EUROPE

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MAPPING PATHWAYS

Developing **evidence-based, people-centred** strategies for the use of **antiretrovirals as prevention**

Foreword by Archbishop Desmond Tutu

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Developing evidence-based, people-centred strategies for the use of antiretrovirals as prevention

Lead author **Molly Morgan Jones**

Contributing authors **Jim Pickett**, **Joanna Chataway, James Swartz, Ohid Yaqub, Philip Smith, Kartika Palar, Jessica Terlikowski, Daniella Mark, William McColl, Petal Hackett, Catriona Manville, and Peter Glick**

Project director **Jim Pickett**

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Preface

Mapping Pathways is a multinational project to develop and nurture a research-driven, community-led global understanding of the emerging evidence base around the adoption of antiretroviral (ARV)-based prevention strategies to end the HIV/AIDS epidemic. The project is based on the premise that the current array of prevention options is not sufficient; new pathways to prevention, based on enhanced assessment and analysis of likely impact, are needed to address new infections adequately.

ARVs are opening up new options for HIV prevention, such as 'treatment as prevention' (often referred to as 'TLC+' [testing, linkage to care], plus treatment), microbicides, oral pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP). There are multifaceted challenges associated with these new prevention strategies related to access, cost, behavioural and health impacts, and implementation.

Decisions about whether and how to implement any new prevention strategies should draw on multiple data sources. *Mapping Pathways – Developing evidence-based, people-centred strategies for the use of antiretrovirals as prevention* is designed to support critical thinking and development of a new research agenda for the analysis of multiple policy options – the pathways – that should be considered by prevention planners, programmers and funders when addressing the opportunities and challenges of the new ARV paradigm.

In this project we used four complementary methodologies to provide a scientific snapshot of the published literature and to highlight the complex and sometimes contradictory perspectives of community members and stakeholders from India, South Africa and the US who in 2011 were grappling with a rapidly evolving scientific landscape in real time. Blending scientific data and community voices into an expansive, people-centred synthesis allows for a deeper, nuanced, and more complete understanding of the promises and perils of ARV-based prevention and the research agenda which accompanies it.

Launched in January 2011, the Mapping Pathways project brought together community-based partners in South Africa (the Desmond Tutu HIV Foundation), India (Naz India) and the US (the AIDS Foundation of Chicago and AIDS United) in collaboration with RAND Europe. Baird's CMC provided communications support. Funding was provided by Merck & Co. and the US National Institutes of Health (NIH) through the initiative Be the Generation Bridge. To date the project findings have been disseminated at various national and international AIDS conferences – including the 2011 International Conference on AIDS and sexually transmitted infections (STIs) in Africa, the Microbicides Conference in 2012, the 2012 US Conference on AIDS, the 2012 Harm Reduction Coalition Conference, the International Association Providers of AIDS Care 2012 Summit on 'treatment as prevention' and PrEP, and the 2012 International AIDS Conference. Findings and stakeholder insights continue to be shared on the Mapping Pathways blog.

This report is recommended for advocates, researchers and policymakers, funders and governmental leaders, healthcare providers, programme planners, people living with HIV and other stakeholders. Individuals from a variety of disciplines who want to enhance their understanding of ARV-based prevention and the potential pathways to implementation will find utility in this document. Readers are encouraged to engage with the monograph in highly

personal ways, and read the chapters in any order they prefer.

Mapping Pathways has been peer-reviewed and published in accordance with RAND's quality assurance standards.

For more information on this monograph or the Mapping Pathways project, please contact Molly Morgan Jones, RAND Europe, or Jim Pickett, AIDS Foundation of Chicago:

Molly Morgan Jones
RAND Europe
Westbrook Centre
Milton Road
Cambridge, CB4 1QB, UK
+44 1223 353329
mmjones@rand.org

Jim Pickett
AIDS Foundation of Chicago
200 West Jackson
Suite 2200
Chicago, IL, 60606, USA
jpickett@aidschicago.org
+1 773 600 6407

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Summary

While the HIV pandemic peaked in the late 1990s, there are still more than 2 million new infections globally every year – the bulk of which occur in sub-Saharan Africa. Approximately 34 million people on the planet are living with HIV, and nearly 2 million people die from the disease each year. Although therapeutic approaches can extend and improve the quality of people's lives, the human and socio-economic cost of ongoing treatment for millions is widely viewed as unsustainable, particularly in the world's poorest countries. We must move beyond treating HIV/AIDS as a chronic condition and improve our ability to stop new infections.

But current prevention strategies need help. The provision of male and female condoms is necessary, and voluntary counselling and testing programmes, sterile syringe exchange, and behavioural counselling remain critical. Increased screening and treatment of sexually transmitted diseases, as well as voluntary male medical circumcision must also be part of a broad array of prevention practices. However, to date all of these strategies have proven to be inadequate to the task of fighting HIV. New pathways to prevention, based on enhanced assessment and analysis of likely impact, are needed to address new infections effectively, as 2 million new HIV infections every year are 2 million too many.

Although some antiretroviral (ARV)-based prevention strategies have recently shown efficacy in clinical trials, real-world, successful programmatic implementation is complex and still relatively uncharted. Significant challenges include cost, access to and appropriate use of ARV drugs, behaviour change, potential behavioural disinhibition, and possible drug resistance. Furthermore, the implementation of each prevention strategy differs across cultural and geographic regions.

Mapping Pathways is the first integrated, research-driven, and community-led study to provide a multi-layered synthesis for ARV-based prevention strategies in a single evidence base. The project's aim is to provide a resource for communities and policymakers with evidence, voices and views about ARV-based prevention strategies from across diverse global contexts, and synthesise this in a manner which lays out a future agenda for policymaking and further research. The findings can be used to help inform the research and analysis that communities and policymakers will need in order to help formulate coherent, evidence-based decisions for HIV/AIDS treatment and prevention strategies in the fourth decade of the HIV pandemic.

The Mapping Pathways project had the following objectives:

- to review the social, economic and clinical impacts of the following ARV-based prevention strategies: TLC+ (testing, linkage to care plus treatment), microbicides, pre-exposure prophylaxis (PrEP), and post-exposure prophylaxis (PEP) in the contexts of South Africa, India and the US
- to translate the perspectives and current state of knowledge of stakeholders at the 'grasstops' and community members at the 'grassroots' into an analysis of what their views mean for future research and decisionmaking
- to explore the views of experts on the state of the evidence base, and determine where they believed further evidence was needed and why

- to synthesise the information, views and interpretations of the evidence base from these multiple perspectives in a manner which would allow us to establish what further research and analysis was needed, and why.

Ours is not an exhaustive study into the nature of the policy contexts, HIV epidemics, treatment options, prevention strategies, healthcare systems, and other relevant areas within which each scientist, community advocate, person living with HIV, policymaker and healthcare worker we engaged with might have found themselves. The findings that emerged from the study, and which we present in this monograph, are a grounded, community-led interpretation of what people in diverse settings think ARV-based prevention could mean for their particular situations, and what questions it raises for them. Participation and engagement is at the heart of our study, and stakeholder input across the community, research, policy and governmental spheres is a core focus. The views and opinions of these groups are as important a part of the evidence base as the peer-reviewed, scientific studies about the efficacy of the prevention strategies themselves. Effective policy answers, and the pathways to them, need to be developed by engaging such a diverse range of voices.

We used four complementary methodologies to provide a scientific snapshot of the published literature and to highlight the complex and sometimes contradictory perspectives of community members and stakeholders from India, South Africa and the US who in 2011 were grappling with a rapidly evolving scientific landscape in real time.

These are the four methodologies we used to assess the empirical evidence base:

- a systematic literature review
- a grassroots, community-based online survey to understand the awareness and concerns of individuals
- semi-structured interviews with stakeholders and grasstops community leaders to identify information needs for decisionmaking
- a Delphi-based, online ExpertLens survey to understand key differences, areas of divergence and fault-lines in the way experts interpret the evidence.

The adaptive approach used in *Mapping Pathways* to inform the evidence base for policy development is a methodological innovation in itself, with experts, stakeholders and communities engaged in reflexive and iterative exchanges of knowledge.

Findings from across the four elements of the Mapping Pathways project indicate broad, divergent and incomplete evidence related to the viability of implementing ARV-based prevention strategies. Though the diverse perspectives highlight strengths and weaknesses associated with each strategy, our aim was not to make a definitive determination about which, if any, of the ARV-based strategies is stronger than any other. Rather, we highlight how the different perspectives and snapshots of the evidence for each strategy bring into focus features which still need to be explored.

The literature review pointed to the dominant role of clinical trials in shaping current policy and the need for further research into the contexts and conditions which will shape the real-world 'trials' that now need to take place as communities consider how these strategies may or may not be implemented. The literature shows there is a strong focus on *efficacy*, but more limited evidence on *effectiveness*. This is crucial, as a theme emerging from all four strategies was that behaviour and adherence will play a central role in the relative successes, and potential failures, of any ARV-based prevention strategy. It is intertwined with efficacy, alongside other parameters which determine effectiveness, such as cost, access, drug resistance, side effects and the wider socio-political context.

The grassroots perspective highlighted that people need more information in order to better understand and make individually appropriate decisions for their communities. There was general support for using ARVs as a prevention strategy, and in particular TLC+ and PrEP, but the types of concerns people expressed about what would happen if these strategies were implemented varied by country. This calls attention to the very real fears the front-line communities have about the effects of these strategies on their communities.

Mirroring this, but coming from the grasstops, the findings from the stakeholder interviews showed the very divergent ways leaders in different countries viewed the scientific evidence base. It was striking that within each country the same sets of scientific data were interpreted, framed and perceived in different ways depending on the local context. Stakeholders in decisionmaking positions seemed highly reluctant to make determinations on the basis of one clinical trial or study. Finally, the ExpertLens exercise highlighted that fault-lines in the evidence base exist, revealing where experts disagreed on the strength of the science in different areas and the implications of that disagreement for decisionmaking.

In India, stakeholders from the grasstops and the grassroots offered the most scepticism throughout and the most hesitancy about the idea that efficacy in a clinical trial means effectiveness on the ground. They often highlighted the different sets of cultural barriers to consider in India, ranging from cultural stigmas against HIV, to the complexity of healthcare treatment and testing facilities. In South Africa, stakeholders were worried about trade-offs and resource decisions that would need to be made. There were also concerns that existing prevention strategies and approaches to treatment might be side-lined in favour of this new science. Stakeholders from the US seemed more willing than other groups to accept scientific data at face value. They were consistently the most positive about each of the ARV-based prevention strategies and raised the fewest concerns about the nature of the science.

