HIV prevention policy and programme planning: What can mathematical modelling contribute?
Hankins, Catherine

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Chapter 1

General introduction
Background

This thesis addresses the topic of policy making and programme planning in response to the global human immunodeficiency virus (HIV) epidemic, with a specific focus on the challenges inherent in attempting to assess the likely epidemic impact and cost of adding novel tools to HIV prevention programming. The emerging biomedical HIV prevention tools that will serve to illustrate these challenges are voluntary medical male circumcision (VMMC), systemic and topical pre-exposure prophylaxis (PrEP), HIV vaccines, and structural interventions for people who inject drugs (PWID). The objective of the thesis is to explore the potential contribution of mathematical modelling to informed decision-making. Its hypothesis is that modelling results are a useful addition to the evidence and other factors that influence the HIV prevention policy and programme development process, if the models from which they are derived are well constructed and parameterised, their structures and results can be compared, and their findings, including the results of sensitivity analyses, are clearly communicated to decision-makers. Examples are provided of modelling consensus exercises, systematic reviews, and modelling of the uncharted territory of changes in risk environments. The thesis concludes with a discussion of the factors that make mathematical modelling relevant to decision-making. This includes the knowledge translation hurdles involved in faithfully and effectively communicating the meaning of modelling estimates to decision makers and being transparent about the inherent limitations of the visions that models paint of potential future scenarios.

This introduction sets the stage, beginning first with some basic background on the state of our knowledge about how HIV attacks the immune system, how many people live with this retrovirus worldwide, and what we understand about the importance of tailored, combination HIV prevention. The second section presents a summary of the current evidence on emerging biomedical HIV prevention tools, with a focus on VMMC, PrEP, and HIV vaccines. The theme of evidence-informed decision making and the contribution that mathematical modelling of novel HIV prevention strategies can make to decision making are introduced in the third section, along with the tenet that triangulation of findings, through consensus processes, systematic reviews, and other methodologies can strengthen this contribution. The introduction concludes with the outline of the thesis.

HIV and the global epidemic it has caused

Thirty-two years after the disease that is now known as acquired immune deficiency syndrome (AIDS) was recognised(1) and more than a century after its causative infectious agent, HIV(2)(3)(4), crossed species from chimpanzees to humans in the Congo River Basin(5), HIV remains a daunting challenge to human health and well being. HIV transmission has slowed in many parts of the world, notably in many of the most heavily affected countries in sub-Saharan Africa. At the same time, scale-up of access to antiretroviral therapy (ART) has accelerated,
permitting people living with HIV to lead longer, healthier lives. The result is that, using improved data and modelling methodologies, UNAIDS estimates that the number of people living with HIV worldwide at the end of 2011 was 34 million [31.4-35.9]. This number is expected to increase over the coming years, even if incidence were to continue to decline, as more people living with HIV access life-prolonging antiretroviral therapy (ART). Global HIV prevalence among adults aged 15 to 49 years at end-2011 is estimated at just under one per cent (0.8%)(6).

The retrovirus HIV can be transmitted through unprotected sexual activity, the use of contaminated injecting equipment, or from a mother to her infant during pregnancy, delivery, or breastfeeding. Once in the body, it attacks the immune system, initially in the gastrointestinal tract, home to the largest amount of lymphoid tissue in the body(7). Its prime target is the T-helper cells that are generated in the thymus and then migrate to the gut associated lymphoid tissue (GALT) and other lymphoid tissues to take up their role as the ‘conductor’ of the immune response. They activate B-cells to turn into antibody-making plasma cells, stimulate other T-cells to mature into memory cells, and signal to macrophages and cytotoxic T-cells that there is work to be done(8)(9). T-helper cells express a signature cell-surface marker called the CD4+ receptor on their outer membrane that provides a landing site for HIV to start its docking process through its glycoprotein (GP) 120 envelope spike(10). The process of docking causes a change in the configuration of gp120 giving the virus access to one of two other receptors, the chemokine receptors CCR5 or CXCR4. This then creates a structural change in the gp41 envelope protein of the virus, permitting the initiation of fusion between the viral envelope and the cell membrane, the first step to cell entry(11).

