011). An increase in risk behaviour could result in an increase in both acquired and transmitted drug resistance (Supervie *et al.*, 2011). Although all three trials (Grant *et al.*, 2010; Thigpen *et al.*, 2012; Baeten *et al.*, 2012) have shown very low levels of drug resistance by those participants who have seroconverted, these results were based on ideal conditions where HIV

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testing was conducted frequently. These same testing conditions may not apply to the real world. Abbas *et al.* (2013) predicts that the drug resistance from ART would far exceed that of PrEP.

2.4 Vaginal Microbicides

Vaginal microbicides are chemical products that can be applied topically to the vaginal mucosa to reduce the risk of HIV infection, as well as infection by other STIs. The mucosal epithelium of the vagina does not have a receptor for HIV-1. For sexual transmission of HIV to occur in females, the virus should thus pass through the vaginal epithelium to the subepithelial tissue which contains the target cells, such as the Langerhans cells, T-cells and macrophages (Minces and McGowan, 2010). Once the virus has passed the epithelial barriers, uptake of the virus by the dendritic cells occurs and the virus is subsequently disseminated to the draining lymph nodes, at which point systemic infection is established (Stone, 2002; Shattock and Moore, 2003).

In order to prevent sexual transmission of HIV, a microbicide should be capable of the following:

- act as a physical barrier at the vaginal mucosa;
- inactivate the virus while it is still in the vaginal lumen;
- prevent the virus from attaching to and fusing with host cells;
- prevent the virus from replicating if infection of the cells has already happened (Stone, 2002).

There are various types of vaginal microbicides. Early generations of microbicide products that did not incorporate antiretroviral agents into the mi-

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crobicides were not very successful in preventing HIV infection (Van Damme *et al.*, 2002; Bax *et al.*, 2002; Peterson *et al.*, 2007*a*; Van Damme *et al.*, 2008; Skoler-Karpoff *et al.*, 2008; McCormack *et al.*, 2010; Ramjee *et al.*, 2010). More recent research has focused on antiretroviral-based vaginal microbicides, which appear more promising than the previous generations of microbicide products. The sections that follow focus mainly on these antiretroviral-based vaginal microbicide products.

2.4.1 Efficacy of Vaginal Microbicides

Effectiveness and safety of 1% tenofovir vaginal gel was assessed by the Centre for the AIDS Program of Research in South Africa (CAPRISA) 004 trial and results showed that the gel reduced HIV acquisition by an estimated 39% overall and by 54% in women with high gel usage (Abdool Karim *et al.*, 2010). In the Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial 5029 women were randomized to use 1 of 3 prevention methods or 2 placebos. The study was conducted in 3 South African sites, 2 Zimbabwean sites and 1 Ugandan site. One of the 3 prevention methods was a tenofovir-based vaginal microbicide gel. The results of this trial were not statistically significant as there were only 15% fewer infections in those women who used the vaginal microbicide gel when compared with those who used the placebo gel (Marrazzo *et al.*, 2013).

Innovations in the field of antiretroviral based vaginal microbicides (ARV-VM) include the development of gel formulations of the nucleotide reverse transcriptase inhibitor (NRTI) tenofovir and non-nucleoside reverse transcriptase inhibitors (NNRTI) dapivirine and UC781. Phase 2 safety trials for dapivirine are currently ongoing in Kenya, Malawi, Rwanda, Tanzania and South Africa.

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UC781 gel is currently in phase 1 testing (Ramjee *et al.*, 2010). Viral entry inhibitors such as chemokine analogues, lectins and monoclonal antibodies are also being evaluated as potential microbicides (Morris and Lacey, 2010).

2.4.2 Acceptability of and Adherence to Vaginal Microbicides

There is a high acceptability (>76%)of vaginal microbicides by women as indicated by various phase 1 and 2 trials that have evaluated the acceptability of the products (Ramjee *et al.*, 2010; Rosen *et al.*, 2008; Altini *et al.*, 2010). Products are generally liked by both men and women, who report that gel increases sexual pleasure (Ramjee *et al.*, 2001). Factors that could influence the acceptability of vaginal microbicides among users are the characteristics of the products, such as contraceptive or noncontraceptive properties, amount of lubrication, timing of insertion and the impact on sexual pleasure (Ramjee *et al.*, 2001). Different product formulations (gel, film, ring) might be preferred by different women, and offering women a selection of different product formulations might increase overall acceptability (Nel *et al.*, 2011). A placebo vaginal ring was found to be highly acceptable among African women in the acceptability study by Van der Straten *et al.* (2012).

Adherence by female participants is generally high. Levels of adherence among women in Zimbabwe to a combination of a gel formulation and a diaphragm or a single product gel formulation was measured in a study by Van der Straten *et al.* (2008). The study showed that although acceptability of the products was high, only 56% reported using the gel at every sex act. In this study, consistent use of the product was significantly associated with older age. Adherence would be less of an issue with the ring than with any of the

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other product formulations (Van der Straten *et al.*, 2012). Of the participants in the CAPRISA 004 trial, 38% were highly adherent (>80% gel adherence), 20% had intermediate adherence (50-80% adherence) and 42% had low levels of adherence (<50% adherence).

Different product formulation options could not only allow for greater acceptability but also for higher adherence levels which could result in a more effective microbicide (Nel *et al.*, 2011).

2.4.3 Mathematical Models of Vaginal Microbicides

Several mathematical modelling studies have evaluated the potential population-level impact of vaginal microbicides. The most important parameter affecting this impact is the assumed efficacy, with greater reduction in HIV incidence expected with a product of higher efficacy (Karmon *et al.*, 2003; Smith *et al.*, 2005; Wilson *et al.*, 2008; Williams *et al.*, 2011). Coverage levels of vaginal microbicides are also vital. For example, Williams *et al.* (2011) predicts a 65% reduction in HIV transmission if the coverage levels are high and only a 53% reduction if coverage is low, in a model based on South African data. Modelling studies have also shown that adherence is a critical parameter determining population-level impact (Karmon *et al.*, 2003; Wilson *et al.*, 2008; Williams *et al.*, 2011).

Early models of vaginal microbicides suggest a concern regarding switching from using condoms to using vaginal microbicides (Foss *et al.*, 2003; Karmon *et al.*, 2003; Eaton and Kalichman, 2007). The impact of vaginal microbicides on HIV incidence could be negated should women choose to use the microbicides in place of condoms. Condoms are more effective in reducing the risk of HIV infection (Pinkerton and Abramson, 1997). There may thus be a trade

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off between uptake and efficacy (Karmon *et al.*, 2003). Risk compensation is thus a factor to consider, as this could also negate the impact of vaginal microbicides on HIV incidence (Eaton and Kalichman, 2007).

The development of ARV drug resistance could increase as antiretroviral microbicides become available for population level use (Morris and Lacey, 2010; Wilson *et al.*, 2008). Wilson *et al.* (2008) predict that regular screening during a trial would mask the true development of ARV resistance and that the ARV drug resistance would be more prevalent if microbicides were introduced at a population level with less frequent screening of HIV-negative women.

Combinations of microbicides with other prevention methods have been modelled. With assumed efficacies of 60% for a microbicide and 60% for male circumcision, Cox *et al.* (2011) predicts that the coverage required to achieve a particular HIV incidence reduction, for a combination of the two prevention methods is much less than that required for either prevention method alone. Calibrated to South African data, a model by Long and Stavert (2013) investigates the impact of a combination of PrEP, MMC and microbicides. The authors predict that this combination would avert 43.5% of HIV infections. By adding ART to the combination, the reduction in HIV incidence would be much greater, 61.9%, over a ten year period.

Although vaginal microbicides are a much needed female-initiated prevention method, the indirect effect on men is also beneficial (Wilson *et al.*, 2008). A decrease in the prevalence of HIV in females would result in less transmission, thus affecting the HIV incidence in men.

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2.5 Conclusion

In this Chapter we reviewed the different studies and models that focus on the sexual behaviour of adolescents. The main concepts included the age of sexual debut, sexual frequency, partnership formation and dissolution, age-mixing and the levels of condom use of adolescents. The prevention methods that we consider are medical male circumcision, pre-exposure prophylaxis and antiretroviral-based vaginal microbicides, and for each of these prevention methods we reviewed studies that considered the issues of the acceptability of and adherence to the prevention methods. Although acceptability of new prevention methods is high, few studies have examined actual uptake, and there remains much uncertainty regarding the potential for risk compensation. For evidence of efficacy of the prevention methods, we reviewed the results of the relevant randomized controlled trials. Although there have been a large number of mathematical modelling studies that have assessed the effect of these new prevention strategies, few have assessed the effect of focused provision of these prevention methods to adolescents. The review of these studies and models assists us in identifying data sources that are relevant in estimating the parameters used in our model.

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Chapter 3

Mathematical Model

3.1 Method

Stochastic individual-based simulations are typically more complex than deterministic compartmental models, but the results are potentially more realistic. Individual-based models can allow for greater heterogeneity in behaviour and susceptibility to HIV than is typically feasible in a deterministic model. The stochastic variation is potentially important in the sample size calculations. The mathematical model developed here is an individual-based stochastic simulation estimating the impact of the various prevention methods on the heterosexual transmission of HIV among adolescents.

Since the model will be used to simulate a hypothetical randomized controlled trial over a short period, it is sufficient to use a static model. We have therefore used a static model with the HIV status of partners not enrolled in the trial being simulated stochastically. Heterosexual HIV transmission is the only transmission mode considered. The model is used to determine the HIV incidence in a cohort of adolescents comparing no prevention methods to a scenario in which adolescents are offered multiple HIV prevention methods. This

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adolescent population is stratified by age and sex. The prevention methods under consideration are medical male circumcision, vaginal microbicides and pre-exposure prophylaxis.

3.2 Modelling the Baseline Characteristics of each Individual

The population in the model is based on the demography of an adolescent population living in urban, informal settlements in South Africa. The model is applied separately to a community in which male circumcision is traditionally practised and another community in which it is not traditionally practised. The levels of acceptability and uptake of male circumcision differ in these two types of communities.

When modelling the baseline characteristics, we first assign sex and age. If the individual is male, we randomly determine whether or not the individual is circumcised at baseline. The age of sexual debut is then assigned to determine whether the individual is sexually experienced at the start of the simulation. Following this, each individual is randomly assigned a risk level (either low risk or high risk). Finally, each individual is assigned an HIV status and a number of partners at baseline.

3.2.1 Sex and Age

The sex of each individual was randomly assigned at the start of the simulation. We assumed a 1:1 ratio between males and females. For the purpose of the initial model calibration each individual is randomly assigned an age between 10 and 20 using a uniform distribution. When simulating the actual conditions

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under which the trial is conducted, a narrower age interval (15–18) is used.

3.2.2 Age of Circumcision (males only)

A function that relates the probability of being circumcised to the age of the individual was used to randomly assign an age at which traditional male circumcision would be performed (in the absence of MMC). The function was modelled using a cumulative Weibull distribution. We used the prevalence data based on Xhosa-speaking males in the traditional male circumcision setting from a study analysing the national survey of 2002 (Connolly *et al.*, 2008*a*). The parameters a and b of the Weibull distribution were estimated based on this prevalence and a mean age of circumcision of 22.8 years (Rain-Taljaard *et al.*, 2003). The cumulative density function, given by

$$C(x, a, b) = 1 - e^{-(\frac{x}{b})^a}, \tag{3.2.1}$$

where the shape parameter a was estimated to be 5.9 and the scale parameter b was estimated to be 24.4, is shown in Figure 3.1 by the dashed line. The solid line indicates the simulated prevalence of male circumcision, where the simulated population consisted of 50 000 individuals.

For males in the community where male circumcision is not traditionally practised, the prevalence of male circumcision is negligible and we thus assumed that none of these males were circumcised at baseline.

3.2.3 Age of Sexual Debut

Each individual's age of sexual debut was randomly assigned at baseline by sampling from a Weibull density with a cumulative distribution function,

$$S(x, c_g, d_g) = 1 - e^{-(\frac{x}{d_g})^{c_g}}. \tag{3.2.2}$$

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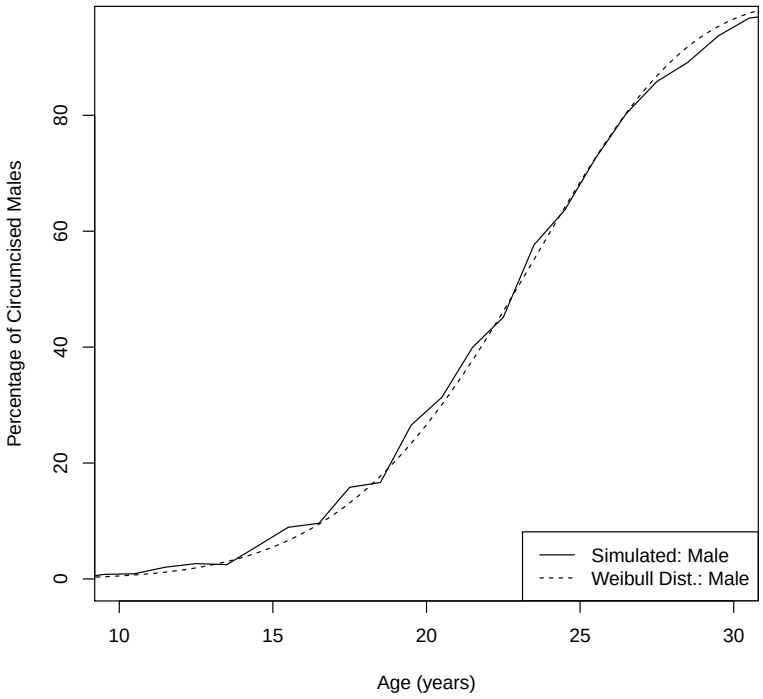

Figure 3.1: The prevalence of male circumcision. The dashed line indicates the function used to relate the probability of being circumcised to the age of circumcision and the solid line indicates the simulated prevalence of male circumcision. A total of 50 000 individuals were simulated, of which 25 333 were males.