Across all countries, stakeholders cared about issues such as costs, resources, efficacy, effectiveness, adherence and resistance, but differed in the weight or priority they gave to a particular concern. Efforts to find pathways for the adoption of evidence-based practices in a given country have to take into account not only the strength of the scientific evidence, but also how that evidence and the study methodology are perceived as being applicable to the particular circumstances in that country.

The findings of this study point to a need for innovation not only in our approach to different prevention strategies for HIV/AIDS, but equally in our approach to policymaking. The opportunities highlighted in the pages of this monograph suggest we can develop much more tightly integrated understandings of both the scientific data about efficacy, which tells us whether recent innovations in the use of ARV drugs work or not, and the 'social', multi-disciplinary data about effectiveness. The right sets of social arrangements and organisational frameworks need to be in place in order for any scientific innovation to be useful, appropriate and adaptable.

The series of Mapping Pathways 'snapshots', culled from a highly dynamic and emerging evidence base, will not provide answers, but they highlight the importance of locally contingent factors in understanding how and why different strategies may or may not be effective in different communities. They help to illuminate the multiple pathways communities and policymakers must take to arrive at their own answers.

Scientific endeavour improves the lives of people living with HIV and provides us with new tools to fight it. However, science is interpreted differently by diverse communities; understood in varied ways for multiple reasons; and utilised for diverse means and ends. Context is critically important and the new scientific findings are only one part of successful ideas, innovations and breakthroughs.

As Archbishop Desmond Tutu says in his foreword, 'all science is local'. The understanding and utility of the scientific evidence base, coupled with the perspectives and views of communities and stakeholders, are local. Pathways are locally developed. ARV-based prevention strategies need to be successful at local levels before they can have a global impact.

Abbreviations

ART	antiretroviral treatment
ARV	antiretroviral drug
CD4	Cluster of Differentiation 4 (also known as t-cell)
CDC	Centers for Disease Control and Prevention
DALY	disability adjusted life year
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HIV/AIDS	human immunodeficiency virus, acquired immunodeficiency syndrome
HPTN	HIV Prevention Trials Network
iPrEx	Iniciativa Profilaxis Pre Exposicion or Pre-exposure Prophylaxis Initiative
M&E	monitoring and evaluation
MSM	men who have sex with men
MTN	Microbicide Trials Network
NGO	non-governmental organisation
NIAID	National Institutes for Allergies and Infectious Diseases (US)
NIH	National Institutes of Health (US)
nPEP	non-occupational post-exposure prophylaxis
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
QALY	quality adjusted life year
RCT	randomised clinical trial
RNA	ribonucleic acid
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
TLC+	testing, linkage to care plus treatment
USPHS	US Public Health Service
WHO	World Health Organization
YLS	year of life saved
μL	micro-litre

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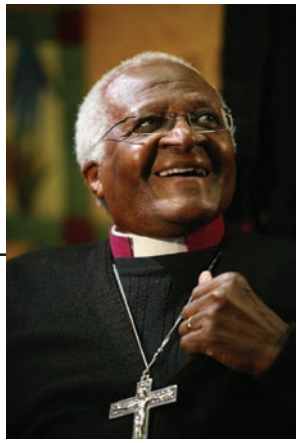
Foreword – All science is local



These are extraordinary times in which we are living. More than three decades into the global HIV pandemic, discussing 'the end of AIDS' is more than a rhetorical flourish, more than political grandstanding, and more than wishful thinking.

At this very moment, we have 'the end of AIDS' in our collective sights in a way we have never had before. Even as the epidemic continues to wreak havoc in the lives of far too many of our precious daughters, sons, sisters, brothers, mothers, fathers, friends and colleagues across the world – new and exciting scientific discoveries are pointing to a future where AIDS is a brutish artefact of history.

Science has shown us that treating HIV-positive people with a combination of antiretroviral drugs (ARVs) is not only good for the individual being treated, but also imparts a prevention benefit for the broader community as well. People on successful treatment do not get sick and die, and are much less likely to pass their infection to their partners.

Science has also shown that ARV drugs provided to HIV-negative individuals can protect them from the virus if exposed, much like anti-malarial drugs prevent malaria. And there are new, user-friendly ways to deliver ARVs being developed and tested at this very moment.

We simply must take the critical next steps to end AIDS now that science proves it can be achieved. If enough global citizens, people of faith, members of the private sector and world leaders summon the courage to accelerate and increase their investments in the global response to overcome AIDS, we have a very good chance of containing the worst viral scourge the world has ever known.

Conducting research in India, South Africa and the US, *Mapping Pathways* has taken such a step, one that helps make 'real-world' sense of the incredibly dynamic nature of the science. With new discoveries and insights coming so quickly it is hard to keep up.

Much like politics, all science is local. The understanding of what this new science means is local. Its utility is local. Yes, we have compelling results from clinical trials, and make no mistake, we will have more. But the opinions, perspectives and lived wisdom of communities, from the grassroots to the grasstops, matter just as much as the peer-reviewed scientific data that are coming at us fast and furiously. How communities absorb, understand and prioritise the science matters.

Placing a premium on a 'people-centred' interpretation of the science, *Mapping Pathways* has tapped the smarts, and the hearts, of advocates, researchers, clinicians, policymakers, pharmacists, funders, public health workers and people living with HIV. The results of their journey are illustrated in this monograph. I hope these findings will help communities across the globe grapple with the promises, and the marked complexities, of this thrilling new prevention paradigm in which we find ourselves.

I recommend *Mapping Pathways – Developing evidence-based, people-centred strategies for the use of antiretrovirals as prevention*. If we are to toss AIDS into the dustbin, we must do our best to understand the intersections of scientific discovery and community wisdom, address the truths in both, and move forward with decisions that take into consideration a full, robust interpretation of the evidence base.

Let us map new pathways together, for our generation and for those who follow. Let us be the generation to make the difference.

Let us be done with AIDS.

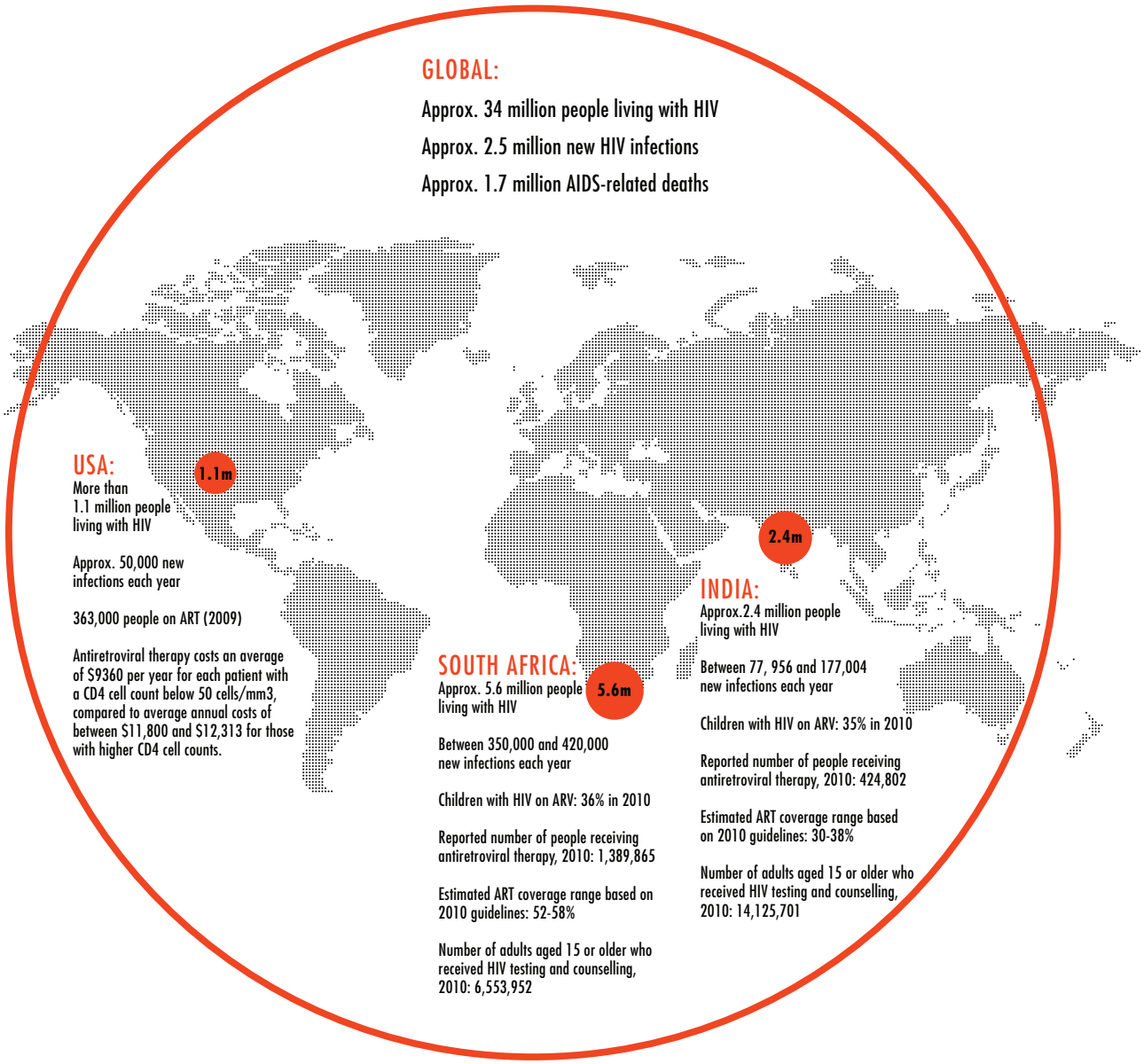
Archbishop Desmond Tutu


1
THE MAPPING PATHWAYS JOURNEY: SNAPSHOTS FROM THE BEGINNING

2011 – The journey begins

The world has made significant progress in containing HIV since the epidemic peaked in the late 1990s. Antiretroviral drugs (ARVs) have transformed the lives of millions of people living with HIV/AIDS. However, there are more than 2 million new infections a year, most of which occur in sub-Saharan Africa, and the disease still poses challenges across the globe: it is estimated that there are over 50,000 new infections in the US each year and analyses of the 'treatment cascade' suggest that of the 1.1 million Americans who are living with HIV, only 66% are linked through to care, only 37% are retained in care, 33% are prescribed antiretroviral (ARV) treatment and a mere 25% are actually virally suppressed (Center for Disease Control and Prevention, 2012).