Once inside the cell, HIV takes over the cell’s genetic machinery to undergo reverse transcription from RNA to DNA. It replicates itself and then breaks open the T-cell, killing it in a process called apoptosis and disseminating itself to infect more T-cells and other cellular targets. This sets up a chronic state of immune system activation that correlates with disease progression(12), with HIV persistence causing immune activation that in turn contributes to HIV persistence(13). Once the CD4+ count in the blood falls below a certain level as capacity to keep up with regeneration declines(14), people become susceptible to other pathogens and begin to feel ill. This process can take months to years as the virus steadily weakens immune system defences. HIV strains that preferentially use the CXCR4 chemokine receptor are associated with faster disease progression(15), as are other factors including host genetics(16). Some HLA (human leucocyte antigen) alleles (HLA-B*57, HLA-B*27; HLA-B*51) are associated with slower disease progression, although the virus itself evolves to counter immune responses (17). The CCR5delta32 mutation, found more frequently in populations of European descent(18) protects against HIV infection when both gene alleles are affected and slows disease progression if only one allele is affected.
Natural history cohorts before the era of ART suggested a mean progression time to AIDS of 10 years, although AIDS can develop in as little as two years in a proportion of patients(19). When people do seek health care to determine the cause of their symptoms, often many years after they first became infected, their CD4+ count levels are often well-below current ART eligibility guidelines(20)(21). Recent figures indicate that although median CD4 cell counts at ART initiation increased between 2000 and 2009, they have remained below 200 cells/μL in low- and middle-income countries and below 300 cells/μL in high-income countries(21). In light of this, it is encouraging that a South African study has demonstrated life expectancies around 80% of normal for patients who start treatment before their CD4 count drops below 200 cells/μL(22).

About 50% of all those living with HIV worldwide are estimated to not know their serostatus(23), meaning that they have never received a test for HIV or, if they have been tested, learned its result. From a prevention perspective, knowledge of HIV status is the doorway to developing the motivation and acquiring the skills and tools to protect oneself from acquiring HIV and to prevent transmission to others if one is already infected. From a treatment perspective, HIV testing is the first step on the road to clinical assessment, care, life-prolonging ART, and support for those found to be HIV-positive. Stigma and discrimination, fear, potential violence and rejection, testing costs, personal expense in time or resources for transport, and other factors impede many from learning whether they have HIV infection or not(24)(25). Those who are unaware of their status may unwittingly transmit the virus to their sexual partners, to those who use their injecting equipment, and to offspring. Despite promising progress in the response to the HIV epidemic, it is clear that unless the barriers to HIV testing uptake are effectively addressed(26) and, arguably more importantly, unless we grapple effectively with the upstream structural determinants of HIV vulnerability and risk(27), HIV will be with us for many decades to come.