The parameters were fitted using data from the NCS survey of 2009 (Johnson *et al.*, 2010). Figure 3.2 shows the simulated proportion of individuals who are sexually experienced at the start of the simulation and how they compare to the survey data. The shape parameter c was estimated to be 8.5 for both sexes, and the scale parameter d was estimated to be 18 for females and 19 for males. The age of sexual debut could be lower than estimated in the survey because when individuals in surveys are interviewed face-to-face, there is the possibility of creating social desirability bias. This social desirability bias is likely to be different in males and females (Mensch *et al.*, 2003).

To determine whether or not an individual is sexually active at baseline, we

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compare the individual's simulated age to the simulated age of sexual debut. If the individual's age is less than the age of sexual debut, then the individual is a virgin at baseline. Otherwise, they are regarded as being sexually active at the start of the simulation.

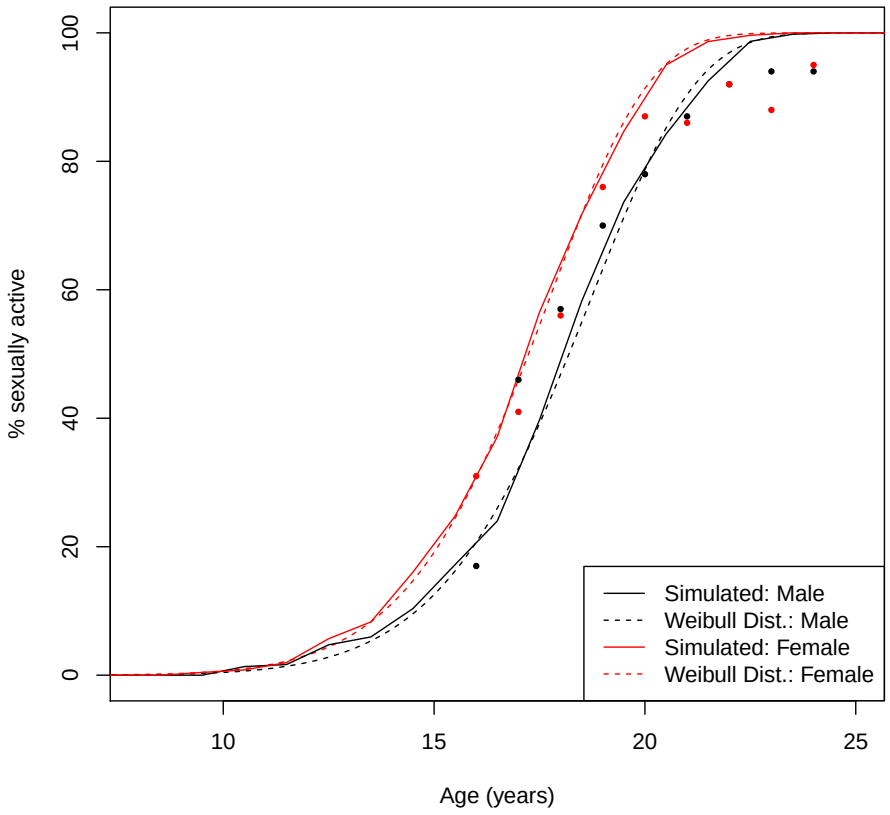

Figure 3.2: Proportions consisting of sexually experienced individuals. The red lines and dots relate to females and the black lines and dots, males. The total simulated population size was 50 000. The solid lines are the simulated proportions of sexually experienced individuals at the start of the simulation. The dashed line indicates the function that was fitted to the data. The dots are data from the National HIV Communication Survey of 2009 (Johnson *et al.*, 2010).

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3.2.4 Risk Level

The adolescent population is split into two categories, namely, a high risk and a low risk category. The high risk category is defined as individuals who have a propensity for concurrent partners and the low risk category consists of individuals who are serially monogamous. The risk level is assumed to depend on the age of sexual debut of the individual based on evidence showing an association between early sexual debut and high risk behaviour (Pettifor *et al.*, 2004*b*; Hallett *et al.*, 2007). We use a logit function to determine the probability that an individual is in the high risk group, i.e.

$$\text{logit } R_g(s) = p_g + q_g s, \tag{3.2.3}$$

where $R_g(s)$ is the percentage of the population of sex g that are high risk if their age of sexual debut is at age s. The parameters, p_g and q_g, are set so that the average proportion of individuals in the high risk group would be 35% in males and 25% in females. These proportions were chosen to be consistent with South African survey estimates of the proportions of people who have ever had concurrent sexual partners (Dunkle *et al.*, 2004; Jewkes *et al.*, 2002). The values of the parameters p and q were calculated to be 0.745 and -0.08, respectively, for males, and 0.44 and -0.09, respectively, for females. The negative values for q reflect the negative association between age of sexual debut, s, and the level of risk behaviour (Eaton *et al.*, 2003; Pettifor *et al.*, 2007; Wilson *et al.*, 2010). Figure 3.3 gives the probability that an individual is in the high risk category given their simulated age of sexual debut.

3.2.5 HIV Status

Data used to estimate HIV prevalence at baseline, is from the loveLife survey of HIV prevalence in South African youth, conducted in 2003 (Pettifor *et al.*,

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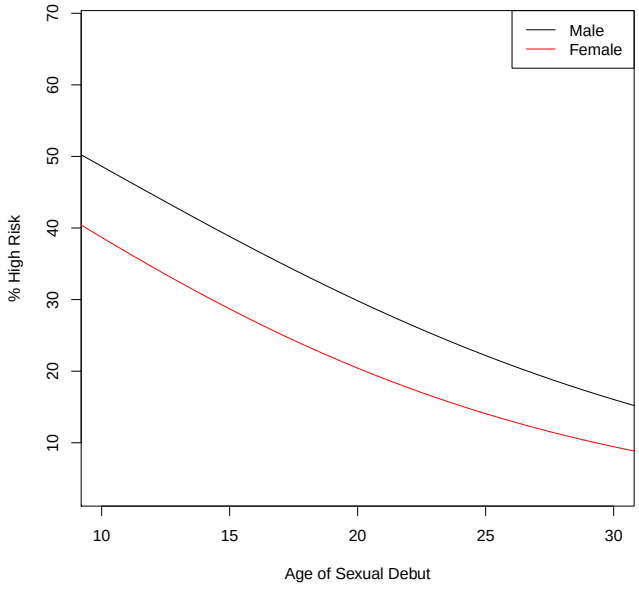

Figure 3.3: The percentage of high risk individuals. The red lines relate to females and the black lines, males.

2004*a*). The data was fitted using a log-normal distribution, similar to that used by Williams *et al.* (2000).

For each sex g, we have $H_g(x)$ which is a function that relates the probability of being HIV infected to the age of an individual. This is given by equation (3.2.4).

$$H_g(x) = \frac{N_g}{\sigma_g\sqrt{2\pi}(x - x_0)} \exp\left\{ \frac{-\left[\ln \frac{x-x_0}{m_g}\right]^2}{2{\sigma_g}^2} \right\}, \tag{3.2.4}$$

where x is age, with offset x_0; m_g the mean; σ_g the scale parameter; and normalized to N_g. The parameter values for each sex g are in Table 3.1. The simulated prevalence of HIV in youth compared to the data is shown in Figure 3.4.

The fitted log-normal distribution was adjusted to determine HIV prevalence in sexually experienced youth, $L_g(x)$, of sex g and age x and is defined

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by the following equation:

$$\begin{aligned} L_g(x) &= \frac{H_g(x)}{S(x, c_g, d_g)} \\ &= \frac{\frac{N_g}{\sigma_g\sqrt{2\pi}(x-x_0)} \exp\left\{\frac{-\left[\ln\frac{x-x_0}{m_g}\right]^2}{2{\sigma_g}^2}\right\}}{1-e^{-(\frac{x}{c_g})^{d_g}}}. \end{aligned} \tag{3.2.5}$$

We then randomly assigned an HIV status to each sexually experienced individual based on the estimated probability of HIV infection in equation 3.2.5. In the case of virgins we assumed the HIV status to be negative.

Table 3.1: The parameter estimates for the baseline characteristics of each individual's HIV status used in equation (3.2.4).

Parameters	**Estimates (Males)**	**Estimates (Females)**
N	7	7
x_0	1	1
σ	0.3	0.32
m	3.6	3.4

3.2.6 Number of Partners

The rates of partnership formation and dissolution are assumed to depend on the individual's risk group r, sex g and the current number of partners. When assigning the number of current partners to an individual at baseline, we consider the individual's rate of partner acquisition ($\lambda_{g,r}$) and rate of partnership dissolution ($\mu_{g,r}$), as well as the extent of their propensity for concurrent partnerships ($\theta_{g,r}$). In deriving the theoretical distribution of partner numbers in a cohort of individuals in the steady state equilibrium, we use the same rates, so that the distribution of partner numbers at baseline depends on sex and

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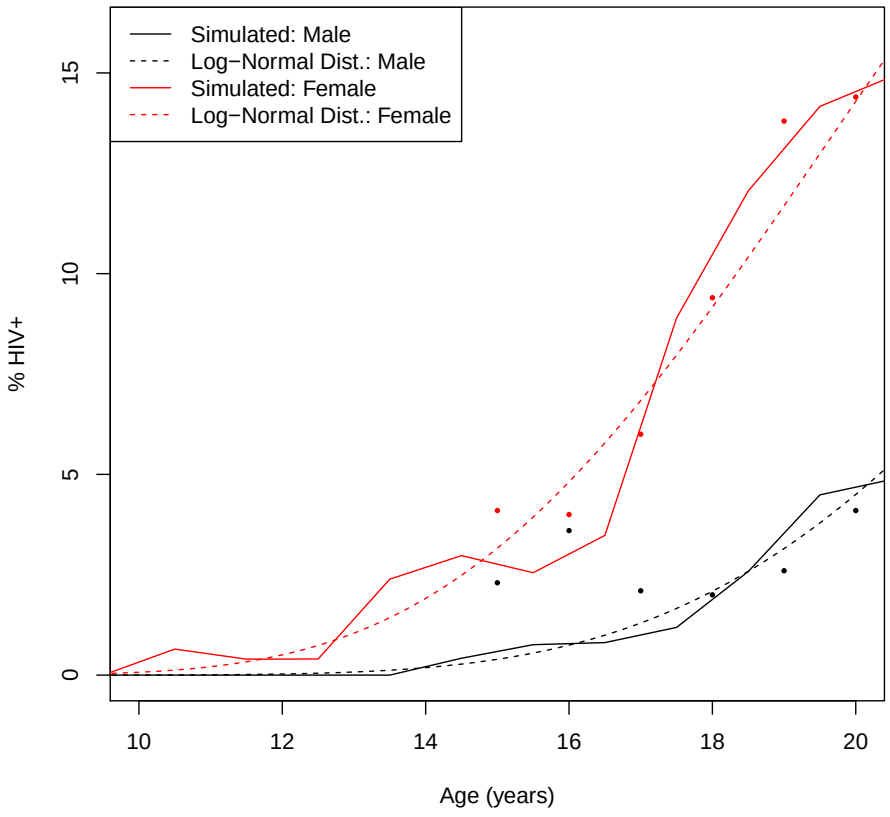

Figure 3.4: The prevalence of HIV in youth. The red lines and dots relate to females and the black lines and dots, males. The solid lines are the simulated HIV prevalence levels at baseline, and the dashed line indicates the fitted log-normal distribution. The dots are the data points from the loveLife survey of 2003 (Pettifor *et al.*, 2004*a*). The simulated population consisted of 50 000 individuals.

risk group. In the multi-state diagram shown in Figure 3.5, X_ρ represents the proportion of the cohort that has ρ current partner(s). Individuals can move between states as they acquire new partners and as existing partnerships are dissolved. We assumed that high risk individuals can have a maximum of 2 current partners. The model used for the low risk population is similar to that of the model used for the high risk population, except that the maximum number of current partners for the low risk group is assumed to be 1, i.e. setting

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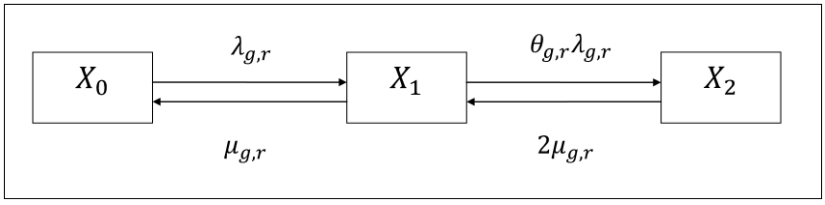

Figure 3.5: A multi-state model of sexual behaviour: used to determine the number of partners of an individual.