Figure 1-1
Snapshots of the HIV epidemic in the US, South Africa and India



Moreover, current funding for ARV treatments does not meet the global demand. This is the case in the US as much as it is in emerging and low-income countries, where annual per person ARV costs range from $10,000 to $13,024 (Gebo et al., 2010), making access difficult for many. Programmes designed to provide medication to people with low incomes are often stretched thin and forced to implement waiting lists and other cost containment procedures. At the same time, limited increases in funding for global schemes which help support treatment in low-income countries mean that these schemes cannot grow adequately to meet the treatment needs of people living with HIV in many developing countries of the Global South. To illustrate this, a 'snapshot' of each country's epidemic shows how the nature and scale of the challenge varies across contexts and cultures[1] (see Figure 1-1).

Thus it has become clear that despite the great steps forward in HIV/AIDS treatment and prevention, more efforts are still needed. In particular, the current toolkit of prevention options, which is broadly seen to include behaviour change, condoms, counselling, voluntary testing, risk reduction counselling, needle exchange and male circumcision (see for example, Coates, Richter and Caceres, 2008), is not sufficient to stem the tide; a broader portfolio of approaches, or pathways, to prevention is needed (Granich et al., 2010; Weber, Tatoud and Fidler, 2010; Lancet, 2011). There is now a growing interest in new types of intervention initiatives, including 'treatment as prevention', or the use of ARVs to prevent the transmission of HIV from seropositive individuals to seronegative ones, and the use of ARVs in seronegative individuals. There are four main ARV-based prevention strategies which fall under these two categories (Box 1-1).

Although there is proven medical utility in some of these ARV-based prevention strategies (as will be discussed in detail in Chapter 2), real-world, successful implementation is currently challenging for PEP, and likely to be complex for TLC+, PrEP and microbicides when available. Significant challenges exist, including, but not limited to, managing cost, ensuring access and appropriate use of medication, reducing negative behavioural impacts, and minimising possible drug resistance. Furthermore, the implementation of each prevention strategy will likely differ across cultural and geographic regions. Deciding which strategy might be appropriate for widely divergent contexts is a complex undertaking.

The Mapping Pathways project

Until now, no single study synthesises clinical, economic, social, political and community issues into a single evidence base and analyses the implications for policy and future research directions. The Mapping Pathways project set out to explore the issues related to ARV-based prevention strategies with the goal of providing a richer, deeper and more nuanced understanding of what the evidence base for policy development of new ARV-based prevention strategies looked like, and how it might be used.

The project's aim is to provide a resource for communities and policymakers which brings together evidence, voices and views about ARV-based prevention strategies from across diverse global contexts and synthesises them in a manner which lays out a future agenda for policymaking and further research. The findings can be used to help inform the research and analysis that communities and policymakers will need in order to help formulate coherent, evidence-based decisions for HIV/AIDS treatment and prevention strategies in the 21st century.

Our project had the following objectives:

- to review the social, economic and clinical impacts of TLC+, as well as microbicides, PrEP and PEP in the contexts of South Africa, India and the US
- to translate the perspectives and current state of knowledge of policymakers at the grasstops and community members at the grassroots into an analysis of what their views mean for future research and decision making
- to explore the views of experts on the state of the evidence base, and determine where they believed further evidence was needed and why
- to synthesise the information, views and interpretations of the evidence base from these mul-

[1] Data are drawn from several sources, including UNAIDS (2012), WHO (2011) and Center for Disease Control and Prevention (2012).

Box 1-1
Four ARV-based prevention strategies[2]

Testing, linkage to care plus treatment (TLC+):[3] Earlier treatment for HIV-positive people has shown a prevention benefit. At present, several countries are revising upwards the recommended CD4 count at which they begin treatment to 500 CD4 cells/mm^3, and it is expected that the World Health Organization (WHO) will soon be following suit.[4] The argument is that if we improved access to treatment for people living with HIV, including the offer of treatment earlier in the course of the disease, there is evidence that the 'community viral load' would fall. Providing effective treatment to more individuals with HIV can reduce onward infections in a community because people on treatment are less likely to transmit the virus. Therefore, the chances of HIV-negative people becoming infected would reduce progressively over time.

Pre-exposure prophylaxis (PrEP): Providing HIV-negative people with ARVs (currently in a pill-based form taken orally) in order to prevent HIV infection. HIV-negative people at high risk of infection can be offered antiretroviral medicines to lower their chances of becoming infected in the future. Recent clinical trial evidence (discussed in Chapter 2) suggests adherence is essential, and with high adherence comes high protection. Future versions of PrEP may include long-term injectables.

Vaginal and rectal ARV-based microbicides: Providing topical, antiretroviral-based microbicides to HIV-negative people to prevent HIV infection. ARVs could be used topically – in a gel or lubricant formulation, vaginal ring or film – in the vagina or the rectum by HIV-negative people. The topical medicine could reduce the risk of HIV acquisition. No ARV-based microbicides are yet on the market, but some are in clinical trials. Recent studies have provided mixed evidence about the degree of efficacy in protecting women from infection, and other early-stage trials have provided encouraging data on other rectal and vaginal products. Though microbicides could be developed that are not ARV-based, we will only focus on those which have an ARV-based formulation.

Post-exposure prophylaxis (PEP): Providing ARVs to HIV-negative people with a recent HIV exposure. This HIV prevention method is currently available and involves taking three antiretroviral medications that are started after someone is potentially exposed to HIV. That exposure could be through unprotected intercourse, syringe sharing, or exposure in a healthcare setting. Generally two types of PEP are discussed: occupational PEP is the use of the prevention strategy for healthcare workers or others exposed as a result of their occupation; while non-occupational PEP is the use of the strategy for people exposed sexually or through injection drug-taking behaviours, outside the healthcare setting. The aim of PEP is to allow a person's immune system a chance to provide protection against the virus and to prevent HIV from becoming established in the person's body. In order for PEP to work, the medications need to be taken as soon as possible after potential exposure to HIV, and not later than 72 hours after exposure. The medications then need to be taken for a full month.

tiple perspectives in a manner which would allow us to establish what further research and analysis was needed, and why.

It is important to set out what our study is, and what it is not. Ours is not an exhaustive enquiry into the nature of the policy contexts, HIV epidemics, treatment options, prevention strategies, healthcare systems and other relevant areas within which each scientist, community advocate, person living with HIV, policymaker and healthcare worker we engaged with might have found herself. To conduct and present this alongside what we have done here would be an exhaustive research endeavour in itself and, moreover, one which has already been undertaken by numerous others.[5] To summarise that here

[2] Evidence for all of these strategies is discussed extensively in the literature review in Chapter 2, so we have not included full referencing details here.

[3] This strategy is known variously as 'test and treat' and 'treatment as prevention', as well as by other names, but is referred to throughout this book as testing, linkage to care, plus treatment (TLC+).

[4] CD4 cells are a type of white blood cell that fights infection. CD4 count, through a blood test, is a measure of strength of immune system. The threshold (measured in cells/mm3) at which to begin treatment for HIV/AIDS is under review.

[5] There is a vast body of literature on this topic. As a start the UNAIDS country reports (available at http://www.unaids.org/en/dataanalysis/knowyourresponse/countryprogressreports/2012countries/, accessed May 2013) are a useful reference guide and introduction to further reading in the field.

would have been artificial at best, and undermined the very nature of its complexity at worst.

What emerges instead over the course of our study, and which we present in this monograph, is an integrated interpretation of what people in diverse settings think ARV-based prevention could mean for their particular situations, and what questions it raises for them which still need to be addressed. Participation and engagement is at the heart of our study, and stakeholder input across communities, researchers, policymakers and governmental spheres is a core focus. This is because as a project team we believe that the views and opinions of these groups are as important a part of the evidence base as the peer-reviewed, scientific studies about the efficacy of the prevention strategies themselves. We don't aim to provide answers; these are for individuals, communities and countries to determine. Rather, we offer a fresh perspective in itself on how a future research agenda should be taken forward, and demonstrate the powerful need to engage a diverse range of voices and views in shaping it.

Six partners, four countries and multiple pathways to map

Mapping Pathways is a multinational project to develop and nurture this research-driven, community-led global understanding of the emerging evidence base around the adoption of antiretroviral-based prevention strategies to end the HIV/AIDS epidemic. It is characterised by a unique global partnership of six organisations possessing complementary skills and specialties. Together, the partnership includes academia, advocacy and a strong connection to impacted communities united in the development of a new framework for considering the allocation of HIV care and prevention resources. Each partner brings a perspective which is rooted in different backgrounds and disciplinary philosophies, thereby enabling a holistic understanding of the broader context and evidence base required to answer the questions we are asking. Community advocacy partners include NAZ India, the Desmond Tutu HIV Foundation, AIDS United and the AIDS Foundation of Chicago. RAND Europe, a policy research organisation, has led the project's research activities, and Baird's CMC, a policy communications group, provided communications support (Figure 1-2).

Mapping Pathways focuses on the US, South Africa and India. All share a policy environment where community groups and research can make a difference and all are democracies with strong civil societies and a vibrant press. Each has an engaged advocacy community and a number of active debates over aspects of HIV policy. All have research communities working in both the medical and socio-economic aspects of HIV and strong government commitment to fighting the epidemic. There are also important differences: prevalence ranges from low (in India) to very high (in South Africa) and incidence varies in each.[6] Each of these factors played a part in the interesting and diverse set of issues that emerged.

As will become apparent throughout these pages, the Mapping Pathways journey, which began in 2011, took place in a dynamic, fast-moving environment. As the imperative to consider new prevention options grew stronger in light of research and clinical trial data showing the extraordinary promise of using ARV-based therapies to prevent the transmission of HIV, so too did the demands and voices of policymakers and advocates to have a better understanding of what these data meant for them. Just as quickly as one piece of scientific evidence was put forward, a new one emerged and the picture changed. Thus, we present our findings throughout this monograph as a series of dynamic snapshots of this fast-paced environment where science, evidence and the needs of stakeholders to understand what to do next were struggling to keep apace. Against this background, and within this dynamic environment, the Mapping Pathways team began its journey. The snapshots in time we captured during this extraordinary period begin here.

[6] Prevalence is the proportion of a population found to have a condition, while incidence rates are the number of new cases in a population, within a given time frame.

Figure 1-2
The Mapping Pathways partners

A journey through efficacy to effectiveness

The imperative for this journey begins with the growing evidence base around the efficacy, effectiveness, economic and ethical issues of using ARVs for prevention. Some of the issues that framed our study from the beginning, as well as some which emerged as it was conducted, are summarised below and discussed fully in Chapter 2.