HIV infection is preventable – no one in this day and age should be acquiring it. Although, despite population growth, the numbers of new cases have fallen from 3.2 million [2.9-3.4 million] in 2001, still during 2011 alone 2.5 million [2.2-2.8 million] people newly acquired HIV infection(6). Each one of these people will eventually require ART for their remaining lifetime once it is initiated. Within 6 months of initiation of effective ART, the risk of transmitting HIV to others falls dramatically to negligible levels. People who have no detectable virus in their bloodstream, as determined by an undetectable plasma viral load measurement, and without any sexually transmitted infection that might increase levels of virus in their genital secretions are highly unlikely to transmit HIV infection to a sexual partner (28)(29). Antiretroviral prophylaxis in the form of antiretroviral drugs taken by women who are pregnant or breastfeeding lowers viral load, resulting in marked reductions in HIV transmission to a foetus during pregnancy or childbirth or to an infant during breastfeeding(30)(31), while delaying HIV progression in the mother(32).
An estimated 9.7 million people were receiving ART at the end of 2012(33), with the current global objective being 15 million people on ART by the year 2015 – known as the ‘15 by 15’ goal(34). However, over 24 million people living with HIV were not receiving treatment in 2012 and each year an additional 2 million or more people newly acquire HIV infection. In July 2013, the World Health Organization (WHO) published updated guidelines recommending ART for all those with a CD4 count below 500 cells/μL(35), swelling the numbers of those that are eligible for treatment according to the previous guidelines of 350 cells/μL from 16.6 to 25.8 million(36). A ‘test and treat’ approach in which all those who test HIV-positive are offered ART, regardless of CD4 count, has been on the conceptual horizon and actively advocated for some time(37). Such an approach could help minimize loss to follow-up in the cascade between testing and eventual treatment that is seen now in high-income settings, such as the USA where over 50% of people who have been diagnosed with HIV are not in care(38), as well as in low- and middle-income countries(39)(40)(41). However, the treatment cascade is not the traditionally conceived linear model it is often thought to be, as people who have never been in pre-ART care can start on ART and those lost to follow-up can re-enter the cascade(42). Furthermore, it remains unclear whether early treatment would reduce or improve quality of life and result in better or worse retention and adherence. As for the individual clinical benefits of early treatment, the START (Strategic Timing of Antiretroviral Therapy) trial(43) underway in 35 countries, which has completed enrolment of 4000 people with CD4 counts above 500 cells/uL(44), should provide the definitive answer. In the long run, early treatment could lead to changes in the population of people living with HIV, with those acquiring HIV in the presence of scaled-up early treatment programmes possibly having weaker immune system function or exceptionally risky HIV-related behaviour(45). Although universal access to ART theoretically could lead to elimination of HIV through reduced HIV transmission if it were to be achieved(46), this scenario is hypothetical and it is evident that other forms of HIV prevention will remain essential to the HIV response in the absence of a cure(47)(48).

**Combination HIV Prevention**

The efforts currently underway to increase ART coverage beyond 9.7 million people will have prevention spin-offs with decreased HIV transmission risk for those on ART(28). Nonetheless, intensifying HIV prevention to stop the incoming flow of people newly infected with HIV makes logical sense. The question is how best to accomplish this. By the mid 1990s it was clear that investments in HIV information-education-communication, known as IEC, had failed to affect risk behaviour outside of specific high-risk settings such as the sex work milieu(49). Individually focused behavioural interventions had assumed that people had the agency to make choices and the wherewithal to enact changes in their lives to protect themselves and others from HIV infection. Attention turned to the societal conditions that create contexts of risk, maintain situations of vulnerability, and undermine people’s ability to act on prevention advice(50). Inspired by countries
such as Brazil, Thailand, and Uganda, all of which had introduced an array of biomedical, behavioural, and structural approaches generating sharp, sustained declines in HIV incidence, the term ‘combination prevention’ was coined. It had become evident that effectively addressing the social drivers of HIV risk and vulnerability meant altering the context within which health is produced and reproduced(51)(52).

The next step was the ‘Know your epidemic, know your response’ strategy(53). It brought together data on the scientific evidence of what worked in HIV prevention, country-specific HIV epidemiological data, trends in HIV transmission determined through the ‘Modes of Transmission’ methodology(54), information on existing prevention resource allocation, qualitative and focused research findings that would help explain trends, and the voices of all stakeholders in a participatory evaluation of a country’s HIV prevention strategy. Revelation of the disconnects between where HIV transmission was happening and where prevention resources were being spent underscored the need for a cost-effective evidence-informed HIV prevention strategy tailored to each country’s own epidemic and addressing the context-specific needs of those most vulnerable to HIV(55). The objective was to combine biomedical, behavioural, and structural approaches to create contexts that empower people to protect themselves, foster healthy choices, and provide people with the tools to enact those decisions, giving them an array of HIV prevention options for different situations and times of their lives(56).