$\theta_{g,r} = 0$. This model can be represented by the following system of differential equations:

$$\begin{aligned}
\frac{dX_0}{dt} &= \mu_{g,r}X_1 - \lambda_{g,r}X_0, \\
\frac{dX_1}{dt} &= \lambda_{g,r}X_0 + 2\mu_{g,r}X_2 - (\mu_{g,r} + \lambda_{g,r}\theta_{g,r})X_1, \\
\frac{dX_2}{dt} &= \lambda_{g,r}\theta_{g,r}X_1 - 2\mu_{g,r}X_2.
\end{aligned} \tag{3.2.6}$$

The steady-state distribution of the number of partners was calculated from the assumed rates of partnership formation $\lambda_{g,r}$ and dissolution $\mu_{g,r}$ by setting the above derivatives to zero and the solutions are:

$$X_0 = \frac{2\mu_{g,r}^2}{2\mu_{g,r}(\mu_{g,r} + \lambda_{g,r}) + \lambda_{g,r}^2\theta_{g,r}}, \tag{3.2.7}$$

$$X_1 = \frac{2\mu_{g,r}\lambda_{g,r}}{2\mu_{g,r}(\mu_{g,r} + \lambda_{g,r}) + \lambda_{g,r}^2\theta_{g,r}}, \tag{3.2.8}$$

$$X_2 = \frac{\lambda_{g,r}^2\theta_{g,r}}{2\mu_{g,r}(\mu_{g,r} + \lambda_{g,r}) + \lambda_{g,r}^2\theta_{g,r}}. \tag{3.2.9}$$

Values used for these parameters are in Table 3.2. The parameter estimates are sourced from a study which considers the dynamics of sexual behaviour in South Africa in different age groups (Johnson *et al.*, 2009). Their estimates were based on fitting their model to reported numbers of partners from a nationally representative survey, as well as to HIV prevalence data. The λ parameters are those estimated for the 15–19 year age group and the parameters μ are based on data from Jewkes *et al.* (2001).

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Table 3.2: Parameter estimates used to determine the steady-state distribution of the number of partners used in equations (3.2.7)–(3.2.9).

Parameters	Estimates (Males)		Estimates (Females)	
	High Risk	Low Risk	High Risk	Low Risk
λ	7.3	1.387	14.6	8.76
θ	0.64	0	0.54	0
μ	2	2	2	2

The number of partners for each individual at baseline was randomly simulated from a multinomial distribution with parameters determined by this steady-state distribution of partner numbers (equations (3.2.7)–(3.2.9)).

3.3 Modelling the Partner's Characteristics

First the sex, then the age and finally the HIV status of the partner(s) of individuals were assigned.

3.3.1 Partner's Sex

Since we are only modelling the heterosexual transmission of HIV, the assigned sex of the partner is the opposite of the individual's.

3.3.2 Partner's Age

The simulated age of the partner was based on data from the various studies previously discussed in section 2.1.4. We assumed an average partner age difference of 3 years. We assumed that the male's age is greater than the female's age, and that age differences followed a gamma distribution. This distribution allows for a high level of skewness in the distribution of partner ages whereas using a Normal distribution would give a completely symmetrical distribution.

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The gamma shape parameter v was set at 1 and the scale parameter w was set at 3.

$$G_g(x, v, w) = \frac{1}{w^v \Gamma(v)} x^{v-1} e^{-\frac{x}{w}}. \tag{3.3.1}$$

We sampled the partner age from this distribution.

3.3.3 Partner's HIV Status

The HIV status of each partner was randomly assigned in the same manner as it was assigned for the individuals, i.e. taking into account the assumed log-normal relationship between HIV prevalence and age, and adjusted for sexual experience.

3.4 Modelling Movements Between States

The method used to model the movements between the states in adolescents is based on a stochastic simulation technique by Hansen (2000). For each individual in the modelled population, we determine the time to their next possible event and then which event it could be. Events include getting circumcised (in the case of uncircumcised males), becoming sexually active, forming a new partnership, dissolving a current partnership and becoming infected with HIV. The primary outcome in which we are interested is new HIV infections, and events occurring after HIV is acquired, such as the HIV disease progression or AIDS mortality, are therefore not modelled. Although we model HIV prevalence, we do not simulate AIDS mortality or non-AIDS mortality as both mortality rates are very low during adolescence (Zaba *et al.*, 2007). A multi-state model based on the characteristics of the model population is used to

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determine the possible events that could occur in an individual, as well as the time to the event. Figure 3.6 shows the multi-state model for an individual in the high risk group. Uncircumcised males are represented in the top half (Figure 3.6) and both females and circumcised males are represented in the lower half (Figure 3.6). Individuals can either be virgins, or sexually active with 0, 1 or 2 partners. In the multi-state model for individuals in the low risk group, the transition rate to the life-state "2 Partners" is set to zero since by definition individuals in the low risk group do not engage in concurrent partnerships.

Uncircumcised males, shown in the top half of Figure 3.6 could get circumcised when they are in any of the states. If they do get circumcised, they move to the corresponding state shown in the lower half of Figure 3.6. Individuals in the "virgin" state move to the "1 Partner" state on becoming sexually active. Once an individual is sexually active with one partner, there are 4 possible events that could occur:

- get circumcised (in the case of uncircumcised males);
- ϖ_1: form a new partnership;
- ϖ_2: dissolve a partnership; or
- ϖ_3: become infected with HIV, if their partner is HIV infected.

The time to circumcision is determined by subtracting the individual's current age from their age at circumcision (determined when simulating the baseline characteristics). Similarly, the time to becoming sexually active is determined by subtracting their current age from their age of sexual debut. The duration to male circumcision could change when we simulate the prevention methods since the prevention package could result in an increase in uptake of medical

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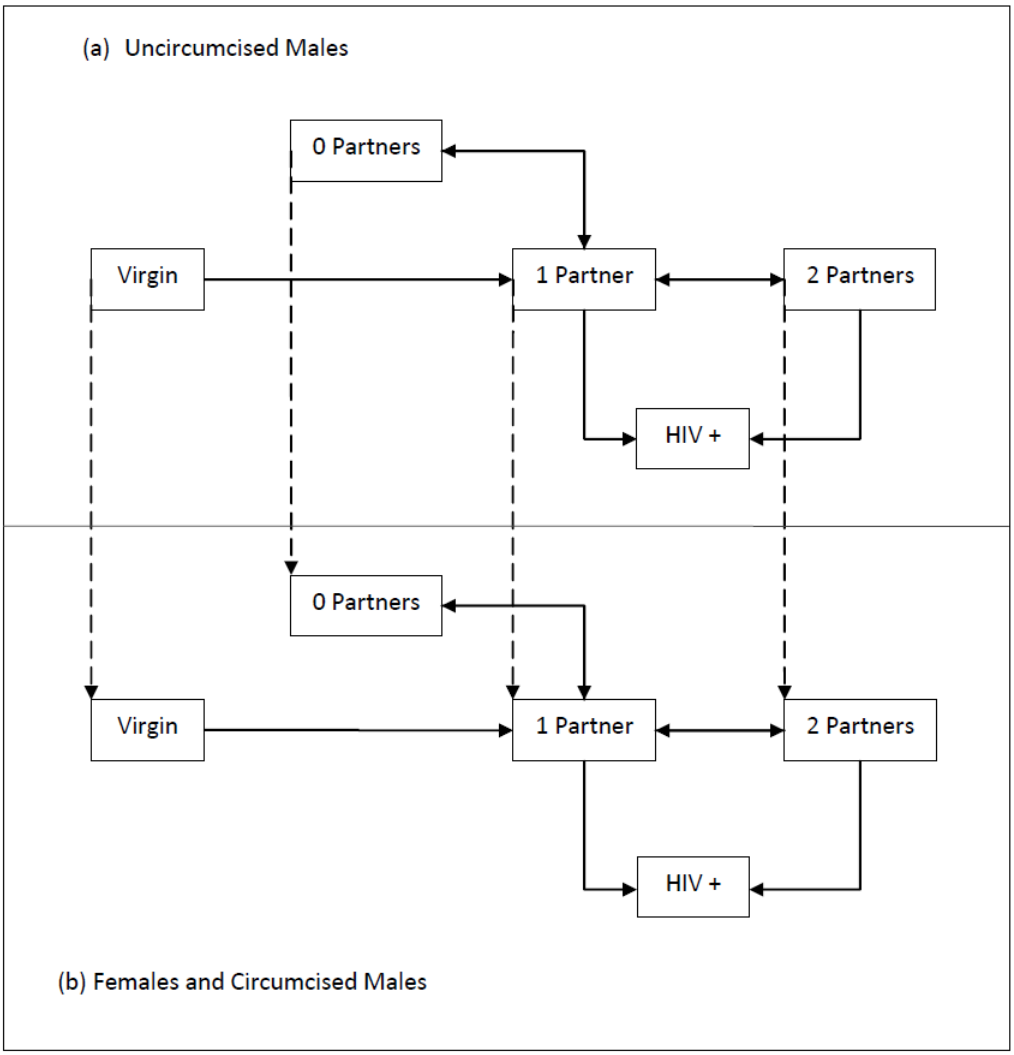

Figure 3.6: Multi-state model of sexual behaviour and HIV transmission: (a) Uncircumcised males; (b) Females and circumcised males. The dashed arrows from life-states in (a) to life-states in (b) indicate male circumcision.

male circumcision. To determine the time to any of the other three remaining possible events for individual i, we set

$$T_i(t) = 1 - exp(-\sum_{q=1}^{3} \vartheta_i(q)t), \tag{3.4.1}$$

where $T_i(t)$ is the probability an event occurs before time t, and $\vartheta_i(q)$ is the rate at which event q occurs in individual i. The rates are defined as follows:

- when $q = 1$, then $\vartheta_i(1)$ is the rate of partnership formation;

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- when $q = 2$, then $\vartheta_i(2)$ is the rate of partnership dissolution; and
- when $q = 3$, then $\vartheta_i(3)$ is the rate of HIV infection, if their partner is HIV infected.

Using equation 3.4.1 and equating $T_i(t)$ to a random number r_1, generated from the uniform $(0, 1)$ distribution, we determine the time to the next event; i.e.

$$t_i = \frac{-\log(1 - r_1)}{\sum_{q=1}^{3} \vartheta_i(q)}.$$

To determine which event occurs, we calculate the probability of each event, $P(\varpi_k)$.

$$P(\varpi_k) = \frac{\vartheta_i(k)}{\sum_{q=1}^{3} \vartheta_i(q)},$$

for $k = 1, 2, 3$. We randomly determine the event by generating a random number r_2 from the uniform $(0, 1)$ distribution, i.e.

- if $r_2 < P(\varpi_1)$ then the event is ϖ_1, or
- if $P(\varpi_1) \leq r_2 < (P(\varpi_1) + P(\varpi_2))$ then the event is ϖ_2, or
- if $r_2 \geq (P(\varpi_1) + P(\varpi_2))$ then the event is ϖ_3.

All the rates $\vartheta_i(q)$ are annual rates, and depend on the individual's sex g, risk level r and current number of partners ρ. The values of $\vartheta_i(1)$ and $\vartheta_i(2)$ are identical to the parameter values for $\lambda_{g,r}$ (the rates of partnership formation) and $\mu_{g,r}$ (the rates of partnership dissolution), respectively, as described in section 3.2.6 in Table 3.2.

3.4.1 The Rate of HIV Infection

The rate of HIV infection $\vartheta_i(3)$ for individual i depends on the following parameters.

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3.4.1.1 The annual rate of sexual contact n:

Estimates from Pettifor *et al.* (2004*a*) and Kelly (2000) were used to determine an estimate for n (described in the section 2.1.2). We assumed n to be 3 acts per 4-week period, i.e. 39 per annum.

3.4.1.2 The probability of condom usage γ:

The NCS of 2009, reports the frequency of condom use at last sex for ages 16–19 as 75% for males and 63% for females, and for ages 20–24 as 68% for males and 49% for females (Johnson *et al.*, 2010). For our simulation we assumed rates of 60% for both sexes, lower than the reported rates to make allowance for probable over-reporting of condom use.