Starting with efficacy, in the past three years several clinical trials have reported on the efficacy of three different ARV-based prevention strategies including vaginal microbicides (CAPRISA 004), PrEP (iPrEx, Partners PrEP, TDF 2), and HIV treatment (HPTN 052). These trial results have been highly influential in changing the way that we think about treatment as prevention. For example, the CAPRISA 004 trial in July 2010 illustrated that tenofovir vaginal gel, applied within 12 hours before and 12 hours after sexual intercourse, provided 39% protection from HIV acquisition, with higher rates of efficacy noted among more adherent users (Abdool Karim et al., 2010). Several trials looked at PrEP as an ARV-based prevention strategy, including the iPrEx trial published in November 2010 (Grant et al., 2010), which illustrated that a once-daily dose of Truvada provided 42–44% protection from HIV acquisition, and potential efficacy as high as 92% among more adherent users. But this protective effect, as seen in the CAPRISA 004 trial, is very much dependent on good adherence. Three other trials, FEM-PrEP (Van Damme et al., 2012), the Partners PrEP (Baeten et al., 2012) and the CDC's TDF2 (Thigpen et al., 2012) clinical trials looked at once-daily doses of Truvada and/or tenofovir. The interim results of FEM-PrEP were inconclusive and the trial was closed for this reason, however the Partners PrEP trial showed that the risk of infection was reduced by 73% in those who received Truvada, and by 62% in those who received tenofovir alone. The trial also reported extremely high adherence, and similar results were seen in the TDF2 trial. The HPTN 052 study in May 2011 (Cohen et al.,

2011), looking at the TLC+ strategy, was the first randomised controlled trial to provide a true impact evaluation of the ability of ARV treatments to prevent transmission as well as assess therapeutic benefits. It showed a 96% reduction in risk of HIV transmission from the treated partner to the uninfected partner when compared against the cases where the treated partner started ARV treatment later.

However, with this promise comes extraordinary complications. Deploying any ARV-based prevention strategy raises a complex array of inter-dependent challenges and issues, including access, cost, impact on behaviour and health, implementation, and the possibility of drug resistance developing. As will be discussed throughout this book, despite the efficacy shown in all of these trials, there are still lingering questions about the *effectiveness* of these different strategies outside the realm of a clinical trial and how they would be implemented in practice.

In addition, though work is being carried out on the health economics of the preventative impact of ARVs, as well as studies engaging entire communities of HIV-infected individuals in certain regions, gaps remain. For example, epidemiological modelling (Dieffenbach and Fauci, 2009; Granich et al., 2009) suggests the potential for universal treatment to actually end the HIV/AIDS epidemic in a decade by reducing prevalence to below epidemic levels. These models show that this reduction can occur because treatment significantly lowers infectiousness. However, some assumptions of the modelling have been questioned. Even frequent testing will probably fail to detect most HIV infections in the acute stage (the first month after infection) when HIV-positive individuals are at their most infectious (Ruark et al., 2009). While making ARVs available appears to lead to increases in testing (Glick, 2005), it is not clear that coverage of testing could increase enough to ensure a major prevention impact – especially since the strategy requires testing individuals who still feel healthy. Moreover, we do not know if treatment will be broadly available, and whether access to treatment will be sustainable.

Finally, there are ethical and socio-clinical issues arising from the recommendation that a therapy with the potential for toxic side effects and long-term complications be initiated at the earliest possible moment (Dieffenbach and Fauci, 2009). While the evidence for individual benefit continues to mount in favour of earlier treatment initiation, we still don't fully understand the long-term implication of starting people on ARV treatment as soon as possible after diagnosis irrespective of CD4 (t-cell) count. Nevertheless, several countries have changed their treatment guidelines to recommend ARV treatment irrespective of CD4 count or beginning when the individual has 500 CD4 cells/mm3 or less (Geffen, 2013). And having already changed its recommended CD4 threshold for treatment to 350 cells/μL in 2009 (Jain and Deeks, 2010), the WHO is revising its treatment guidelines once again, and is expected to change the recommended threshold to 500 cells/μL (Geffen, 2013). While there will be cost and access issues associated with a change in treatment thresholds in addition to the other challenges mentioned, evidence of improved survival and reduced HIV-related illnesses with earlier initiation of therapy is compelling (WHO, 2009). As we continue to learn more about the optimal time to begin ARV treatment for the individual, and gain a greater appreciation for the secondary prevention benefits associated with individuals maintaining undetectable viral loads, testing and treatment should remain voluntary and free of coercion. The decision to initiate therapy is one that lasts a lifetime. For both treatment and prevention benefits of ARV therapy to be realised, an individual must be ready, willing and able to adhere and remain connected to quality, continuous care services with ongoing access to ARVs and other medications for co-morbid conditions as necessary.

This is just one snapshot of the growing areas of research and debate in the advocacy and scientific communities. They raise important questions regarding the potential benefits of earlier ARV treatment, both for treatment of individuals with HIV as well as a prevention tool, and about the types of evidence needed. Efficacy is only part of the puzzle. If we have learned anything from the past 30 years of AIDS research, it is that all prevention, no matter the method or mode of action, is predicated on behaviour change at multiple levels, and an understanding of effectiveness that is deeply rooted in cultural contexts. Mapping Pathways provides a starting point.

A journey rooted in a participatory philosophy

The Mapping Pathways partners firmly believe that the evidence base comprises more than scientific data derived from clinical research. We believe that statistically significant p-values and strong confidence intervals are necessary but not sufficient for jurisdictions and countries to make decisions on the potential deployment of any ARV-based prevention strategy. The perspectives, experiences and collective wisdom of community members and key stakeholders must be valued along with statistically significant trial results. Moreover, views and behaviours are in constant flux and the dynamic nature of shifting perspectives and responses must be taken into account regularly. Decisions about possible ARV-based prevention strategies will need to draw on multiple sets of data, of various types, and will pose difficult questions for policymakers. This information, which must draw on multi-disciplinary and diverse data sets, needs to be synthesised in a research-based manner and informed by inputs from policymakers, community members and scientists in order to reflect the diverse perspectives and framings within them.

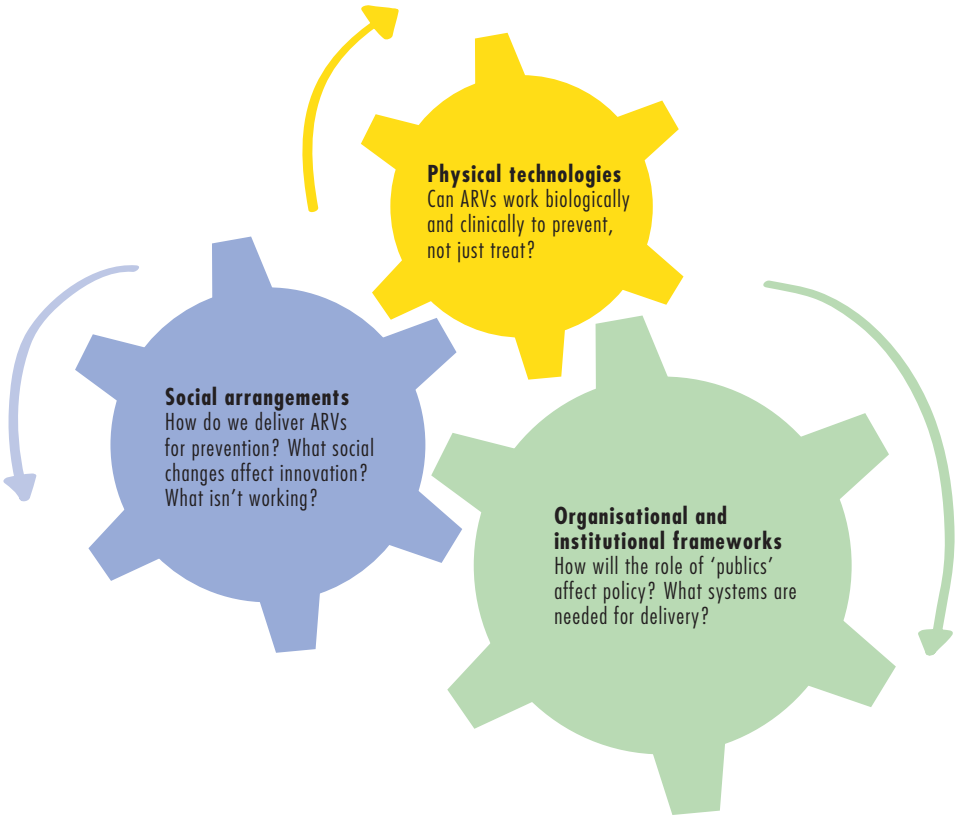
The project's aim, as stated earlier, is to provide a new perspective on the future agenda for research and analysis that communities and policymakers need in order to help formulate coherent, evidence-based decisions for HIV/AIDS treatment and prevention strategies in the 21st century. The evidence, views and interpretations provided will allow policymakers to re-examine, and perhaps update, treatment and prevention policies and the research needed to underpin them. It will allow communities to better understand how to go about making decisions about which strategies make sense in their context and how they should be explored. It will allow researchers across multiple fields and disciplines to see where gaps may exist, and how future research agendas can be set out. Our aim is to make it clear to all stakeholders where there are still questions to be answered, incomplete states of evidence, and where even existing evidence may be called into question depending on one's views and needs.

Four separate methodologies were used to access diverse stakeholder perspectives and assess the evidence base, looking specifically at South Africa, India and the US:

- **Analysis of the global evidence base**: We conducted a systematic literature review to map and analyse existing empirical data on ARV prevention strategies. It provides valuable insights into potential pathways and outcomes, highlighting knowledge gaps, and providing an important empirical grounding for the study in the peer-reviewed international literature.
- **Assessment of grasstops policy perspectives**: We conducted semi-structured stakeholder interviews with 38 opinion leaders and policy stakeholders and sought their views on the strength of the evidence base for different ARV prevention strategies, implementation challenges in their countries, and evidence needs.
- **Engagement with grassroots community members**: An online survey engaged 1,069 advocates and a range of stakeholders and interested members of the public in the three countries. We asked about the importance of different ARV-based prevention strategies, implementation challenges, concerns and additional evidence needed.
- **Providing an ExpertLens on the evidence**: Thirty-two AIDS experts participated in an online Delphi-based discussion called ExpertLens – a process that harnesses group wisdom in an iterative way and enables understanding of what and why the group 'thinks'. We asked about factors that might affect the effectiveness of different strategies, such as socio-economic and clinical delivery contexts.

Such an approach to understanding the evidence base for future policy development is an inherently adaptive one. It is adaptive in the sense that grassroots communities and grasstops stakeholders and experts are engaged in reflexive and iterative exchanges of knowledge, which responds to new data in real time. It is also adaptive in the sense that it allows for a critical examination of the evidence base from multiple perspectives and with multiple lenses.