Emerging biomedical HIV prevention approaches

A number of biomedical approaches to HIV prevention have been the focus of randomised controlled trials since 2003. Following almost two decades of observational evidence from a number of studies that male circumcision (MC) was associated with lower HIV prevalence(57)(58), three large clinical trials of medical male circumcision (MMC) got underway in South Africa, Kenya, and Uganda. Recruiting 10,000 men to be randomised to circumcision right away or wait for 24 months before being circumcised, these trials produced consistent and compelling findings by late 2006(59)(60)(61). All three trials were stopped early on the recommendation of their data safety monitoring boards (DSMB) when it was deemed unethical to continue to withhold MMC from the control arms. Given the level of HIV risk reduction seen in the trials (about 60%), WHO and UNAIDS produced recommendations in March 2007 recommending MMC as an important additional HIV prevention strategy in areas of high HIV incidence, low MC prevalence, and with a predominantly heterosexual epidemic(62). In the ensuing years, the original study sites have documented sustained (58% in Kenya (63)) or increasing protection (73% in Uganda(64)) or lowered community HIV prevalence(65) and incidence(66) (Orange Farm, South Africa). Devices that can reduce both the surgical time and the level of health cadre required to perform male circumcision, without increasing adverse events, now show promise(67)(68)(69)(70). One elastic ring radial compression device(71)(72) was
approved for marketing by the USA FDA in 2012(73) and prequalified by WHO in 2013(74), however it is currently unclear that its use would result in cost savings in sub-Saharan Africa compared to the standard forceps-guided method used for adult male circumcision(75).

Pre-exposure prophylaxis (PrEP) with antiretroviral (ARV) drugs for HIV-seronegative people has also been the focus of a number of clinical trials. Topical PrEP in the form of 1% tenofovir gel applied vaginally before and after sex reduced HIV acquisition by 39% in the CAPRISA 004 study of 889 women, increasing to 54% for women who reported using the product as instructed in more than 80% of their sex acts(76). Tenofovir gel in the same 1% formulation and used peri-coitally as in CAPRISA 004 is currently the focus of the large FACTS 001 study in South Africa(77). Daily oral PrEP tablets taken to achieve systemic levels of tenofovir (TDF) and emtricitabine (FTC) provided 44% protection in the iPrEx trial involving 2499 men and transgendered women who have sex with men in Peru, Brazil, Ecuador, South Africa, Thailand, and the USA(78). The same combination of TDF/FTC reduced HIV risk by 75% in the Partners’ PrEP trial among 4758 serodiscordant couples in Kenya and Uganda(79) and by 62% among 1219 heterosexual men and women in the TDF-2 trial in Botswana(80). The TDF-only arm of Partners’ PrEP demonstrated a 67% reduction in risk(79). Relative risk reductions among active arm trial participants found to have detectable plasma tenofovir diphosphate, the active form of tenofovir disoproxil fumarate, were 92% in iPrEx(78), 86% in the Partners’ PrEP TDF arm, and 90% in its TDF/FTC arm(79).

Based on the iPrEx and Partners’ PrEP results, the US Food and Drug Administration (FDA) in 2012 approved daily TDF/FTC to be used in combination with safer sex practices for the reduction of risk of sexually acquired HIV among adults at high risk of HIV exposure(81). Also in 2012, WHO published guidance on the use of oral PrEP for serodiscordant couples and for men and transgender women who have sex with men at high risk of HIV infection in the context of demonstration projects(82). In 2013, the last of the original placebo-controlled PrEP trials, the Bangkok Tenofovir Study, reported a reduction in HIV risk of 49% in a study of 2,413 men and women who inject drugs in Bangkok, Thailand(83).

Other trials of topical and oral PrEP have produced conflicting results. The VOICE trial of daily oral TDF, daily oral TDF/FTC, or 1% tenofovir gel applied daily tested against placebo tablets or gel, conducted among 5000 women in South Africa, Zambia, and Zimbabwe, closed trial arms early for futility or completed them with lack of efficacy(84)(85). The Fem-PrEP trial of oral TDF/FTC among 2120 women in Kenya, South Africa, and Tanzania concluded with no indication of effectiveness(86). Although differences in the trial populations, their sexual behaviours, genital mucosal integrity, and other co-factors for HIV acquisition may have played a role(87), the critical difference both within and between trials was adherence(88). Clearly, just like male and female condoms, oral and topical PrEP only have a chance to work if they are used.
An HIV vaccine is likely to be some years away although promising proof of concept has been shown in the RV144 trial involving more than 16,400 community-recruited people in Thailand. It evaluated the efficacy of a prime-boost regimen of 4 doses of ALVAC recombinant canarypox vaccine accompanied by 2 doses of AIDSVAX B/E matched to HIV clades circulating in Thailand(89). Over 42 months of follow-up, the vaccine arm had a 31% reduction in the risk of HIV acquisition. Building on these results, the Pox-Protein Public-Private Partnership or ‘P5’ that was established in 2010 is developing, analysing, and selecting protein components of a vaccine and accompanying adjuvants (substances that serve to enhance the immune response to a vaccine) in order to advance and ultimately license an HIV pox-protein vaccine candidate(90). Analysis of the immune correlates of HIV infection risk in the RV144 trial indicates that plasma IgG antibody levels against the HIV envelope’s variable region 1 and 2, known as V1/V2, are associated with a lower infection risk while anti–HIV-1 envelope plasma IgA antibody responses correlate directly with infection risk(91). The first safety trial in infants born to HIV-infected women of the ALVAC-HIV vCP1521, the vaccine that was used as the prime in the RV144 trial, has been completed in Uganda with no safety concerns(92).