3.4.1.3 The efficacy of a condom in preventing HIV transmission E:

We assumed an efficacy of 90% (Pinkerton and Abramson, 1997).

3.4.1.4 The probability of HIV transmission per act of unprotected sex with an HIV infected partner β_i:

We assumed a value of 0.0128, (Baeten *et al.*, 2005), for the female-to-male HIV transmission probability for all uncircumcised males in the simulation. For the male-to-female HIV transmission probability, an estimate of 0.04 was assumed (Pettifor *et al.*, 2007).

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3.4.1.5 Efficacy of male circumcision in preventing HIV transmission ϕ_i:

For circumcised males, an efficacy of 60% was assumed (Mills *et al.*, 2008). For females and uncircumcised males, $\phi_i = 0$.

The annual rate at which an individual becomes infected if their partner is HIV-positive is given by the equation:

$$\vartheta_i(3) = n\beta_i(1 - \gamma E)(1 - \phi_i). \tag{3.4.2}$$

In the event that a high risk individual has two HIV-positive partners, the rate of becoming HIV infected is doubled. We are not considering any variation in the annual rate of HIV transmission per sex act and thus the stages of HIV that impacts the rate of HIV transmission are not considered in our model.

Once an event, ϖ_k, is determined, the appropriate adjustments to the individual's characteristics are made. We simulate the sequence of events occurring in each individual, over a fixed period, and then aggregate the results for all individuals to calculate HIV incidence and HIV prevalence at the end of the period.

3.5 Model Estimates of HIV Incidence and HIV Prevalence in the Baseline Scenario

HIV incidence in the cohort of adolescents is the main output of the simulation. We simulated a population of 50000 individuals over a 4 year period. For the purpose of calibration, we simulated a cohort that was initially aged 10–24 years. We simulated individuals from urban informal settlements, where the HIV prevalence is relatively high. The simulated HIV incidence and age-specific incidence was then compared to previously-published estimates of HIV

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incidence in South African youth (Johnson *et al.*, 2012; Rehle *et al.*, 2010; Shisana *et al.*, 2009).

Figure 3.7 shows the simulated change in age-specific HIV prevalence over the four year term of the projection for both males and females. If HIV incidence rates were stable over time, we would expect no change in prevalence over the four year term of the simulation. The HIV prevalence comparisons for females aged 14–19 years illustrates a decline in prevalence. For females aged 20–24 years, there is an increase in the simulated HIV prevalence. This could be due to the fact that the model does not allow for marriage/long-term relationships. Females who do enter long-term relationships will generally be at a lower risk of HIV, and they will be a substantial proportion of 20–24 year olds but a small fraction of 15–19 year olds (Bongaarts, 2007). The model also does not account for the age-related changes in cervical ectopy which is more prevalent in younger females than older females (Myer *et al.*, 2006). Cervical ectopy is associated with greater HIV susceptibility (Moscicki *et al.*, 2001; Moss *et al.*, 1991), and the assumption that the transmission probability in 20–24 year old females is the same as that in the 15–19 year old females may therefore be leading to exaggerated estimates of HIV prevalence in 20–24 year old females. The male age-specific HIV prevalence levels do not change substantially over the four year projection term.

The age-specific HIV incidence for the simulation was calculated using the following formula:

$$\text{Incidence at age } x \quad = \quad \frac{H_x}{P_x},$$

where H_x is the number of new HIV infections at age x and P_x is the number of HIV negative person-years for age x. We calculated the HIV incidence for age groups 15–19, 15–24 and 20–24 year olds, which we used to compare to

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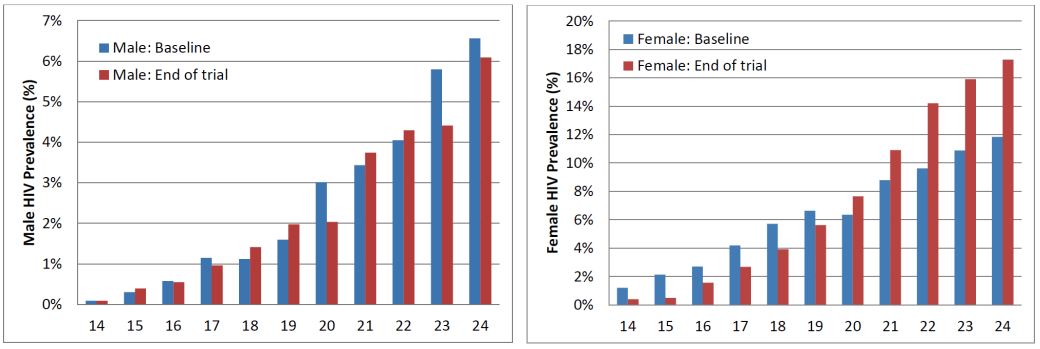

Figure 3.7: Simulated HIV prevalence comparisons for males (left) and females (right): at baseline and at the end of the trial.

other model estimates (Rehle *et al.*, 2010; Johnson *et al.*, 2012).

Figure 3.8 shows the comparison between the simulated HIV incidence and the HIV incidence rates estimated by the STI-HIV model and the ASSA2003 model (Johnson *et al.*, 2012) at the start of 2008. The simulated incidence for females in the 15–19 year age group is roughly consistent with the STI-HIV model but slightly lower than the ASSA2003 model. The simulated incidence for females in the 20–24 year age group is much higher than that of the other 2 models. This again could be due to the model not allowing for the change in the transmission probability at older ages or entry into long term relationships. Although the model estimates are likely to be unrealistic for women aged 20–24, this is not a major concern as we are primarily interested in HIV incidence in adolescents (aged < 20). For males in the 15–19 year age group, the simulated incidence is slightly higher than that of the other 2 models. Both the STI-HIV and ASSA2003 models consistently underestimate the HIV prevalence for this age group (Johnson *et al.*, 2012), thereby underestimating the incidence. In the 20–24 year age group, the simulated male incidence is consistent with both the STI-HIV and ASSA2003 models. However, the model estimates for this group do not reflect the overestimated incidence as that of

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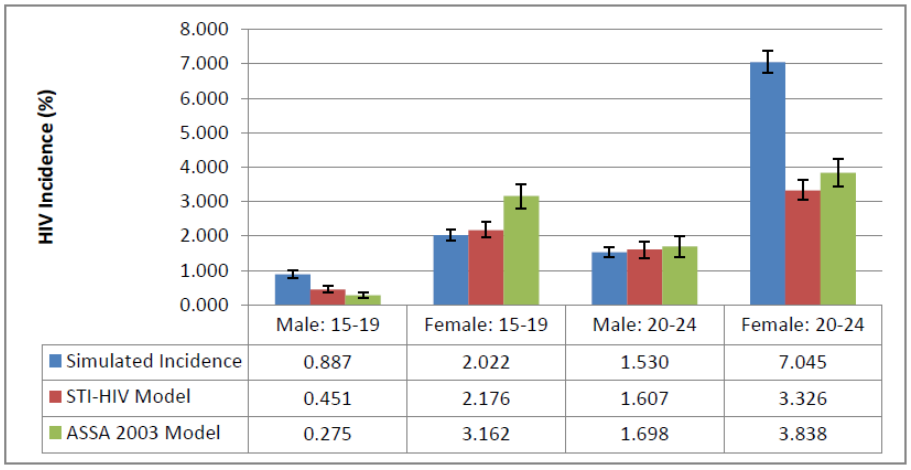
their female counterparts. The transmission probability for males remains the same because males are less likely to enter in long term relationships at young ages, unlike their female counterparts, and the cervical ectopy does not apply to men. Since the model is static, not dynamic, the overstated HIV prevalence in women aged 20–24 has no effect on the model estimates of male prevalence in the 20–24 age group.



	Male: 15-19	Female: 15-19	Male: 20-24	Female: 20-24
Simulated Incidence	0.887	2.022	1.530	7.045
STI-HIV Model	0.451	2.176	1.607	3.326
ASSA 2003 Model	0.275	3.162	1.698	3.838

Figure 3.8: HIV incidence comparisons: for males and females between the STI-HIV Model (Johnson *et al.*, 2012), ASSA2003 Model (Johnson *et al.*, 2012) and the simulated incidence over a four year period for the age groups 15–19 and 20–24.

Figure 3.9 illustrates the comparison between the simulated incidence and the incidence estimated by Rehle *et al.* (2010) for both males and females in the age group 15–24 years. Rehle *et al.* (2010) uses data from the HSRC national household surveys of 2002, 2005 and 2008 to determine the HIV incidence over the periods between the surveys. For males, our model estimate of incidence is higher but not much different from the HSRC estimates and for females, the simulated incidence lies in between the HSRC estimates for the 2002–2005 and 2005–2008 periods (Rehle *et al.*, 2010).

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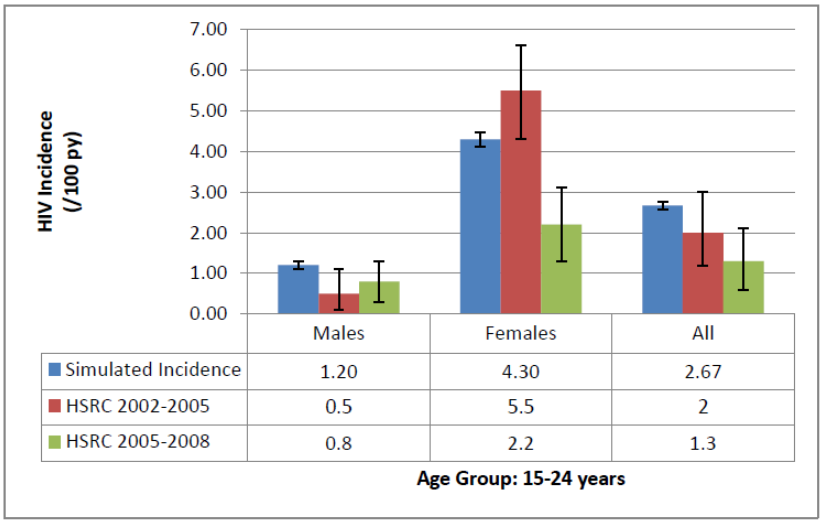

Figure 3.9: HIV incidence comparisons: for males and females between the HSRC 2002–2005 (Rehle *et al.*, 2010) and the HSRC 2005–2008 (Rehle *et al.*, 2010) and the simulated incidence over a four year period for the age group 15–24.

3.6 Conclusion

In this Chapter we developed an individual-based stochastic simulation that we use to estimate the HIV incidence among a cohort of adolescents, with no prevention methods. We used a multi-state model of sexual behaviour and HIV transmission, based on the characteristics of the modelled population of adolescents, to model the movements between the different states. Since the focus is HIV incidence, no events after HIV infection, such as HIV disease progression or AIDS mortality, is considered. The model is calibrated to South African data. The estimates of HIV incidence and HIV prevalence of this base-case model is roughly consistent with other South African estimates of HIV incidence. In the next Chapter, we extend this model to simulate a hypothetical individual-based randomized controlled trial where the individuals in the intervention arm are offered a choice of different prevention methods.

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Chapter 4

Clinical Trial Simulation

By extending the base-case model, we now simulate a hypothetical individual-based randomized controlled trial. A sample population is randomly assigned to either the control arm or the intervention arm of the trial. We use the model to determine the impact of various intervention packages on HIV incidence over a hypothetical trial duration of 3 years. We then compare different prevention packages, and by determining the relative risk of HIV incidence for each package, we select the best package to offer as an HIV intervention strategy.

4.1 The Baseline Characteristics

Using the model developed in Chapter 3, we simulated a sample of 2000 individuals. The sex, age of sexual debut, risk level and number of partners were simulated in the same manner as described in section 3.2. The remaining baseline characteristics were simulated as follows:

- **Age:** For the purpose of the trial, we assumed adolescents would only be recruited in the age range of 15–18 years.

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- **Male circumcision:** Taking into account that trial participants would be from different sites in which different cultural norms apply, we first selected the circumcision setting/background for each male. Fifty percent of the males were assumed to be from a setting that practises traditional male circumcision, where the individual is then assigned an age of traditional circumcision (in the same way as described in section 3.2.2), and the remaining 50% are from a setting where male circumcision is not practised traditionally and these males were assigned a status of not circumcised at baseline. Both the control arm and the intervention arm then consists of males that are from both settings. Males in the intervention arm were offered MMC at baseline. Uptake of MMC was assumed to be lower for males from the traditional male circumcision setting than from the setting in which male circumcision is not traditionally practised (Scott *et al.*, 2005; Mark *et al.*, 2012; Gray *et al.*, 2012).

- **HIV status:** All individuals were assigned a negative status, since the trial would only recruit adolescents who are initially HIV negative.

The characteristics of the partners were simulated using the method described in section 3.3, first assigning a sex, then an age, followed by an HIV status. Once all individuals are created, we randomly assigned half the sample to a control arm. The remaining half was assigned to the intervention arm. The intervention arm was then offered a selection of prevention methods.