Figure 1-3
Interactions within the Mapping Pathways analytical lens



A journey towards innovation in drug treatment regimes and prevention paradigms

Mapping Pathways seeks to develop this adaptive approach to policy development, where users, stakeholders and communities are engaged in reflexive and iterative exchanges of knowledge about the evidence needed for policy development around HIV prevention strategies, including but not limited to ARV-based ones. Throughout the pages of this book we will reflect on how this approach can be embedded and in the final chapter (Chapter 6) we will extend the implications for biomedical innovation and prevention paradigms more broadly. But what will these pathways look like, how do we know how to follow them, and where will they lead?

To answer these questions, we propose using an analytical lens based on one previously developed in the innovation policy literature (Nelson and Sampat, 2001; Chataway et al., 2010) that distinguishes between *physical technologies*, for example the protocols and clinical trials for developing safe and efficacious PrEP pills, microbicides or TLC+ strategies, which prevent transmission at a *biological* level, and *social arrangements*,[7] for example the firms that produce the drugs, the healthcare clinics that deliver the drugs, the community centres that provide education, and the partnerships developed, which will be critical to *effective* implementation. Figure 1-3 shows how these two elements operate and interact against a wider *organisational and institutional framework*, including national and global fund-

[7] This concept is derived from the innovation policy literature, in particular Chataway et al. (2010) and Nelson and Sampat (2001), which distinguish physical and social technologies in relation to actual technical innovations. Here, the language seems too stark, and so we refer to social arrangements, or partnerships, throughout the text.

ing structures, regulatory frameworks, healthcare systems and broader governance structures. These organisations and institutions provide the setting and in many cases will need to respond iteratively and react to changes in the development of the physical technologies and evolution of social arrangements. We believe this framework is useful because it calls attention directly to the idea that it is only by working together, with all three cogs turning, that effective and efficacious outcomes can be achieved.

The analogy of baking a cake has been used to describe the distinction between the three cogs described above. Physical technologies are the things we can put our hands on, the actual technical mechanisms through which a new strategy or intervention is introduced. They are the 'recipe' for baking a cake, or in the case of ARVs, the protocol for making the drug in the laboratory. Social arrangements and partnerships are those things which support the application of the physical technologies; they are the social relations involved in coordinating production, development, delivery and feedback. Finally, organisations and institutional frameworks are the operating 'theatre', or the kitchen in our cake analogy, in which all the interactions happen. They can provide rules and structures for how you can interact, or what you can do. They set out the institutional parameters within which you have to operate.

The value of this analytical lens is that it allows us to see beyond the clinical trial data to the importance of human agency and local context in delivering effective HIV prevention strategies. Thus, we see our role in Mapping Pathways as using the information and perspectives gathered to unpack the iterative nature of the relationships that will make the wheels of prevention strategy delivery turn most smoothly, be most effective and reflect local needs. Shifts at any level will change the way knowledge progresses and is used and we must stay on top of this and understand how this affects the wider system. For example, the efficacy data from recent clinical trials are raising fresh questions about the social arrangements and organisational structures and institutions in place to fight the pandemic. We would argue that though the evidence base is rapidly moving forward on the physical technology side, we don't know enough about what direction the social arrangements and organisational structures are going in, or should move.

The subsequent chapters of this book develop this theme further – presenting data from each of the four methodologies and linking them to our adaptive policy development framework. This allows us to see how and in what ways our adaptive approach, which focuses on the co-production of knowledge across different stakeholder perspectives, can help us to develop a deeper and richer evidence base, which captures the views of those who will be implementers of, and those affected by, the future of HIV prevention strategies.


2
SNAPSHOTS FROM THE EMPIRICAL LITERATURE

The literature provides a neutral, or objective, grounding for the Mapping Pathways project. At the time this study began, the evidence was beginning to emerge and we sought a better understanding of what its shape and content were, and could be.

Introduction – why the empirical literature?

At the time this study began there was some evidence to suggest that ARV-based prevention strategies were efficacious, but it was limited and there was less evidence about what the wider implications of their implementation would be. This is apparent from the two reviews of the empirical literature we conducted. Our initial search in May 2011 retrieved close to 5,811 articles covering the previous 11-year period, of which 310 were deemed relevant to our project. In June 2011, several major trials showing the efficacy of ARV-based prevention began reporting, including the HPTN 052 treatment trial, and the Partners PrEP and TDF2 trials on PrEP. Since we could not omit these papers from our study, and in light of the apparent growth of publications in the field, we ran another systematic search of the literature in June 2012, which covered just the previous years' worth of publications. We found 1,299 papers matching the same search criteria, 210 of which were deemed relevant. In just one year, then, nearly as many relevant papers were published as in the previous ten and a half year period. This enormous increase in the published literature reflects the dynamism of ARV-based prevention research.

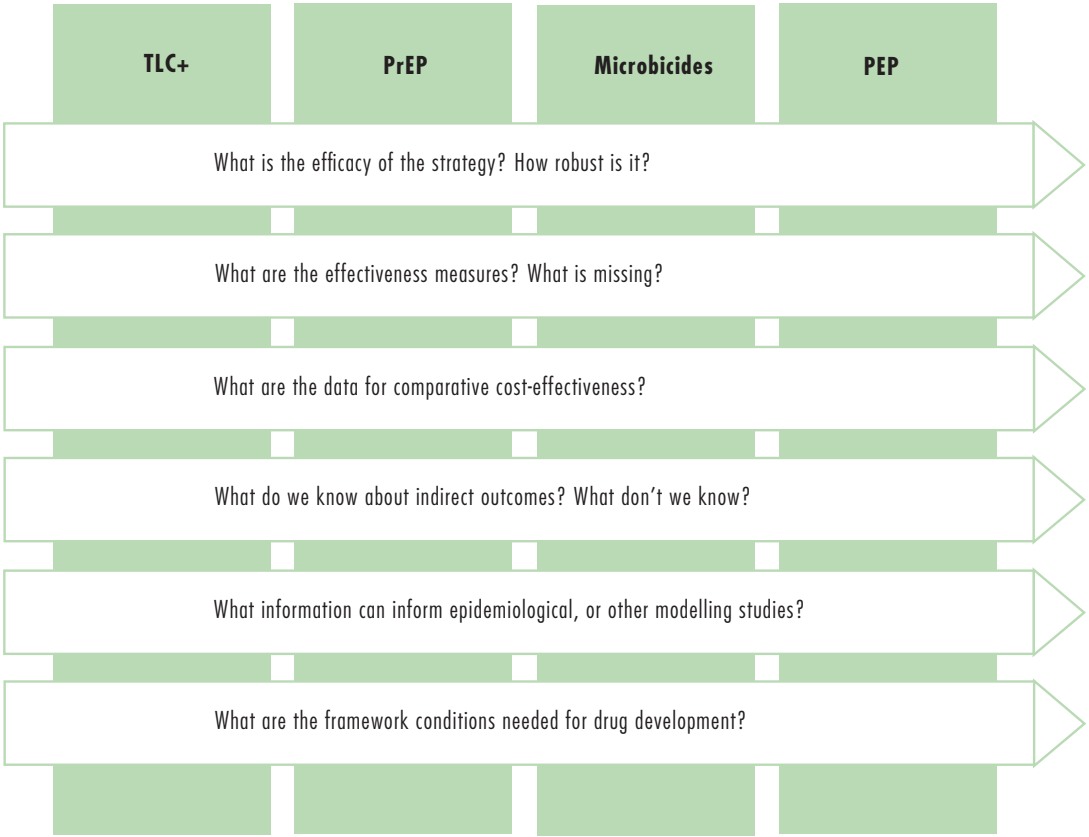
In light of this quickly shifting landscape, empirical, peer-reviewed studies about ARV-based prevention strategies provide an important grounding. This literature review provides a systematic and structured overview of the evidence base for ARV-based prevention strategies. It allows us to understand and analyse the state of research in the area and provide a foundation on which to begin identifying key evidence gaps and further research needs.

Our main research questions

Inevitably, peer-reviewed literature lags behind the pressing questions of the moment, but nevertheless it is an important starting point if we are to consider what questions need to be asked in future, and why. The question that framed this literature review was *'what is the evidence base for ARV-based prevention, including the different strategies and possible outcomes within them, and where do the gaps exist?'* Sub-research questions which cut across all the strategies are shown in Figure 2-1.

It is worth briefly reflecting on the kinds of evidence we thought might emerge from these sub-questions. First, efficacy refers to whether the strategy is able to produce a therapeutic or beneficial effect in a clinical trial or laboratory setting, in other words, whether it has been shown to prevent the transmission or infection of HIV. Effectiveness refers to evidence about whether the strategy works in medical practice. Here, we might expect to find information about the variables and influencing factors, such as behaviour, adherence, adverse effects, pregnancy and socio-political barriers, which can effect whether the strategy works or not. Third, cost-effectiveness evidence includes variables and influencing factors on the success of the strategy, such as costs per case averted and cost savings. Indirect outcomes can also be thought of as roughly comparable to the more economic concept of 'spillovers'. Economists use spillovers to describe the idea that some of the economic benefits of research accrue to organisations, regions (clusters) and countries that did not undertake the initial research. We borrow from this term, but extend it using the idea of 'indirect outcomes', and use it to refer to evidence about the follow-on implications of the strategies, such as wider health system benefits like infrastructure building or strengthened delivery services, economic impacts and cultural effects, and/or their implications on R&D models. Fifth, epidemiological evidence includes any analysis of public health implications, incidence, transmission rates and prevalence. Finally, by framework conditions we refer to any evidence about analysis of variables which might affect drug development, delivery and implementation.

Figure 2-1
Literature review schematic



Methodology

The literature review covers empirical data, published reviews and surveys, and commentary pieces. However, our in-depth, full text review focused on *empirical* sources of new evidence from three main categories: clinical trials and studies in a clinical setting; modelling and cost-effectiveness studies; and longitudinal, cross-sectional or other epidemiological studies. In addition to synthesising the existing evidence base, we analysed it to identify knowledge gaps in order to generate new questions which could help shape the future research agenda in the field. The outputs of the literature review are thus two-fold:

- systematic mapping of the literature, which provides a guide for identifying evidence gaps and the state and quality of existing data across different ARV-based prevention strategies and our research questions
- narrative syntheses, which analyse the strength of evidence for different strategies, the uncertainties within them, and the assumptions needed for outcomes to be realised (such as type of population, [medical] infrastructure of the country, etc).

We focused the literature review specifically on the 'ARV-based prevention' literature, but acknowledge there would be useful insights to be gained from elsewhere, for example, literature about wider initiatives, such as efficacy of vaccines, condom use or cultural acceptance of male circumcision. However, the analysis and synthesis of these literatures was outside the scope of this review.