While the RV144 trial was underway, discouraging news came from the STEP Study (USA) and Phambili trial (South Africa) that were testing a Merck product consisting of 3 vaccinations of adenovirus that had been synthetically modified to contain gag, pol, and nef proteins from HIV. The replication-deficient adenovirus vector was intended to carry the HIV genes into the cell, generating both humoral and cellular immunity(93). Not only did the vaccine regimen not show protective efficacy against HIV but risk appeared to be enhanced in trial participants who had pre-existing immunity to the adenovirus vector(94). Then in 2009 exciting news emerged about broadly and potent neutralising antibodies. New technologies in the form of high-throughput neutralization had permitted the screening of antibody-containing culture supernatants from activated memory B cells in the blood of a clade A-infected African donor. The result was the isolation for the first time of two monoclonal antibodies that target a broadly neutralizing antibody epitope*, are potent in minute concentrations, and bind tightly to the virus’ antigenic site(95). Within months, two broadly neutralising antibodies, VRC01 and VRC02, from another HIV-positive person, were found to neutralise over 90% of 190 viral strains representing all major circulating clades and including viruses from both people with acute and those with chronic HIV infection(96).

Discouragingly, the latest clinical trial (HIV Vaccine Trials Network 505) of a recombinant DNA priming vaccine given 3 times, followed by a recombinant

* An epitope is that part of an antigen that the immune system recognizes. A broadly neutralizing antibody epitope is an epitope that evokes antibodies that are broadly neutralizing.
vaccine boost using a weakened adenovirus type 5 (Ad5) vector, involving 2504 circumcised, adenovirus-5 antibody-free men who have sex with men (MSM) study participants, was recently halted by its DSMB when it observed a non-statistically significant increase in HIV acquisition among volunteers in the investigational vaccine group compared to those in the placebo group. Furthermore, the vaccine regimen failed to reduce viral load in those who became infected, which was an additional trial endpoint(97). On a counterpoint, a promising area of current investigation uses bioinformatics to model back to find the unmutated common ancestor B-cell that initially responded to the virus. If we could mimic the subsequent evolution in the virus that exposed epitopes to which we then responded, we could better understand how to stimulate neutralising antibody and extend its breadth(98). However, an HIV vaccine that has proven efficacious in clinical trials still seems a considerable time away(99)(100)(101).

VMMC scale-up is well underway in a number of sub-Saharan African settings with high HIV prevalence(102) and the feasibility is being assessed of establishing oral PrEP demonstration projects, outside specific short-term post-trial access programmes such as iPrEx OLE(103) and Partners’ PrEP(104). The extent to which HIV prevention trial results can be reproduced in real word settings remains to be seen. In addition to the considerable concerns of delivery logistics and financing are the challenges of matching supply and demand, minimising drug resistance, and determining with which people what prevention options would best suit them for what period of their lives. Clinical trials are designed to study potential HIV prevention tools in a controlled way with strict inclusion and exclusion criteria for trial participation. All trial arms receive a standard of prevention package including condoms, treatment for sexually transmitted infections (STIs), and frequent HIV testing and counselling. Initiatives aiming to translate HIV prevention trial results into programmes on the ground may encounter constraints and challenges in trying to reproduce trial findings or may find synergies when other HIV prevention modalities are being scaled up community-wide at the same time and new social and sexual community norms are forming. Four large cluster randomised controlled trials of combination prevention are underway in heterogeneous community settings in Zambia and South Africa(105), Hlabisa, South Africa(106), Botswana(107), and Iringa, Tanzania(108) with the objective of determining the impact on HIV prevalence and incidence of implementing diverse community-wide combination HIV prevention and treatment programmes.