4.2 The Prevention Methods

Individuals in the intervention arm of the trial are offered prevention methods from a prevention package. The options for males included:

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- medical male circumcision(MMC) - for uncircumcised males and
- PrEP.

For females, the options were either

- Vaginal microbicide gel formulation (VM-gel),
- Vaginal microbicide ring formulation (VM-ring), or
- PrEP.

When accounting for the impact of the prevention methods, we considered

- the acceptability of the prevention methods,
- the adherence to the products, and
- the efficacy of the different prevention methods.

Prevention method choices and levels of adherence were randomly generated for each individual. The simulation of the choice by an individual is described in the section 4.2.2.

4.2.1 Condom Use Consistency

Condoms are considered to be a highly effective method of HIV prevention. In the previous model we assumed no heterogeneity in condom use with an overall rate of condom use of 60% (subsubsection 3.4.1.2). However, consistency of condom use varies from individual to individual. We adapted the model to allow for the heterogeneity in condom use because there may be important interactions between consistency of condom use and uptake of other prevention methods. According to the loveLife survey of 2003, 33% of youth reported always using condoms, 31% reported never using condoms, and the overall

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proportion who used condoms at last sex was 52% (Pettifor *et al.*, 2004*a*). Taking this variation in condom use into account, each individual was assigned their own level of condom use. We referred to this as a condom use score $\mathcal{S}_{con}$ which was assumed to beta-distributed. By simulating a random number z_1 from the uniform U(0,1) distribution, we determined the pth quantile of the beta distribution using the inverse of the cumulative distribution function.

$$\mathrm{F}(p, w, y) = \frac{1}{B(w, y)} \int_0^p t^{w-1}(1-t)^{y-1} dt, \tag{4.2.1}$$

where $B(w, y)$ is the beta function. $B(w, y)$ is defined in terms of the gamma function $\Gamma(\cdot)$, i.e.

$$B(w, y) = \frac{\Gamma(w)\Gamma(y)}{\Gamma(w+y)}, \tag{4.2.2}$$

where the shape parameters, w and y, are defined in terms of the mean η_{con} and variance κ_{con}. The first shape parameter $w = \left(\frac{1-\eta_{con}}{\kappa^2_{con}} - \frac{1}{\eta_{con}}\right)\eta^2_{con}$ and the second shape parameter $y = w\left(\frac{1}{\eta_{con}} - 1\right)$.

The mean η_{con} of the beta distribution is the average rate of condom use. We assumed an average rate of condom use of 60%, the same as for the model in section 3.4.1.2. The variance parameter κ_{con} was set at 0.15, which leads to 20% of youth using condoms in less than 10% of sex acts and 39% of youth using condoms in more than 90% of sex acts (roughly consistent with the observed heterogeneity in consistency of condom use).

4.2.2 Modelling the Acceptability and Uptake of the Prevention Methods

In our model we assume a positive correlation between condom use and the acceptability of other prevention methods. This implies that if an individual has a high rate of condom use, they are more likely to accept other forms of

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prevention methods, whereas individuals who do not use condoms would be less interested in other prevention methods.

The assumption of positive correlation based on data showing a positive association between consistent condom use and PrEP acceptability (Eisingerich *et al.*, 2012). When modelling the acceptability of a prevention method, each individual was assigned their own level of acceptability for each prevention method. Acceptability scores were assumed to follow a beta distribution. Using a new random number z_2 and assuming a positive correlation between condom use and acceptability of other prevention methods, we used the inverse cumulative distribution function of the beta distribution to randomly assign an acceptability score $\mathcal{S}_{acc}^{I}$ for each prevention method I to each individual. The probability argument z_2 used to determine the pth quantile of $\mathcal{S}_{acc}^{I}$, was determined as follows

$$z_2 = b_1 z_1 + (1 - b_1) q_1, \tag{4.2.3}$$

where q_1 is a random number from the uniform U(0,1) distribution and b_1 lies between $(0, 1)$. When $b_1 = 0$ there is no correlation between acceptability and consistency of condom use, and when $b_1 = 1$ there is perfect correlation. For our simulation we assumed $b_1 = 0.5$. z_1 is the same random number used to determine the condom use score $\mathcal{S}_{con}$. For each prevention method I we assumed different mean levels of acceptability η_{acc}^{I} and standard deviations of acceptability scores κ_{acc}^{I}.

- MMC

  For males from a setting that practises traditional circumcision, we assumed a mean level of acceptability of MMC of 0.10 (Mark *et al.*, 2012). For males from a setting that does not practise traditional circumcision, the mean level of acceptability assumed was 0.8 (Scott *et al.*, 2005; Lis-

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souba *et al.*, 2011; Gray *et al.*, 2012).

- PrEP

  The mean level of acceptability of PrEP for both males and females was assumed to be 0.70 (Eisingerich *et al.*, 2012).

- VM-gel formulation

  We assumed a 0.70 mean level of acceptability for this formulation (Ramjee *et al.*, 2010; Altini *et al.*, 2010; Rosen *et al.*, 2008).

- VM-ring formulation

  A mean level of acceptability of 0.90 was assumed for the ring formulation of vaginal microbicide (Van der Straten *et al.*, 2012).

The product formulation of vaginal microbicides plays a vital role in acceptability of the product. It has been shown that a product, like the gel formulation, requiring frequent application is less acceptable than one that has a once off application, like ring formulation (Montgomery *et al.*, 2012). Thus the mean level of acceptability for the VM-ring formulation was assumed to be higher than that of the VM-gel formulation.

The assumed variance κ^I_{acc} used in the calculations of $\mathcal{S}^I_{acc}$ was determined as follows:

$$\begin{aligned} &\text{if} \quad \eta^I_{acc} \geq 0.5, \qquad \text{then} \quad \kappa^I_{acc} = \left(\frac{1}{2}(1-\eta^I_{acc})\right)^2; \\ &\text{if} \quad \eta^I_{acc} < 0.5, \qquad \text{then} \quad \kappa^I_{acc} = \left(\frac{1}{2}\eta^I_{acc}\right)^2. \end{aligned}$$

These variance assumptions have been set arbitrarily, as we lack the detailed data required to determine the variation in acceptability.

For females, once an acceptability score for each prevention method $\mathcal{S}^I_{acc}$ was assigned, we then determined the uptake of a prevention method. Females

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were not allowed to use more than one prevention method simultaneously (otherwise there would be an overdosing of tenofovir/truvada). We generated a random number r_1 from the uniform U(0,1) distribution and also calculated the individual's highest level of acceptability score $\max(\mathcal{S}^I_{acc})$. If $\max(\mathcal{S}^I_{acc}) \geq r_1$, then the female was allocated the prevention method with the highest acceptability score, otherwise no prevention method was allocated. Since males may have the option of selecting both MMC and PrEP, we first simulated whether or not they selected MMC, then we simulated whether they selected PrEP or not. Again, the allocation of MMC was determined by comparing the $\mathcal{S}^{MMC}_{acc}$ to a random number r_2 generated from the uniform U(0,1) distribution. If $\mathcal{S}^{MMC}_{acc} \geq r_2$ then the male was allocated MMC. The determination of whether or not the male accepted PrEP was simulated in the same manner.

4.2.3 Modelling of Adherence to the Prevention Methods

Once an individual has selected a prevention method, they are then assigned their own level of adherence to this prevention method. This level of adherence is represented by an adherence score $\mathcal{S}^I_{adh}$, which is assumed to be beta-distributed. We assume a positive correlation between the level of acceptability of a prevention method and the level of adherence to the prevention method, based on data showing the relationship between microbicide acceptability and adherence (Van der Straten *et al.*, 2008). We use the inverse cumulative distribution function of the beta distribution to determine the pth quantile, $\mathcal{S}^I_{adh}$. The random number z_3 used to sample from this beta distribution is:

$$z_3 = b_2 z_2 + (1 - b_2) q_2,$$

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where q_2 is a random number from the uniform U(0,1) distribution. Again we assumed $b_2 = 0.5$. Based on the specified studies the assumed mean levels of adherence to the prevention methods are:

- PrEP - 70% (Thigpen *et al.*, 2012; Baeten *et al.*, 2012)
- VM-gel formulation - 60%. Although Van der Straten *et al.* (2008) and Abdool Karim *et al.* (2010) measured adherence levels of 80% and 72%, respectively, the adherence levels of the VOICE trial suggest much lower adherence levels (Microbicide Trials Network, 2011).
- VM-ring formulation - 90%. Montgomery *et al.* (2012) measures adherence levels of above 90% for a vaginal ring.

Product application affects the level of adherence to products. Since the VM-ring formulation requires less frequent application, the level of adherence to a ring formulation of the vaginal microbicide would probably be higher than that of a gel formulation. If no prevention method was assigned as a choice, then $\mathcal{S}^I_{adh} = 0$. The assumed variance, κ^I_{adh}, used in the calculations of $\mathcal{S}^I_{adh}$ is determined as follows:

$$\begin{aligned} &\text{if} \quad \eta^I_{adh} \geq 0.5, \qquad \text{then} \quad \kappa^I_{adh} = \left(\frac{1}{2}(1-\eta^I_{adh})\right)^2; \\ &\text{if} \quad \eta^I_{adh} < 0.5, \qquad \text{then} \quad \kappa^I_{adh} = \left(\frac{1}{2}\eta^I_{adh}\right)^2. \end{aligned}$$

The variance assumption is arbitrary because we do not have detailed data on the extent of the heterogeneity in adherence.

4.2.4 Efficacy of the Prevention Methods

Based on randomized trials, we assumed the following efficacy levels $\mathcal{E}^I$ for each prevention method I, if adherence is perfect:

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- Male circumcision - 0.60 (Auvert *et al.*, 2005);
- PrEP - 0.85 (Grant *et al.*, 2010; Thigpen *et al.*, 2012; Baeten *et al.*, 2012);
- VM-gel formulation - 0.65 (Abdool Karim *et al.*, 2010);
- VM-ring formulation - 0.65. This is assumed to be the same as that for the gel since there have not been any trials that indicate the efficacy of the ring formulation of vaginal microbicides.

The levels of efficacy assumed for the last three prevention methods are based on an adherence level of 100%.

Table 4.1 summarises the estimates for the mean levels of acceptability of and adherence to the prevention methods, as well as the efficacy of the various prevention methods when we assume perfect adherence.

Table 4.1: Summary of parameter estimates used to determine each individual's level of acceptability and adherence, and the efficacy of the prevention methods when assuming complete adherence.

Intervention	**Mean Acceptability**		**Mean Adherence**		**Efficacy**	
	Male	Female	Male	Female	Male	Female
MMC	Trad: 0.1 Medical: 0.8	NA	NA	NA	0.6	NA
PrEP	0.7	0.7	0.7	0.7	0.85	0.85
VM-Gel	NA	0.7	NA	0.6	NA	0.65
VM-Ring	NA	0.9	NA	0.9	NA	0.65

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4.3 Modelling the HIV Incidence in Trial Participants

4.3.1 Intervention Arm of Trial

At the start of the trial, using the acceptability score for MMC, $\mathcal{S}_{acc}^{MMC}$, assigned to uncircumcised males, we randomly assigned whether or not the individual selected this prevention method as an option. For those who opted for MMC, we updated their circumcision status to circumcised. The uncircumcised males, who have been assigned an age of traditional circumcision, could get circumcised during the course of the trial through traditional ceremonies. The method used to model individual i's movements between the different states is the same as described in section 3.4, but the annual rate of HIV infection $\vartheta_i(3)$, if their partner is HIV infected, is now calculated as follows:

$$\vartheta_i(3) = n\beta_i(1 - E\mathcal{S}_{con,i})(1 - \phi_i)(1 - \mathcal{S}_{adh,i}^{I}\mathcal{E}_i^{I}), \tag{4.3.1}$$

where n is the annual rate of sexual contact, E is the efficacy of a condom in preventing HIV transmission, β_i is the probability of HIV transmission per act of unprotected sex with an HIV infected partner, and ϕ_i is the efficacy of male circumcision in preventing HIV transmission, the same as in section 3.4. I represents the antiretroviral prevention method chosen by individual i (in the event that no antiretroviral prevention method is chosen, $\mathcal{S}_{adh,i}^{I}$ is 0). The condom score $\mathcal{S}_{con,i}$, the adherence score $\mathcal{S}_{adh,i}^{I}$, and the efficacy of the prevention method $\mathcal{E}^{I}$, are determined for each individual as explained before.

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4.3.2 Comparison with the Control Arm

Modelling of movements between states in the control arm of the trial is the same as in section 3.4. The only change is that the probability of condom usage γ, from equation (3.4.2), is replaced with the individual condom score, $\mathcal{S}_{con,i}$. Thus the annual rate of HIV infection $\vartheta_i(3)$, if their partner is HIV infected, is now

$$\vartheta_i(3) = n\beta_i(1 - E\mathcal{S}_{con,i})(1 - \phi_i). \tag{4.3.2}$$

At the end of the 3 year time period, we determine the HIV incidence, I, in both arms of the trial. Using these incidence values, we determine the relative risk of HIV infection RR as follows:

$$RR = \frac{I_{intervention}}{I_{control}}.$$

The trial is simulated 1000 times. The 95% confidence intervals around the mean relative risk of HIV infection are reported.