Once this boundary was established, our research questions fell into the six categories summarised in Figure 2-1 above: efficacy, effectiveness, cost-effectiveness, indirect outcomes, epidemiological modelling, and the wider framework conditions needed

Table 2-1
Types of studies identified in the literature review

Type of study	Description for our purposes
Cross-sectional study	Looking across a population at a single point in time to describe features of that population
Descriptive study	Characterising a population of patients
Evidence-based commentary	Commentary where an opinion expressed or a comment is being made, but it is based on evidence presented
Clinical study	Randomised clinical trial or a clinical study
Literature review	Literature review with an explicit methodology, possibly systematic, or rapid review of evidence where the aim is to understand the state of the evidence base in a particular area.
Longitudinal study	Includes a follow-up study or prospective cohort study, starting at time 0
Modelling	Studies which use mathematical models to produce an assessment of the future, with some element of the hypothetical or probabilities used in the analysis
Patient case study	Clinical/patient case studies of a single patient or group of patients
Qualitative case study	Social science case study where a particular phenomenon is investigated within a real-life context
Retrospective study	Case control studies, looking backward from the effect to ascertain the possible cause
Scientific study	Lab studies, often pre-clinical, of a biological phenomenon in a laboratory setting

for drug development and testing. Structuring our review around each of these questions helped us to think through what needed to be asked of the literature in a systematic way.

We followed a modified methodology for a systematic literature review (The Cochrane Collaboration, 2011), including: defining inclusion and exclusion criteria for the studies retrieved, determining a list of search terms, developing a list of databases to search, establishing information management systems, conducting the literature search, assessing study relevance, extracting data and information from the papers, and synthesising the information.[8]

Three academic databases – PubMed, Cochrane and EmBase – were selected in consultation with trained librarians who have detailed knowledge of their content and coverage. After pilot testing and refinement of the search strategy, 7,110 articles were retrieved. The titles and abstracts of these articles were reviewed for relevance to ARV-based prevention strategies and empirical methodology of the study. These 520 articles were categorised according to prevention strategy, type of study, and findings to produce an overview based on the article abstracts which could be used for high-level analysis. The types of study identified are summarised in Table 2-1.

Once the abstract overview was completed, we reviewed and assessed the quality of the remaining papers. First, we applied inclusion and exclusion criteria related to the type of study. All clinical intervention, modelling and cost analyses, and longitudinal and cross-sectional studies were included, along

[8] Our approach deviated from a standard systematic review methodology in that we did not conduct a meta-analysis of data and we did not perform a formal Kappa test for inter-rater reliability at the selection stage, though the two reviewers had extensive discussions to ensure similar approaches and selection standards were used.

with systematic literature reviews, descriptive studies and qualitative case studies, as we only wanted to review in detail those papers which provided new empirical evidence or data. We then used a set of pre-defined quality inclusion criteria to further select papers for review. These were clear presentation of evidence and data; clarity of study design, including use of appropriate comparators; evidence of data collection methodology; and transparency of data analysis. We extracted data from 119 papers in total and conducted a narrative empirical synthesis of the selected papers, including summary tables where relevant. We recorded evidence in each of the review categories (efficacy, effectiveness, etc) and analysed them by looking across the different categories to develop findings. We reviewed the commentaries (which made up the majority of the relevant articles) rapidly to provide an overall picture of context. They are not referenced specifically in the narrative discussions below, but are included in the overview of the literature presented below.

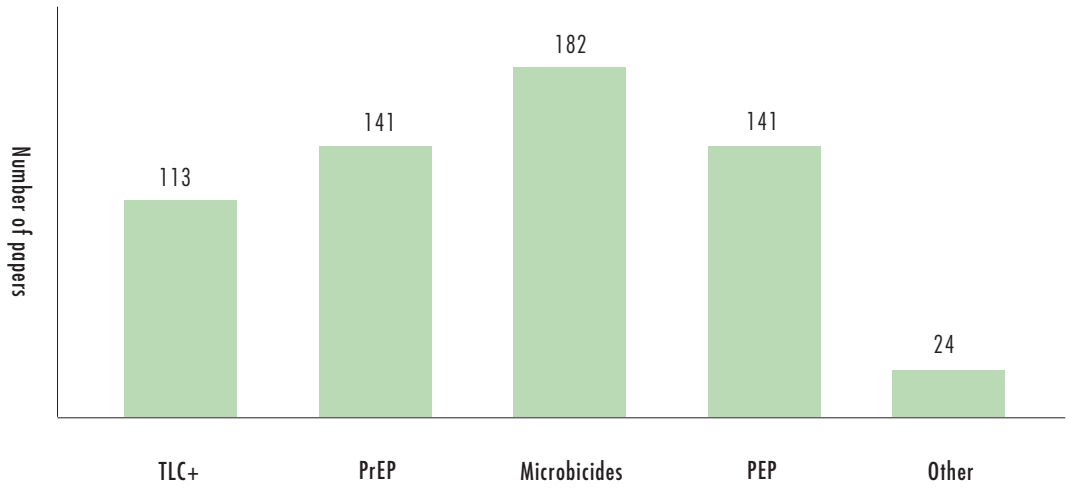
Our search of the literature did not find any prior study attempting to synthesise the existing evidence base for ARV-based prevention strategies as we have done here. The literature review discussed here therefore fills an important gap in the evidence base in and of itself. This is crucial, as a community invested in developing new and appropriate prevention strategies, for our ability to understand what we do know, what gaps in knowledge still remain, and how we might go about addressing the divide.

Snapshots from the literature

Abstract overview

The abstract overview of all the relevant articles we retrieved (including those not in the full text review) provides us with a good synopsis of the type of studies and research questions addressed across the breadth of the published literature we searched. A significant number of reviews and commentaries discussed more than one strategy, but our literature review still offers a good indication of which of the strategies are discussed most frequently. We discuss several different elements of the literature, beginning with a basic overview by ARV-based prevention strategy, illustrated in Figure 2-2, followed by more specific breakdowns of the literature by type of study and type of research question addressed in Figure 2-3 and Figure 2-4.

Figure 2-2
Literature summary by type of ARV-based prevention strategy[9]



[9] More than one strategy or literature review question may be discussed per article, so the numbers in this figure and Figure 2-4 exceed 520.

Figure 2-3
Distribution of type of study by prevention strategy

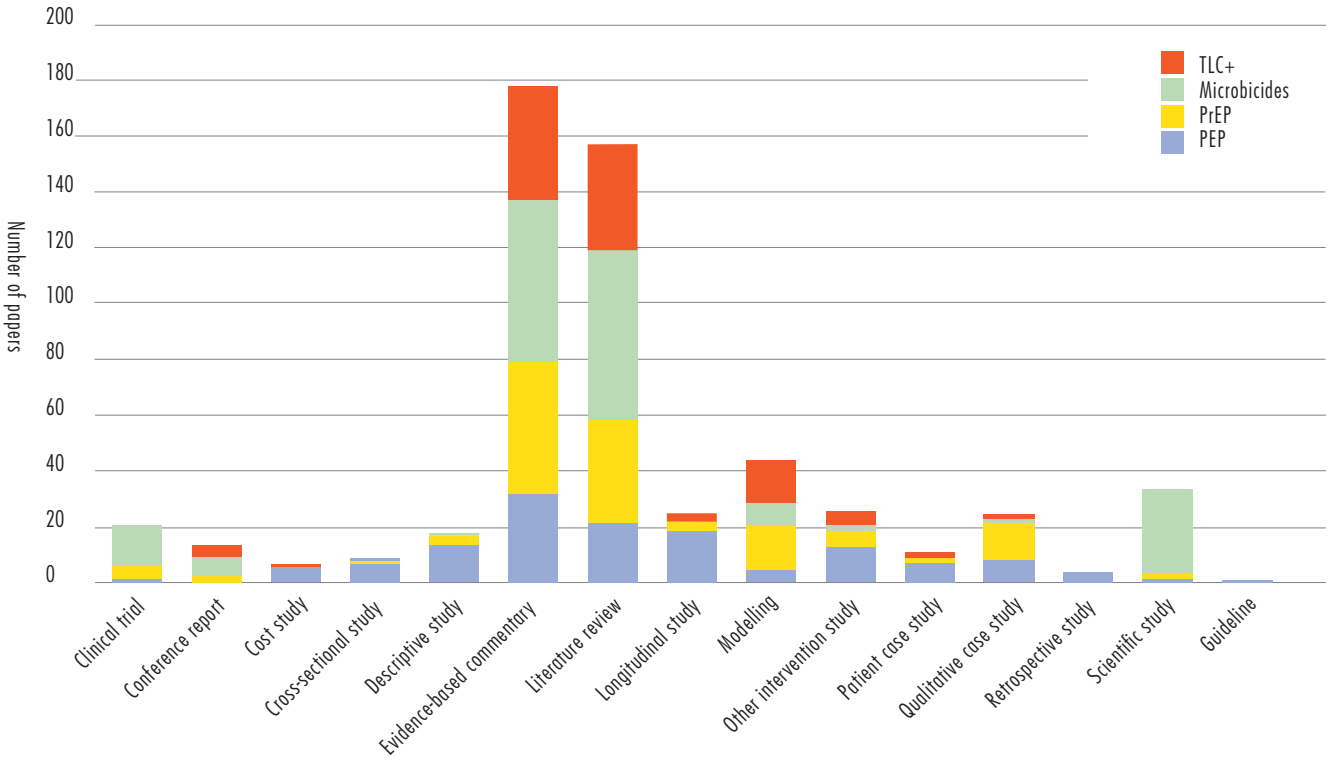
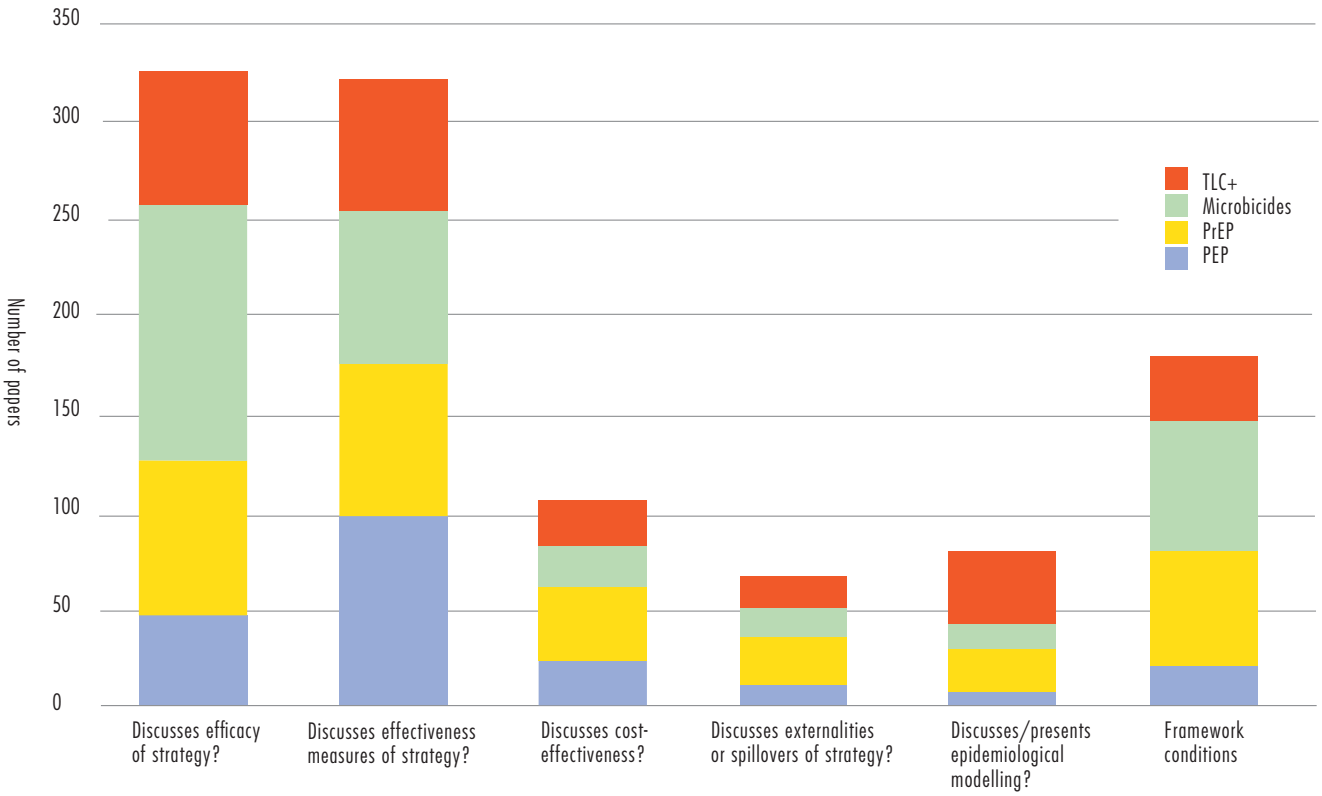