Evidence-informed decision-making and the contribution of mathematical modelling of HIV prevention strategies

Evidence-based decision-making in public health has been defined as making decisions based on the best available scientific evidence, using data and information systems systematically, applying program-planning frameworks, engaging the community in decision making, conducting sound evaluation, and disseminating what is learned(109). In the real world, it is evident that the process
of making health policy is not divorced from politics, although this relationship is often neglected despite the fact that content, context, process, and actors all inter-relate during policy formulation(110). Thus, rather than the term ‘evidence-based’, the term ‘evidence-informed’ more accurately reflects what is a complex and dynamic process that does not start and end with only the scientific evidence. The expression ‘evidence-informed’ recognises the fact that many other elements play a role in decision-making, including cultural appropriateness, concerns about equity and human rights, feasibility, and opportunity costs(111). Thus, scientific research can identify problems, propose solutions, and forecast the likely effects of different policy choices but it cannot be the only consideration(112). On the other hand, it is unconscionable to not consider the evidence when making policy on health issues, as may be seen when vested interests either seek to ensure their own priorities are accommodated or act to keep issues off decision-making tables(113).

Mathematical modelling and other advanced analytical methods have been used to make better military and industrial choices(114). In the HIV field, mathematical modelling can contribute to HIV policy making processes by, for example, predicting the future course of the HIV epidemic; estimating the need for prevention, treatment, care, and support services; assessing the impact of past programmes; and shedding light on what the alternative choices might cost and what impact they might have. Thus, mathematical modelling can inform optimal resource allocation decisions, answering key policy formulation questions such as: ‘What will happen if we do this?’, ‘What is the best way to do this?’, and ‘How much will it cost?’(115). However, mathematical modelling can highlight but not answer questions about acceptability, ethical choices, or equity concerns. It generally does not address prevailing cultural, social, political, or moral/legal norms that clearly can influence feasibility. However, it can draw out the implications of the prioritisation of certain programmes to specific populations, with respect to cost and potential epidemic impact.

Among the models used in the HIV field, the Estimation and Projection Package (EPP) and Spectrum are often used together to produce national trends in HIV prevalence and incidence, AIDS deaths, numbers of children orphaned by AIDS, and numbers of people newly needing ART(116)(117). The Modes of Transmission model of new infections pinpoints where new infections are occurring in a population to inform prevention programming tailored to local epidemics (118)(119). All three models, which have been iteratively revised as new information has emerged, would be substantially improved by valid, reliable HIV incidence assays(120). Such assays could also help determine the impact of large-scale interventions on the incidence of new infections, when triangulated with other epidemiological and programme implementation information(121).

Modelling used to assess the potential cost and impact of strategies such as VMMC, PrEP, HIV vaccines, and ‘Test and Treat’ has involved a number of
different approaches, primarily using transmission models. These have included compartmental models in which individuals in the population are assigned to different subgroups or compartments and move to other compartments at determined rates as opposed to being part of a distribution that changes; stochastic simulation models in which random variations occur in one or more inputs over time versus deterministic models in which events are not subject to chance; and micro-simulation models in which the effects of changes in policy are simulated at the level of the individuals, i.e at the micro level, rather than at the population level. Cost-effectiveness models have generally been either transmission models or Markov models in which risk is continuous over time and there is a known probability or rate of transition from one health state to another. Some models include unit costs derived locally through facility-based costing exercises whereas others extrapolate from other costing exercises or desk reviews.