4.4 Results

In this section we focus on the impact of different intervention packages on HIV incidence and we consider different trial sample sizes. All the results are based on the assumption that there is positive correlation between the assumed levels of condom use and the acceptability of other prevention methods. As a sensitivity analysis, we illustrate the impact of a package when we assume a negative correlation between condom use and acceptability of other prevention methods.

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4.4.1 Intervention Packages

In order to determine the mean relative risk of HIV infection, we ran 1000 trial simulations for a sample size of 2000 individuals, 1000 individuals in each arm, for each of the packages described in Table 4.2.

Table 4.2: The different prevention methods included in the various packages used in the model.

Package	Prevention Methods
1	MMC, PrEP, VM-gel and VM-ring
2	MMC, VM-gel and VM-ring
3	MMC, PrEP and VM-ring
4	MMC, PrEP and VM-gel

For the simulation of package 1, out of a mean total of 486 males in the intervention arm, 64 (13%) chose only MMC , 213 (43%) chose only PrEP, 139 (28%) chose both prevention methods and 70 (14%) chose neither prevention method. For the remaining 514 females, 465 (90%) chose the VM-ring option, 1 (<1%) chose the VM-gel option, 1 chose PrEP (<1%) and 39 (8%) did not opt for a prevention method. The model estimate for the mean HIV incidence rate (Figure 4.1) in the intervention arm is 0.92 per 100 person-years (95% CI 0.91–0.93 per 100 person-years), and the estimate in the control arm is 1.73 per 100 person-years (95% CI 1.71–1.75 per 100 person-years). The mean relative risk of HIV infection (Figure 4.2) is 0.54 (95% CI 0.53–0.55).

The impact of package 1 is greater in males than in females, with the mean relative risk of HIV infection for males at 0.51, lower than that for the females, 0.57 (Figure 4.2). The main reason for this is that males can choose both MMC and PrEP prevention methods, whereas females can choose only 1 of the 3 applicable options. Females were more likely to choose the vaginal ring over PrEP, because the assumed mean acceptability level for the vaginal

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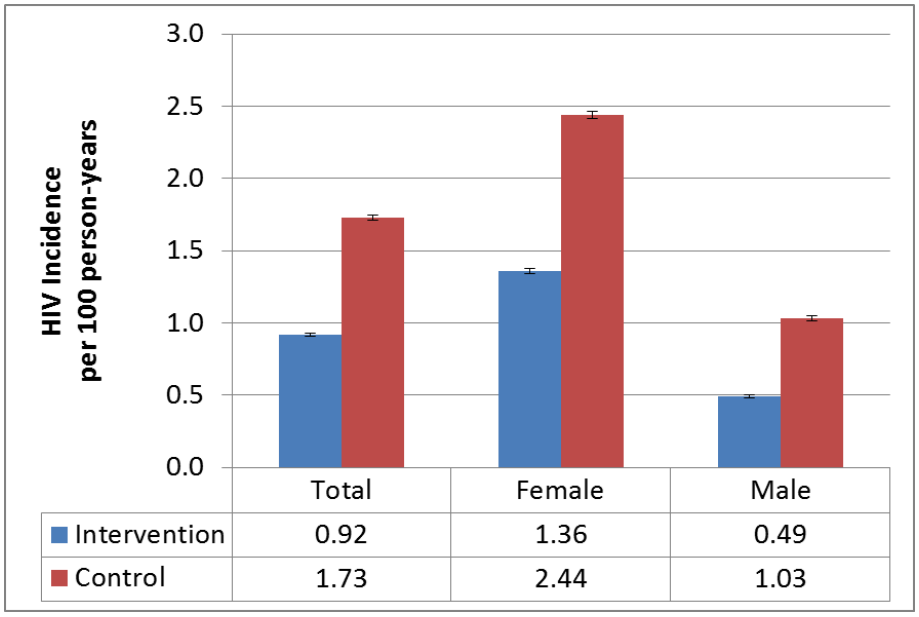

Figure 4.1: HIV incidence rate: for males, females and in total. The HIV incidence rates are given per 100 person-years and were determined for 1000 trial simulations for a sample size of 2000 individuals offered package 1, over a 3 year trial period.

ring (90%) was much higher than that for PrEP and the vaginal gel (70%). Having the option of both MMC and PrEP, most males opted to use PrEP, regardless of whether they chose MMC or not. Although the stated efficacy assumptions are based on an assumption of perfect adherence, we allow for imperfect adherence in the model which reduces the actual effectiveness of the prevention method.

4.4.1.1 Various Intervention Packages

The mean relative risk of HIV infection with 95% confidence intervals was calculated for each of the four packages for the sample in total, as well as for each sex. Figure 4.2 shows the comparisons for the mean relative risk of HIV infection between the different packages.

For males, package 1, 3 and 4 have the same components, and thus the

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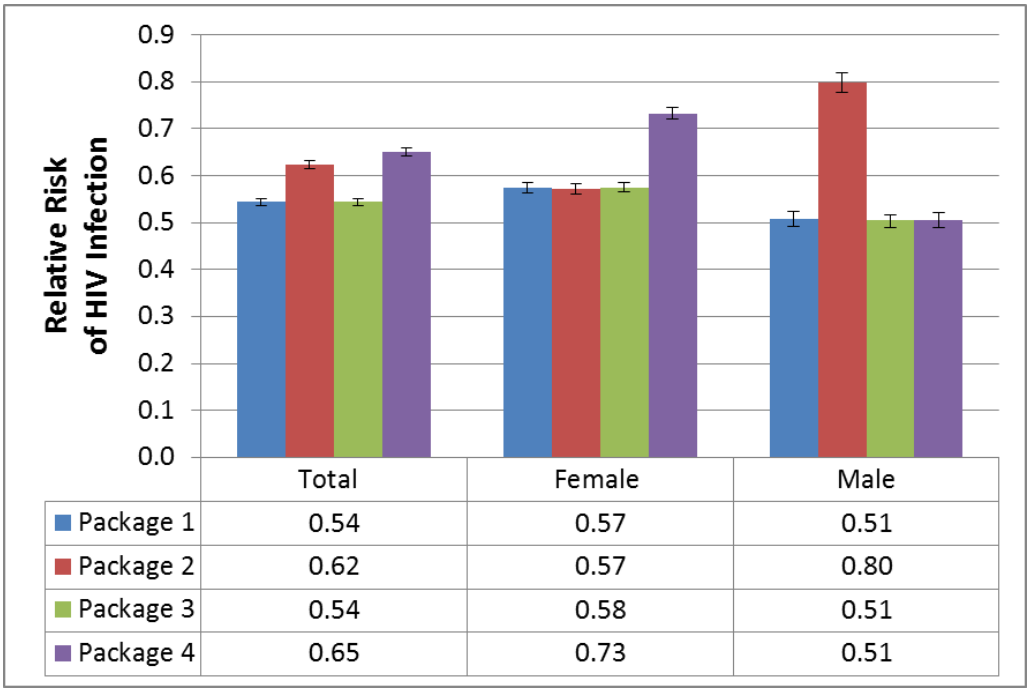

	Total	Female	Male
Package 1	0.54	0.57	0.51
Package 2	0.62	0.57	0.80
Package 3	0.54	0.58	0.51
Package 4	0.65	0.73	0.51

Figure 4.2: Comparison of relative risk estimates for different intervention packages. The mean relative risk of HIV infection was determined for 1000 trial simulations for a sample size of 2000 individuals over a 3 year trial period.

results for the relative risk of HIV infection are similar (0.51). For package 2, males only have the option of MMC. This results in an estimated relative risk of HIV infection of 0.80, much higher than that estimated for the other packages. With the high levels of acceptability and overall efficacy of PrEP, we find that the exclusion of PrEP from a prevention package increases the mean relative risk of HIV infection although this exclusion only has a material impact on HIV incidence in men.

For females, the mean relative risk of HIV infection is almost identical for packages 1, 2 and 3. Uptake estimates of the VM-ring option for these packages are similar to that of package 1 ($\approx$90%) and this results in similar estimates for the relative risk of HIV infection. When we compare the impact of packages 1, 2 and 3, where more than 90% of the women chose the VM-ring

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option that has an assumed efficacy of 0.65 with a mean level of adherence of 90%, to the impact of package 4, where the assumed levels of efficacy of PrEP (0.85) and VM-gel (0.65) are different with both having lower mean levels of adherence (70% for PrEP and 60% for the VM-gel), we find that estimates of HIV incidence are much lower for the first 3 packages. Thus, as with package 4, our model suggests that the exclusion of the ring formulation results in a higher mean relative risk (0.73) for females.

We also simulated the impact of the individual prevention methods. Figure 4.3 illustrates the impact of the prevention methods for males (upper panel) and females (lower panel). For the males, the combination of the prevention methods has a greater impact on HIV incidence. The VM-ring, as a single intervention for the females, has the lowest mean relative risk of HIV infection, with PrEP having the next lowest. The aggregate levels of effectiveness depend on acceptability, adherence and efficacy. VM-ring, having the highest mean level of adherence, would result in a much higher level of efficacy as compared to the other prevention methods. The higher the assumed efficacy, the lower the mean relative risk of HIV infection.

4.4.2 Sensitivity Analyses

We conducted a sensitivity analyses around the impact of different sample sizes, as well as the correlation between levels of condom use and the levels of acceptability of other prevention methods.

4.4.2.1 Sample Size Consideration

Sample size plays a vital role in determining statistical significance and it is important that the sample size chosen is sufficient to ensure that the trial is

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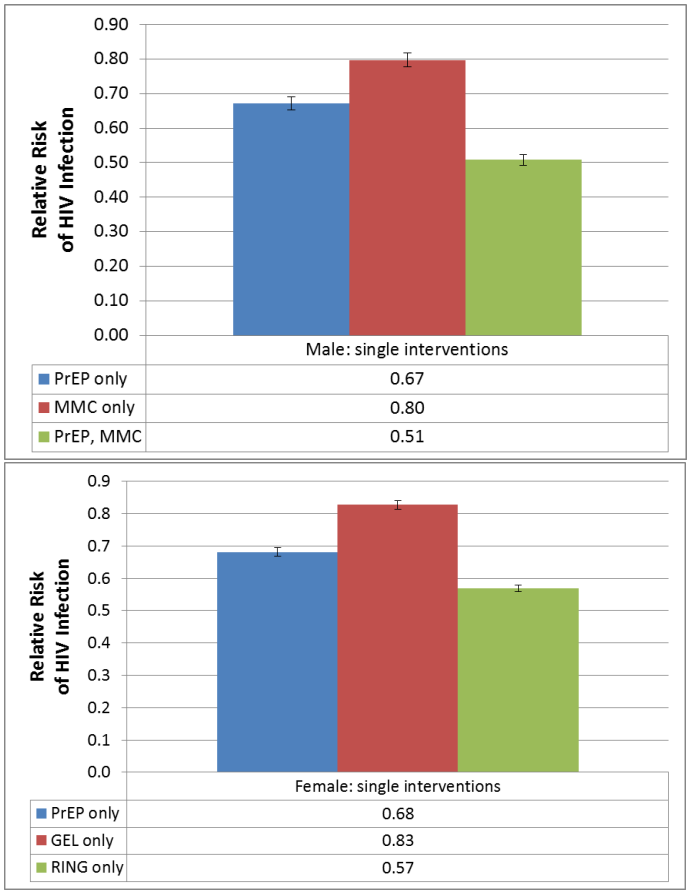

Figure 4.3: Comparisons of the mean relative risk estimates for individual prevention methods: for males (above) and females (below). The mean relative risk of HIV infection was determined for 1000 trial simulations for a sample size of 2000 individuals over a 3 year trial period.

adequately powered to detect the expected effect on HIV incidence. We ran another 1000 trial simulations with a sample size of 500 individuals in each simulation to illustrate the importance of sample size. Figure 4.4 compares the mean relative risk of HIV infection for samples of 500 and 2000 individuals who were offered intervention package 1. The mean relative risk of HIV infection is reported together with the 2.5 and 97.5 percentiles of the distribution of relative risk values generated from the 1000 simulations (95% C.I.). The relative risk of HIV infection for the smaller sample is 0.58 (95% CI 0.16–1.29) and for the larger sample is 0.54 (95% CI 0.33–0.87). The confidence interval is

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therefore substantially narrower when the sample size is larger. With sample size 2000, we would expect the relative risk of HIV infection to be below 1 in at least 97.5% of trials, though it would not necessarily be significantly below 1 in all 97.5% of the simulations.