Figure 2-4
Relevance of literature to research questions by prevention strategy



We can see that most papers discussed the use of microbicides, with PEP and PrEP being the next most covered strategies.[10] Less was written about TLC+ over the period. In addition, the following themes emerge when looking across all the strategies (drawing on data shown in Figure 2-3 and Figure 2-4):

- The majority of the 113 articles about TLC+ are reviews and commentaries of the literature (74), along with a number of modelling studies (15). Most of the literature addresses questions about efficacy (66) and effectiveness measures (66), as well as epidemiological modelling (37) and cost-effectiveness (22). There is one clinical trial about TLC+ (the HPTN 052 trial).
- There are more clinical trials about PrEP strategies than TLC+ or PEP (see Table 2–2), and the greatest number of modelling studies (16). The articles focused fairly evenly on questions regarding efficacy (77) and effectiveness measures (74), and there were more papers than other strategies discussing cost-effectiveness (35) and indirect outcomes (24) of the strategies, although interestingly there were few specific cost-effectiveness studies in the literature for PrEP.
- There are more articles addressing questions about effectiveness measures for PEP (95) and there are primarily longitudinal (19) or descriptive (14) studies for this strategy. There was one randomised clinical study comparing the efficacy of different PEP treatment regimes.
- When looking across the research questions, we see first that most studies discuss efficacy and effectiveness measures of the prevention strategies, whereas relatively fewer focus on cost-effectiveness, spillovers and epidemiological modelling. Second, there is a predominance of articles about framework conditions, which are related to the need for continued development and testing of microbicides and PrEP.

Once all the abstracts were summarised, the quality inclusion review discussed above allowed us to select only those papers which presented new empirical evidence or data for a full text review. The breakdown across strategies investigated in the full text review is provided in Table 2-2.[11] In addition, 14 commentaries and 14 systematic literature review papers were reviewed.

All the clinical study papers were published between 2003 and June 2012 and the majority focused on efficacy of the different prevention strategies. Funding for the majority of the clinical trials came from government or academic sources, particularly the US NIH, the US Agency for International Development and the US Centers for Disease Control. The Bill and Melinda Gates Foundation has also been involved in funding clinical trials. In studies testing Truvada and tenofovir as PrEP, the pharmaceutical company Gilead, which manufactures these ARVs, provided them at no cost.

Of the modelling papers, the majority were modelling studies looking at a range of non-mutually exclusive outcomes, including efficacy, effectiveness, cost-effectiveness and externalities or spillovers. Several other modelling studies presented results on epidemiological modelling and two papers were surveys of the modelling literature, summarising and drawing out the key messages and key shortcomings of work in this particular area.

The majority of the cross-sectional, longitudinal and other intervention studies (qualitative case studies, descriptive studies and patient histories) we reviewed are on PEP studies. There are little data about efficacy of the strategies apparent in any of the studies, but they all provide indications of different effectiveness measures as measured by adherence and seroconversion after treatment. Many of the studies also provide information relevant to the indirect outcomes of the strategies, including behavioural effects (increase in risk behaviours), drug toxicity and side effects. These three types of studies are discussed together in the narrative syntheses below.

[10] It was not possible to tell from the abstracts in all cases whether the paper discussed ARV-based microbicides or other types of microbicides. At this stage all papers on microbicides were included, and as a result the findings likely overstate the prevalence of ARV-based microbicides in the literature.

[11] We originally found 13 papers about clinical trials or studies of microbicides, but only six reported on ARV-based microbicides.

Table 2-2
Summary of empirical papers included in the full text review, by strategy

	TLC+	PrEP	Microbicides	PEP	Multiple strategies used	Total
Clinical studies	2	11	5	3	1	22
Modelling studies (including cost and epidemiological modeling)	14	9	6	9		38
Cross-sectional studies	1	1		4		6
Longitudinal studies	1			14		15
Other interventional studies	1		1	8		10
Literature review and evidence-based commentaries					28	28
Total	19	21	12	38	29	119

Several of these themes are further developed and explored in the narrative syntheses, or 'snapshots' for each ARV-based prevention strategy. We do not necessarily present data from every single paper reviewed, but highlight the themes most strongly supported by the evidence.[12] In addition, within the snapshots below, we discuss clinical studies (including clinical trials), modelling studies and the remaining 'intervention' studies in turn, before presenting a final synthesis for each strategy.

Snapshots from the literature on TLC+

Clinical studies

Both papers reviewed in this category were reports of the same clinical trial, the HPTN 052 clinical trial supported by the National Institutes for Allergies and Infectious Diseases (NIAID) (Cohen et al., 2011). This was the first, and to date only, randomised clinical trial to test the efficacy of ARV treatment in preventing the transmission of HIV and which evaluated 'the effect of combination antiretroviral therapy on the prevention of HIV-1 transmission to uninfected partners and on clinical events in infected persons' (Cohen et al., 2011, p. 2). Specifically, the study looked at whether treating HIV-positive people earlier, when their CD4 counts were between 350 and 550 cells per cubic millimetre, meant they were less likely to transmit the virus to an uninfected partner than those who were treated later in the course of the disease, when their CD4 counts were under 250 cells per cubic millimetre. There were 1,763 heterosexual, serodiscordant couples enrolled in the study, which was conducted in Brazil, India, Kenya, Malawi, South Africa, Thailand, the US (Boston) and Zimbabwe. The infected partners were randomised in equal numbers across the early and delayed therapy groups. The same combination of ARV drugs was used across the study sites.[13]

The study findings show that early ARV treatment reduced the risk of transmission to an uninfected partner by 96%. Specifically, there were 39 HIV transmission events between partners in the

[12] Unless noted otherwise, all data presented from the papers are statistically significant.

[13] These included Combivir, efavirenz, atazanavir, nevirapine, tenofovir, lamivudine, dizovudine, didanosine, stavudine, Kaletra and Aluvia, ritonavir and Truvada.

entire study: four in the early therapy group and 35 in the delayed therapy group. In the early therapy group, in only one instance was there an infection where the virus was genetically linked to a partner, so in three of the four transmission events for the early therapy group it is likely that infection occurred through someone outside the clinical trial study group and likely not on the appropriate ARV treatment regime (Cohen et al., 2011; Eshleman et al., 2011).

To measure effectiveness, the study looked at adherence, and clinical and adverse events. Both offer some insight into behavioural and other responses of participants to the treatment. First, adherence was measured by self-reported pill counts and blood testing. There was at least 95% reported adherence in 79% of participants in the early therapy group and 74% in the delayed therapy group. Adverse and clinical events were not major, but were present and slightly more participants in the early therapy group experienced these symptoms. Some evidence of the impact of socio-cultural factors on effectiveness is shown in the data that 82% of the new infections between partners happened in Africa, where there are higher risk factors than elsewhere, including higher viral load, a more common type of HIV, and more frequent sexual encounters with decreased condom use.

The findings from the study have important implications for public health policy, particularly in relation to national and international guidelines about the point at which treatment begins, and its role in protecting uninfected individuals. There are also encouraging indications that there are individual benefits to earlier treatment, though the point at which this earlier treatment might begin is contested. For some the argument is political and related to higher costs associated with earlier treatment. For others the argument is related to the individual as it is not always desirable for both political (higher costs) and individual (ARV treatment is an individual choice) reasons.

Modelling studies

Several modelling studies have been undertaken in various contexts on the projected effectiveness of TLC+ strategies where there is earlier ARV treatment to prevent the transmission of HIV.[14] Many are optimistic about the potential for earlier ARV treatment to make a contribution to prevention strategies, but the fact that papers tend to use different sets of assumptions has implications for the types of findings which result.

Early studies on US epidemics were based on data from gay men and other men who have sex with men (MSM) in San Francisco, and were relatively optimistic about the potential for the expansion of ARV therapy to prevent the spread of HIV. However, they did not model specific 'test and treat' prevention strategies. Velasco-Hernandez, Gershengorn and Blower (2002) looked at conditions under which ARVs could eradicate the HIV epidemic, including assuming that levels of ARV coverage could reach 50–90% of the HIV prevalent population. They found that increasing ARV coverage of prevalent cases could greatly contribute to eradicating the epidemic. Porco et al. (2004) used probabilistic risk modelling to estimate how much the probability of infection decreased after actual introduction of ARV treatment in San Francisco and found that ARVs did reduce infectiousness and had the potential to contribute to prevention.