The parameters and underlying assumptions in the ‘black box’ of mathematical modelling can vary tremendously. Making these explicit and engaging in transparent discussions about them can help untangle the disparate results of different modelling exercises that seemingly have addressed the same question. For example, in the case of modelling the impact of a novel HIV tool to prevent sexual transmission, differing assumptions may be made about the frequency of sexual activity, type of sexual activity (vaginal, anal, oral), type of sexual partnership, extent of assortative mixing, probability of unprotected sex, background HIV prevalence, knowledge of serostatus, the force of infection, and other factors, even before assumptions are made about acceptability, efficacy, durability, effect on risk behaviour, cost, and likely uptake in prioritised or non-prioritised populations.

Different modelling approaches assessing the impact of a novel HIV prevention technology can be applied independently by experts to a variety of settings using assumptions that are informed by all available data relevant to each setting. The findings may or may not have much relevance for local decision-making or have a more general application, unless the ‘black box’ of assumptions can be interrogated. In light of the heterogeneity of modelling results, it is the hypothesis of this thesis that not only is it possible but that it is critical to come to a broad consensus about the utility of a new technology and its potential, or lack thereof, to contribute meaningfully and cost-effectively to national HIV prevention strategies, depending on country context. The focus needs to be less about the precision of estimates and more about identifying good decisions(122), if mathematical modelling is to contribute tangibly to policy decision-making. The challenge then becomes one of knowledge translation and how best to formulate the findings in a way that will provide decision makers with crisp, clear, and easy-to-communicate arguments. They need these if they are to introduce the idea of a new HIV prevention modality at the policy-making tables that assess the opportunity costs of acting or not acting.
Outline of the thesis

Part 1 describes the current state of the HIV epidemic worldwide before addressing trends in HIV prevalence and incidence in 18 sub-Saharan African countries and issues related to key populations. These populations are key to the dynamics of an epidemic and key to effective responses to it. Their explicit and active engagement in the design, implementation, and evaluation of an HIV prevention programme are essential to its effectiveness. What population constitutes a key population is context-specific and can include men who have sex with men, sex workers, transgendered people, people who inject drugs, young women in high HIV prevalence settings, prisoners, fisher folk, and migrants, among others (Chapter 2)(123). The concept of evidence-informed and human rights-based HIV prevention combining behavioural, biomedical, and structural approaches is introduced, with a focus on realigning national resource allocation and tailoring programmes to local epidemics. Emphasis is placed on the importance of intensity, quality, and scale to have an impact, along with monitoring and measuring impact and triangulating data to build an evidence base on synergies between the different levels and components of combination HIV prevention (Chapter 3)(124). In Chapter 4 a recommendation is made to speed up the testing of novel biomedical HIV prevention tools through accelerated assessment of potentially beneficially combinations in innovative randomised controlled trials that assess more than one biomedical tool against a common control. These could include VMMC for male partners and 1% tenofovir gel for seronegative female partners, early treatment for HIV-positive people and oral PrEP for their seronegative partners, oral PrEP combined with immunization, co-formulation of an HIV vaccine and an antiretroviral-containing microbicide (topical PrEP) in a vaginal ring, or combining a vaccine and a long-acting injectable PrEP agent(125).

In Part 2, the policy background to VMMC is described through an assessment of the observational and randomised controlled trial evidence for action on male circumcision, published shortly after UNAIDS and WHO issued recommendations on male circumcision for HIV prevention. It includes a random-effects meta-analysis of the trial data compared with observational evidence collected since 1986, demonstrating virtually identical findings of a 58% protective effect (Chapter 5)(126). Chapter 6 is a systematic review of the implications of male circumcision for women(127) while Chapter 7(128) explores the social and legal barriers to male circumcision as an HIV prevention strategy in sub-Saharan Africa, with a focus on acceptability, availability, and good quality of services as a requirement of the international human right to health. Informed consent, privacy, and confidentiality are highlighted for men, as are the human rights of their female partners and the importance of social change communication strategies that effectively convey the partially protective effect of male circumcision. An update on the evidence
concerning MC and other sexually transmitted infections, MC and women, and MC for MSM is provided in Chapter 8, along with an outline of operational research issues(129). Factors influencing key barriers and facilitators influencing the speed of VMMC scale-up at country level are explored using the Diffusion of Innovation framework(130) in Chapter 9(131).