We calculated the power to detect a statistically significant difference for each sample size by determining the proportion of simulations in which the upper 95% confidence interval limit of the relative risk was lower than 1. For a trial of sample size 500 we estimated only 23.1% power, whereas for a trial of sample size 2000 we estimated a power of 78.1%. This model output is verified using the R statistical software package. With an input of 78.1% power, an incidence rate of 1.73 per 100 person-years in the control arm, and a relative risk of 0.54, and using a two-sided test with an alpha level of 0.05, the programme estimates a sample size requirement of ∼966 individuals per trial arm or about 1932 in total (similar to the sample size of 2000 in our model). Using the sample size estimation function in R, we calculated that a sample size requirement of ∼1013 in each arm of a trial would achieve 80% power, with a two-sided alpha level of 0.05, to detect a relative risk of HIV infection of 54%, with a mean incidence rate of 1.73 per 100 person-years in the control arm.

4.4.2.2 Correlation Between Condom Use and Acceptability of Other Prevention Methods

In all of the previous simulations we assumed a positive correlation between the level of condom use and the level of acceptability of prevention methods. We now consider the impact of the packages on HIV incidence when we assume a negative correlation between the level of condom use and the acceptability of the other prevention methods, and then we compare the results to that of

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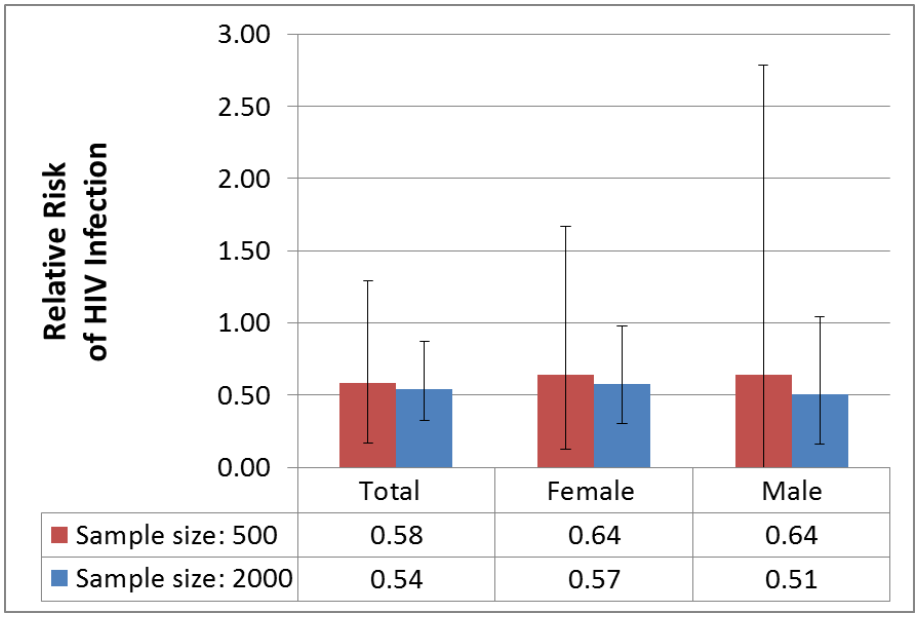

Figure 4.4: Comparisons of relative risk estimates for different sample sizes: for males, females and in total. The RRs are determined for 1000 trial simulations for each of the sample sizes of 500 and 2000 individuals over a 3 year trial period. The confidence intervals are calculated from the 2.5 and 97.5 percentiles of the distributions of simulated RR values.

our previous simulations. A negative correlation can be interpreted as follows: individuals who have a high rate of condom use do not see the need for any other prevention methods and are thus less likely to accept any other prevention method, and individuals who have a low rate of condom use would find other prevention methods more appealing and thus have a higher chance of accepting other prevention methods. To allow for this negative correlation we modify equation 4.2.3 as follows

$$z_2 = b_1(1 - z_1) + (1 - b_1)q_1, \tag{4.4.1}$$

and again we assume b_1 to be 0.5. Each individual is again assigned an acceptability score, $\mathcal{S}^I_{acc,i}$ for prevention method I based on this value for z_2, and the rest of the model remains the same. Figure 4.5 illustrates how this negative correlation affects the relative risk of HIV infection for intervention package 1.

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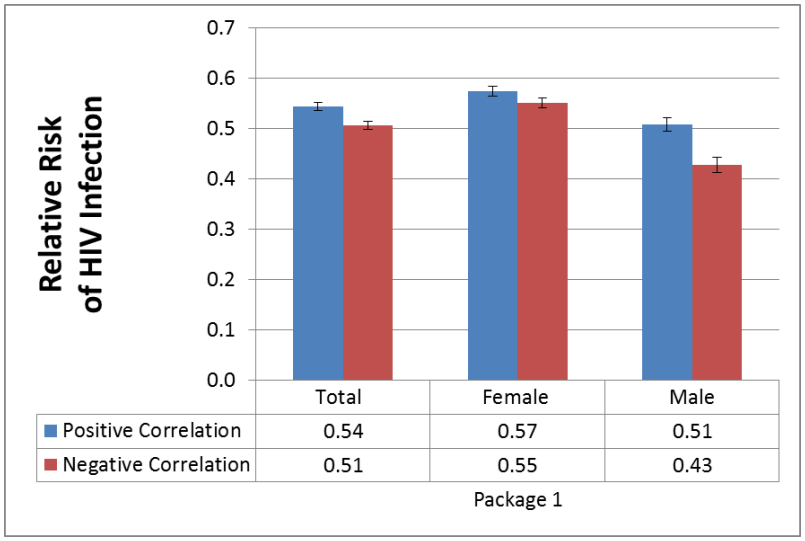

Figure 4.5: Comparison of the relative risk estimates when assuming negative correlation and when assuming positive correlation, between the level of condom use and the level of acceptability of other prevention methods. In each, we simulated 1000 trial simulations for a sample size of 2000 individuals over a 3 year trial period for a full package.

The relative risk of infection when assuming a negative correlation between condom use and the acceptability of a prevention method is 0.51 (95% CI 0.50–0.52). This is lower than the relative risk of HIV infection when assuming a positive correlation, 0.54 (95% CI 0.53–0.55). The effect of negative correlation in males is greater than that in females. The prevention methods for the males are not mutually exclusive, so there is a compounding of the correlation effect. Also, when assuming a positive correlation, the proportion of males that are not selecting any method in package 1 is much higher than that of the females.

We simulated the impact of a single prevention method, PrEP, assuming first a positive then a negative correlation between the level of condom use and the acceptability of PrEP. The relative risk of HIV infection is 0.66 (95% CI 0.65–0.67) when assuming a positive correlation and 0.60 (95% CI 0.59–0.61)

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when assuming a negative correlation. Figure 4.6 illustrates this comparison. For PrEP, we find that the differences between males and females are similar.

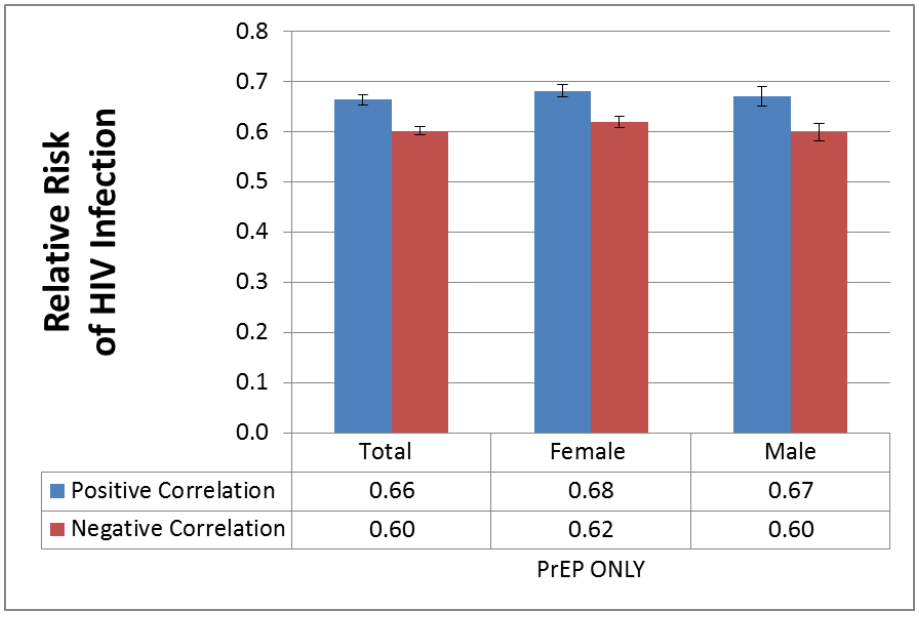

Figure 4.6: Comparison of the relative risk estimates when assuming negative correlation and when assuming positive correlation, between the level of condom use and the level of acceptability of PrEP. In each, we simulated 1000 trial simulations for a sample size of 2000 individuals over a 3 year trial period for the single prevention method, PrEP.

The assumption of negative correlation gives a higher impact because individuals who have a low level of condom use are now more likely to use other prevention methods thereby decreasing their relative risk of HIV infection and individuals with high levels of condom use are already protected due to the high levels of condom efficacy. Although individuals with a high level of condom use are opting for additional protection by using another prevention method when we assume positive correlation, the interaction between the combination of the prevention methods are redundant. By not opting for additional protection, individuals with a low level of condom use are not effectively reducing their relative risk of HIV infection.

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Based on the definition of "*synergy*" by Alsallaq *et al.* (2013), we determined the levels of interaction between PrEP and condoms for both the assumptions of positive and negative correlation between levels of condom use and the acceptability of PrEP using the following formula:

$$synergy = (RR_{condom} * RR_{PrEP}) - RR_{combination}. \tag{4.4.2}$$

If "*synergy*" $= 0$, then there is no interaction between the prevention methods. However, if "*synergy*" > 0, then the interaction between the prevention methods exhibits synergy and if "*synergy*" < 0, then the interaction is redundant.

The results of our calculations are in Table 4.3. For positive correlation, we find that the interaction between condoms and PrEP are redundant for males, females and in total. Although we find that PrEP and condoms interact synergistically and thus complement each other in the prevention of HIV transmission when we assume a negative correlation, the interaction is modest with "*synergy*" values very close to zero.

Table 4.3: Results of the measure of "*synergy*" measuring the interaction between condoms and PrEP when we assume positive or negative correlation between condoms and the acceptability of PrEP, based on equation (4.4.2).

Correlation Assumption	**Males**	**Females**	**Total**
Positive	-0.056	-0.004	-0.023
Negative	0.045	0.022	0.026

4.5 Conclusion

In this Chapter we focussed on the impact of different prevention methods, both individually and in various combinations of prevention methods, on HIV incidence when we simulated a hypothetical randomized controlled trial. We allowed for heterogeneity in levels of condom use, levels of acceptability of

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different prevention methods and levels of adherence to different prevention methods, and the variation in local male circumcision norms and practices. We accounted for correlation between the level of condom use and the level of acceptability of other prevention methods, as well as a correlation between the levels of acceptability of a prevention method and the levels of adherence to the prevention method. We found that for females, the ring formulation of vaginal microbicides had the greatest impact on HIV incidence, and for males, offering both the MMC and PrEP resulted in a greater effectiveness than offering either prevention method alone. Since the model sample size of 2000 individuals achieved a power value similar to that produced by the sample size estimation function in the R statistical software package, we then determined that the sample size required to achieve 80% power to detect statistical significance is $\sim$1013 per arm. A sensitivity analyses demonstrated the impact on HIV incidence when we assumed either a positive or a negative correlation between the levels of condom use and the acceptability of other prevention methods. The levels of interaction between condoms and PrEP only exhibited synergy when a negative correlation between the levels of condom use and the acceptability of PrEP was assumed.

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Chapter 5

Conclusion and Discussion

The model developed here is a stochastic individual-based simulation. The main aim of the model is to determine the impact of an HIV intervention package on HIV incidence among adolescents participating in a hypothetical trial, over a relatively short three year term. The package, consisting of medical male circumcision, pre-exposure prophylaxis and antiretroviral-based vaginal microbicides, both a gel formulation and a ring formulation, are only offered to individuals in the intervention arm of the trial. All individuals are HIV-negative and aged 15–18 years old at the start of the trial.

Although the prevention package that we are simulating is a fairly comprehensive package, the relative risk of HIV infection is estimated at only 0.54 (95% CI 0.52–0.55). The estimate for females is 0.57 (95% CI 0.56–0.58) and the estimate for males is 0.51 (95% CI 0.49–0.53). For females, the relative risk estimate when only offering the ring formulation of the vaginal microbicide is the same as the full package, 0.57. The ∼40% reduction in HIV incidence is not the massive impact we expected from such a comprehensive package.