**Part 3** examines the contribution of mathematical modelling and costing to policy-making on VMMC, beginning with an assessment of the results of six simulation models exploring the population-level impact of VMMC scale-up in high HIV prevalence settings. Eight key questions are addressed: the expected impact on population HIV incidence, the overall impact on HIV incidence in women, the impact of circumcising HIV-positive men, the effect of risk compensation, the impact on incidence by age group circumcised, the effects of speed of service scale-up, the impact if other prevention initiatives are scaled up at the same time, and the discounted savings (Chapter 10)(132). A Decision-Makers Programming Planning Tool (DMPPT) based on these findings and incorporating country-specific epidemiology and facility-based costing information was used to estimate the costs and potential impact of scaling up VMMC to reach 80% coverage by 2015 in 13 priority countries of sub-Saharan Africa. Chapter 11 presents the cumulative number and percentage of infections that would be averted between 2011 and 2025 by this strategy in each country and the actual achievement of each country toward its 80% objective(133). The cost of this strategy would be 1.5 billion USD between 2011 and 2015 with an additional 0.5 billion USD required to maintain coverage out to 2025, by which time the net savings would be 16.5 billion USD in averted ART costs. This would entail a total of 20.34 million adult male circumcisions between 2011 and 2015 and 8.42 million more between 2016 and 2025 (Chapter 12)(133). Chapter 13 describes the components of demand creation for VMMC and the challenges of costing it for inclusion in resource needs estimates(135).

**Part 4** presents the promise of PrEP using antiretroviral drugs to prevent HIV acquisition, emphasising that PrEP programmes should be tailored to those most likely to be adherent, providing them with state-of-the-art counselling and support to achieve high adherence during the period of time that they choose to use this method of prevention (Chapter 14)(136). In a systematic review of cost-effectiveness modelling studies addressing the cost and impact of PrEP for HIV prevention, 13 studies were included. PrEP for key populations at highest risk of exposure was the most cost-effective strategy. Underlying assumptions about cost, epidemic context, individual adherence, programme coverage, and prioritisation strategy were the considerations that most influenced cost-effectiveness (Chapter 15)(137).

In **Part 5**, teams of modellers were asked to assess the potential impact of RV144-like vaccines on HIV transmission in terms of infections averted over a 10-year period by single mass vaccinations of 30% and 60% of sexually active adults.
They were provided with unpublished information on interval-specific vaccine efficacies that included 60% efficacy at 12 months post-vaccine regimen. Some modellers included the hypothetical effect of boosters at 1 year and 5 years. Overall, a vaccine regimen similar to RV144 would avert 5-15% of infections and would be cost-effective in high incidence countries. If it were to be as effective in key populations, such as MSM, as it was among Thai heterosexuals then prioritising such populations for vaccination would be more efficient (Chapter 16)(138).

In Part 6, after a systematic literature review to identify environmental (macro and micro) determinants of HIV risk among people who inject drugs, three cities with severe injecting-associated epidemics, Odessa (Ukraine), Karachi (Pakistan), and Nairobi (Kenya) were chosen to model the potential impact of changes in the risk environment. The hypothetical structural interventions examined were elimination of police beatings in Odessa, Ukraine; actions to reduce the rate of transition from inhalation and smoking to injecting in Karachi, Pakistan; and removing legal impediments to needle-syringe programmes (NSP) and opioid substitution treatment (OST) in Nairobi, Kenya. The models suggested that between 4-19% of new HIV infections in Odessa, 65-98% in Karachi, and 14% in Nairobi could be averted by structural changes to the risk environment. Further, reducing unmet need by 60% for NSP, OST, and ART from 2010 to 2015 could prevent 41%, 43%, and 30% of incident HIV infections in these three cities, respectively. The literature review found that less than a quarter of epidemiological studies were designed to assess environmental influences and less than a third of studies had been conducted in those countries with the greatest burden of HIV among people who inject drugs (Chapter 17)(139).

The thesis concludes with a discussion in Chapter 18 that reflects on the lessons learned about the potential role of mathematical modelling in the HIV policy-making process, the extent to which modelling can inform decision-making, and the conditions under which this can occur. Other factors influencing decision-making are highlighted, including equity and ethical considerations, and suggestions are made about how best to interpret and communicate with stakeholders about estimates derived from modelling exercises.
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