Based on our model, in the case of the prevention package for females, we found that the exclusion of the ring formulation of vaginal microbicides signif-

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icantly affected the mean relative risk of HIV infection. For males it is evident that offering both the medical male circumcision and PrEP results in a greater effectiveness than offering either prevention method alone. This suggests that when developing a combination prevention package for adolescents, it will be important to offer both MMC and PrEP to males, but it may be sufficient to offer only a vaginal ring microbicide to females. However, the efficacy of the vaginal ring approach to microbicide delivery has not yet been established, and our model findings may need to be revised once vaginal ring trial data have been published. Further investigations, such as cost-effectiveness analyses of the prevention methods and more acceptability and adherence studies, will also be important in determining which prevention methods are most appropriate to exclude from a prevention package.

It is generally assumed that combination prevention methods would have a greater impact on HIV incidence than would be expected with any single intervention but we show that this is not necessarily the case. Our simulations suggest that offering women a selection of different antiretroviral-based prevention methods would not lead to any additional benefit over offering only a vaginal ring, if vaginal rings would be substantially more acceptable than other delivery methods. More options could result in a trade-off between acceptability and efficacy, as individuals may find a less effective option more acceptable. Strategies that target acceptability, uptake and adherence issues should be investigated.

When comparing our model results to other models, we first focus on the impact of the individual prevention methods. Most studies that have modelled the impact of male circumcision have suggested that over a 5–15 year period it would reduce HIV incidence by 8–23% (Hallet *et al.*, 2008; Londish

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and Murray, 2008; White *et al.*, 2008; Williams *et al.*, 2006). For example, White *et al.* (2008) estimated that offering male circumcision to 15–49 year old population over a ten year period would reduce male HIV incidence by 23%. Our model estimates a relatively large reduction in HIV incidence, 20% over three years, when compared with these other studies. This is likely to be because we simulated a hypothetical randomized controlled trial in which there is a high rate of uptake, whereas these other models estimated a population level impact. Our model allows for traditional male circumcision, as well as variation in acceptability of medical male circumcision, which other models have not allowed for.

Other studies that have modelled the impact of PrEP have found reductions in HIV incidence of 3.2–28% over an average of 5–10 years (Abbas *et al.*, 2007; Desai *et al.*, 2008; Paltiel *et al.*, 2009; Pretorius *et al.*, 2010). This is less than what our model estimated, a reduction of 34%. For example, when targeting women aged 15–35 years old, Pretorius *et al.* (2010) estimated a lower reduction in HIV incidence (10–25% over a period of ten years) if the coverage of PrEP was between 30% and 60% of the population. Again, our higher estimate is likely to be because we are simulating a randomized trial. A model by Cremin *et al.* (2013), calibrated to KwaZulu-Natal data, estimates a 3.2% reduction over ten years for 15–24 year olds, with 7.3% coverage. The percentage reduction in HIV incidence for that population is roughly half the coverage. Our model also suggests that the percentage reduction in HIV incidence in youth is approximately half the PrEP coverage (72% coverage of PrEP reduces HIV incidence in adolescents by 34%). However, the model by Cremin *et al.* (2013) is taking into account the secondary benefits of PrEP; i.e. that a person who is less likely to acquire HIV is less likely to transmit

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HIV. The effect of this over the short term is less substantial than over the long term.

Our model estimates that the impact of the combination of both formulations of the vaginal microbicides compared to the impact of the ring formulation alone is the same, a reduction in HIV incidence of 43%. The impact estimated for the gel formulation alone is 17%. Although our study assumes the same efficacy for both the formulations, the difference in the impact of the vaginal microbicides is due to the different assumptions regarding the levels of acceptability of and the levels of adherence to the products. A model by Wilson *et al.* (2008) estimates the cumulative incidence reduction for females in a resource-limited setting over a one year trial period of vaginal microbicides to be 15% (IQR: 12–19%). This is thus comparable to the reduction estimated for the gel formulation in our model but not the ring formulation. Most other modelling studies only considered the impact of a single mode of delivery (Foss *et al.*, 2003; Wilson *et al.*, 2008; Karmon *et al.*, 2003). What is new in our study is that we have considered different forms of vaginal microbicide administration.

When considering the combined impact of male circumcision and vaginal microbicides, our model estimates a reduction in HIV incidence of 38%, with an uptake of 46% for male circumcision and an uptake of 91% for vaginal microbicides. The model by Cox *et al.* (2011) estimates that with similar coverage of microbicides and male circumcision, HIV incidence would reduce by 35–40%, similar to our model. When estimating the impact of the combination of male circumcision, PrEP and vaginal microbicides at a population level, the model by Long and Stavert (2013) estimates that the combination would avert 43.5% of HIV infections over ten years. Our model estimates a similar risk

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reduction of ∼40% over a three year period. Both the Cox *et al.* (2011) and Long and Stavert (2013) estimates are for a population level impact, whereas our model estimates are within the context of a randomized controlled trial.

Our stochastic microsimulation allows for heterogeneity in behaviour among adolescents. The model accounts for variation in local male circumcision norms and practices (Connolly *et al.*, 2008*b*; Mark *et al.*, 2012). The model allows for heterogeneity in levels of condom use (Pettifor *et al.*, 2004*a*; Shisana *et al.*, 2009; Johnson *et al.*, 2010), heterogeneity in the levels of acceptability and uptake of prevention methods (Westercamp and Bailey, 2007; Ramjee *et al.*, 2010; Rosen *et al.*, 2008; Altini *et al.*, 2010; Guest *et al.*, 2010; Heffron *et al.*, 2012; Lissouba *et al.*, 2011) and heterogeneity in the levels of adherence to the different prevention methods (Nel *et al.*, 2011; Van der Straten *et al.*, 2008; Baeten *et al.*, 2012). Most other models do not allow for this heterogeneity in uptake and adherence.

When taking into account the correlation between the level of condom use and the acceptability of other prevention methods, both a positive and negative correlation was modelled. A negative correlation, meaning that adolescents who have a high rate of condom use do not see the need to use any other prevention method, was found to be associated with a greater prevention programme impact. This illustrates the sensitivity of the model results to the assumption about correlation and further research is required to understand these correlation coefficients.

Correlation between the level of acceptability of a prevention method and the level of adherence to the products is also modelled. A positive correlation between the acceptability of and adherence to a microbicide has been shown (Van der Straten *et al.*, 2008). Although acceptability of prevention methods

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is strongly associated with younger ages (Eisingerich *et al.*, 2012), adherence is significantly higher at older ages (Marrazzo *et al.*, 2013). This suggests that the true association between acceptability and adherence may be confounded by factors such as age. More investigations into acceptability, uptake and adherence of different prevention methods among adolescents are needed, as the level of adherence to a prevention method impacts the overall efficacy of that prevention method (Abdool Karim *et al.*, 2010; Grant *et al.*, 2010; Baeten *et al.*, 2012).

An analysis was performed to determine the effect of different trial sample sizes. Since power calculations are vital in determining the optimal sample size required to achieve statistically significant results (Schulz and Grimes, 2005), the results of our analysis are important in deciding the appropriate sample size when conducting a randomized trial. The model calculations of the required sample size were roughly consistent with results obtained when we used R statistical software. Our method for calculating the sample size takes into account variability in HIV incidence rates across adolescent sub-groups, yet produces a similar estimate of required sample size to that calculated in R, which does not explicitly allow for heterogeneity in event rates. This suggests that heterogeneity in HIV acquisition risk does not substantially compromise the sample size estimation.

A complication affecting the design of the randomized controlled trial is the need to provide the current standard of care. The standard of care package is a minimum for both the intervention and control arms (Bucher *et al.*, 1997; Miller and Silverman, 2004; Crepaz *et al.*, 2006). Since medical male circumcision is already being scaled up nationally (South African National AIDS Council, 2012), offering the option of medical male circumcision to partici-

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pants in the control arm could be regarded as part of the standard of care for all participants. Should this happen, the model would then be overestimating the overall effectiveness of the prevention package for males. However, in South Africa there is some controversy around the promotion of medical male circumcision for adolescents (McQuoid-Mason, 2013), so it might not become standard of care. Also, an important part of the intervention package might be offering the various services in an adolescent-friendly environment, which would increase uptake (this is not part of the current standard of care which involves providing male circumcision in regular clinics that are not particularly adolescent-friendly).

The model has a number of limitations. Firstly, the model was limited in that no variation in the rate of HIV transmission per sex act was allowed. Cervical ectopy (Myer *et al.*, 2006) and pregnancy (Moodley *et al.*, 2009) affects the risk of male-to-female HIV transmission. Factors such as HIV viral load (Attia *et al.*, 2009), which impact the level of infectiousness, and other STIs, which impact both the level of susceptibility and the level of infectiousness (Boily *et al.*, 2009), were not accounted for. The effect of antiretroviral therapy on the level of infectiousness of the HIV infected partner (Attia *et al.*, 2009; Reynolds *et al.*, 2011) has also not been accounted for. By not allowing for all this variation caused by biological and behavioural factors (Chen *et al.*, 2007), we could be underestimating variation in HIV incidence rates and hence the width of the 95% confidence intervals around the relative risk of HIV infection.

The true dynamics of relationships are complex (Morris and Kretzschmar, 1997; Delva, 2010; Epstein and Morris, 2011; Mah and Shelton, 2011) and the model only allowed for a maximum of two concurrent partnerships for individuals who were classified as high risk. The model did not allow for

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heterogeneity within a risk group. Thus all individuals in a particular risk group were assumed to have the same behavioural characteristics, such as rates of partnership formation and dissolution, over the trial period. The heterogeneity in risk that we are not capturing could lead to the variability in HIV incidence rates being underestimated and hence underestimation of the sample size required. The association between risk group and HIV status, in section 3.2.5, has also not been modelled.

In our model we have assumed that all adolescent virgins are HIV negative. This is probably unrealistic as there is increasing evidence of survival of vertically-infected children into adolescence (Ferrand *et al.*, 2009).

Another limitation of this analysis is that the variance assumptions for the levels of acceptability and adherence were set arbitrarily. A review of data on variation in the acceptability of and adherence to the different prevention methods is required. Pilot studies are currently being conducted in South Africa to assist with the estimation of these variance parameters.

Our model does not account for the possible impact of risk compensation. Risk compensation, either a decrease in condom use or an increase in risk behaviour, has been shown to negatively affect the impact of prevention methods on HIV incidence (Hallett *et al.*, 2007; Van de Vijver *et al.*, 2009; Cremin *et al.*, 2013; Abbas *et al.*, 2007; Supervie *et al.*, 2010; Eaton and Kalichman, 2007). Although most of the RCTs have not shown evidence of risk compensation, one would not expect to see much risk compensation when subjects are blinded to their assignment to the intervention/control arm. In the intervention trial we are evaluating, subjects would know which products they are using and how effective they are, and the likelihood of risk compensation would thus be much greater.

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In setting the initial HIV prevalence assumptions, we used data from the 2003 loveLife survey (Pettifor *et al.*, 2004*a*). It is important to note that the HIV prevalence in youth has declined since the time of the 2003 loveLife survey, and the data could thus be an overestimate of the current HIV prevalence. However, the survey was nationally representative and our model population is a sub-population representing a relatively high risk group. Since we anticipate the trial participants would be recruited mostly from informal settlements where the HIV risk and prevalence is much higher, the loveLife survey estimates could also be underestimates of the HIV prevalence. Thus these biases may cancel each other to some extent.

There is much uncertainty regarding the acceptability, efficacy and adherence parameters, especially for the vaginal ring which has not yet been proven efficacious. The model is limited in that we did not do a formal uncertainty analysis. This was mostly due the very long run time of the simulations in R. One simulation, consisting of 1000 trials with 2000 participants per trial, would take approximately a day to run. Running more than one simulation at a time would occasionally freeze the computer system. The runtime was also affected by the specifications of my laptop, an Intel Pentium®Dual CPU T3400 / 2.16 GHz with 2.9G RAM. It may be necessary to explore uncertainty analysis techniques that have recently been developed for microsimulation models, which take account of the long run times typically associated with microsimulation models (O'Hagan *et al.*, 2007).

The model is a static model, and all the model assumptions are fixed, due to the short three year duration of the hypothetical trial period. Further work is required to extend the model from a simulation of a hypothetical randomized trial to a model of the impact that a combination prevention package may

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have when introduced at a population level. The extent to which adolescents interact with the adult population needs to be accounted for (Chapman *et al.*, 2010), as well as the extent to which adherence to different prevention methods is sustained as adolescents enter into adulthood. Another reason for extending the model to the rest of the population is that it allows us to quantify the primary prevention benefits of the intervention (i.e. with earlier diagnosis of adolescents with HIV, we can quantify the impact of changes in their sexual behaviour once diagnosed). Even if PrEP and microbicides prove to be safe and efficacious, concerns regarding their effective implementation include adherence and related drug resistance concerns (Supervie *et al.*, 2010; Van de Vijver and Coucher, 2010). In addition, the increasing use of tenofovir in first-line ART, and the potential for rising tenofovir resistance due to poor ART adherence, has important implications for the effectiveness of tenofovir-based prevention methods. Including the impact of drug-resistance in the extended model could address this issue.

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