More recent modelling studies in the US have investigated TLC+ strategies more explicitly, and often consider wider populations. Findings from these studies are mixed. Walensky et al. (2010) found that a hypothetical 'test and treat' strategy implemented in Washington DC would reduce time a patient spends with transmissible HIV RNA levels by ~15–27% over five years, implying there is a prevention effect. Charlebois et al. (2011) used data from local health departments and the San Francisco General Hospital HIV outpatient clinics to estimate the impact of three TLC+ prevention strategies on HIV infections averted in gay men and other MSM in San Francisco over a 20-year horizon. Their model predicts that in all the strategies, a significant number of infections could be averted

[14] We should clarify that all TLC+ strategies involved earlier ARV treatment. We may not always use the specific language of TLC+ in these sections because that would imply the authors used that language, which was not always the case. Thus, the two should be read as interchangeable for our purposes.

within a five-year window, with the largest effects anticipated for an intensive-testing-and-treatment strategy. Sorensen et al. (2012) look at gay men and other MSM in New York City and explored the effect of increasing testing rates, linkages to care, and early initiation of ART on the cumulative number of HIV infections over a 20-year period. The model predicts that doubling annual testing rates and initiating ARV treatment at CD4 cells less than 500 per mm^3 could reduce cumulative infections by 39.3%, with the largest effects coming from the increase in testing rates. Further, it is anticipated that implementation of the proposed strategies at 'best case' levels could result in a 69.1% reduction in cumulative infections. Another study of a localised epidemic, this time in South Australia, found that the effects of different testing and treatment regimes vary depending on whether one is engaged in the community or not (Heymer and Wilson, 2011).

While these studies have looked at single cities, only one study in our review looked at TLC+ strategies for the US population as a whole. Long, Houston and Hershfield (2003) found that earlier initiation of ARV treatment – with CD4 cells greater than 350 per mm3 – could prevent 20–28% of infections. Still, the authors conclude that such a programme would be insufficient to substantially reduce the HIV epidemic without major reductions in high-risk behaviour.[15]

For developing countries, modelling exercises have generally produced optimism about TLC+ as a strategy for HIV prevention, with caveats that lack of behaviour change and increased resistance could undermine the preventative effects of expanded treatment. For example, Nagelkerke et al. (2002) modelled hypothetical prevention scenarios like TLC+ in Botswana and India and found that high ARV coverage (50%) and low generation of resistant strains could result in remarkable decreases in HIV incidence in the short term.

Even more optimistic are the findings presented in two papers by Granich et al. (2009, 2010) showing results on successive modelling exercises on TLC+ strategies based on South African data. They find that universal voluntary HIV testing and immediate offers of HIV treatment, combined with current public health prevention approaches, could have a significant impact on severe generalised HIV epidemics, and reduce prevalence of HIV to less than 1% in 50 years.

El-Sadr, Coburn and Blower (2011) look at serodiscordant couples in a developing country context, but go beyond TLC+ and also model the combination of other biomedical prevention strategies. The study estimates the effect of male circumcision combined with TLC+, provided to infected partners in Ghana, Lesotho, Malawi and Rwanda, on HIV incidence and infections averted. They find that while the intervention is expected to lead to significant numbers of infections prevented in all countries, the impact on country level incidence is not straightforward, as it depends on the epidemiological and demographic data.

While most modelling papers have been relatively optimistic about the extent to which TLC+ reduces the number of new infections, one paper we reviewed suggested otherwise. Using a model based on data in Malawi, Baggaley, Garnett and Ferguson (2006) found that in the absence of significant changes in behaviour, the introduction of ARV treatment could actually result in prevalence increasing with earlier use of ARVs. This somewhat counterintuitive result stems from the assumption that wider coverage increases the emergence and transmission of disease resistant strains. Although those treated are living longer, a fraction of them may remain infectious; as a result, the number of infections passed on per treated person could potentially rise and the total number of persons living with HIV would potentially rise as well.

Other intervention studies

The remaining intervention studies we reviewed show a positive relationship between earlier ARV treatment and prevention of HIV transmission. Rieder et al. (2010) looked at transmission dynamics using molecular epidemiological modelling and

[15] The meaning of the phrase 'high risk behaviour' has evolved during the years over which literature was analysed. In earlier years it was taken to include insertive or receptive vaginal or anal intercourse without a condom, or multiple partners, or concurrency. But the phrase is coming to have a meaning closer to 'unprotected vaginal or anal intercourse without a male/female condom or a form of chemoprophylaxis'.

Table 2-3
Summary of literature snapshots for TLC+

Type of literature review questions[16]	Summary of findings
Efficacy	Strong evidence from HPTN 052 - 96% efficacy and observational studies
Effectiveness	Strong evidence from clinical trials and observational studies that it could be effective. However, dependency on high access/adherence rates Gaps in evidence about adverse effects in the long-term and impact of behaviour and socio-cultural factors
Cost-effectiveness	Mixed and dependent on assumptions
Indirect outcomes	Little to no evidence across studies
Epidemiological implications	Strong evidence of reduction in transmission rates in developed and developing countries Epidemiological effects may be dependent upon testing and behaviour change assumptions
Framework conditions	Implications for national and international public health guidelines about the point at which therapy should begin

phylogenetic clustering analyses based on longitudinal clinical data. They estimate that 3.5 infection events per person year occurred prior to treatment initiation and 1.8 events per person year occurred after cessation of the early treatment. Del Romero et al. (2010) estimated the risk and probability of transmission between serodiscordant partners. They found that of 144 partners where the index partner was taking antiretroviral combined therapy, there were over 7,000 reported acts of intercourse without condoms and no HIV seroconversions of the non-index partner. This is compared with five seroconversions among 341 couples where the index partner was not on ARV therapy and where 11,000 acts of condomless intercourse occurred. Mugavero et al. (2012) evaluated the factors associated with viral load suppression. Their findings show that higher rates of early retention in HIV care are associated with achieving viral load suppression and lower cumulative burden on the individual. Two recent systematic reviews also found that studies show a largely positive effect of earlier ARV treatment on reducing the likelihood of HIV transmission between serodiscordant sexual partners. They concluded that the HPTN 052 study, combined with other historical analyses and observational studies in the literature, such as those summarised above, provided good evidence of the effectiveness of earlier treatment in preventing transmission of HIV (Siegfried, Uthman and Rutherford, 2010; Anglemyer et al., 2011).

Conclusion

The literature provides strong evidence for the efficacy and potential effectiveness of TLC+ as a prevention strategy, which is summarised in Table 2-3, but there are still gaps in the evidence base. For example, the HPTN 052 study looked only at stable couples, who may not be representative of the entire population. Counselling and condoms may also have contributed to low rates of transmission in this study, though there were many pregnancies. These types of complicating factors mean it will be important to

understand the dynamics between ARV-based and other, more social derived prevention strategies such as counselling.

Looking across this summary table (Table 2–3), there also seem to be gaps on the wider implications of these strategies, particularly in relation to broader health systems factors and other indirect outcomes. These are not easy to determine, but should be derived from models which take into account a wide range of effectiveness measures based on real data. The problem is that while the majority of modelling studies suggest that TLC+ strategies could be successful in significantly reducing HIV transmission, the results of these studies are sensitive to assumptions about:

- the proportion of those tested
- the proportion of those tested and treated who actually achieve viral load suppression, and maintain it
- the efficacy of ARVs in reducing transmission from those reaching viral load suppression to partners
- treatment coverage of the population
- current levels of linkage relative to the anticipated improvements.

Small changes in these fundamental parameters can result in very different results and some studies have critiqued the modelling literature in this vein. As an example, many of the studies reviewed here make assumptions about testing coverage, but in practice testing remains largely voluntary.[16] Therefore if individuals have a low self-perceived risk of contracting HIV, then actual testing behaviour may result in lower than assumed coverage rates, on average. Nattrass (2007) highlights the way in which choices of modelling framework may drive results, considering as an example different models exploring the potential for ARV treatment in South Africa. As there are differences in the models' abilities to handle heterogeneity in sub-groups of the population, one model might predict a significant reduction in HIV transmission, and another might predict no reduction in transmission for the same ARV treatment intervention. Punyacharoensin et al. (2011) survey the modelling and cost studies in the field over the past 25 years and note that this aspect of the literature has highlighted the need for more empirical work to be carried out, not least to provide an evidence base for several critical kinds of model assumptions. The variation in predicted infections averted also implies there is variation in predicted cost-effectiveness of the strategy, as do the implications of different behavioural assumptions, especially about the degree of faithfulness to partners and risk disinhibition. These all have very real impacts on the modelling results and if not adequately understood and explained could lead to misinformed policy decisions.

Snapshots from the literature on PrEP

Clinical studies

One of the first clinical studies of PrEP took place in 2003 and tested the safety, tolerability and drug trough levels of oral nevirapine among uninfected, high-risk individuals in the US (Jackson et al., 2003). The study found that the regimen was well tolerated over the short term (12 weeks) and not associated with any serious adverse effects during this time. In 2007, an unsuccessful trial tested tenofovir disoproxil fumarate (TDF, known as tenofovir) among HIV-negative, high-risk women in Cameroon, Ghana and Nigeria (Peterson et al., 2007). However, those carrying out the trial were not able to identify an effect on HIV transmission because study sites closed during the course of the trial. The trial was highly controversial as local residents had ethical concerns about the low levels of counselling, healthcare support provided, and provisions for treatment if infection occurred. International demonstrations and the very public cancellation of the trial highlighted the complicated and controversial nature of running clinical trials of PrEP (Bernard, 2005). Moreover, the authors noted at the time that lower than expected HIV incidence was likely to be an increasing problem in HIV prevention trials from the perspective of being able to detect statistically significant differences.

[16] Certain instances of mandatory testing exist, such as mandatory HIV screening for entry and/or stay of immigrant workers to or in Canada, Malaysia, Saudi Arabia, Singapore, South Korea and the UAE, among others.

Since then the field has developed and a further four clinical trials have published results on the efficacy of PrEP in preventing HIV infection, with mixed results. All were placebo controlled, randomised trials: the iPrEx study conducted by Grant et al. (2010), the Partners PrEP study (Baeten et al., 2012), and the TDF2 study (Thigpen et al., 2012). Clinical studies for PrEP have also been conducted revealing important contextual information related to the safety and adherence likelihoods under different drug regimens (Mutua et al., 2012) and a scientific study of ARV drug exposure to understand which ARVs would make the best PrEP candidates (Dumond et al., 2007). Each clinical trial is now addressed in turn.

In the iPrEx study, oral emtricitabine and tenofovir disoproxil fumarate (TDF-FTC (Truvada)) was tested among men and transgender women who have sex with men in six countries (Brazil, Ecuador, Peru, South Africa, Thailand and the US). They found that there were 44% fewer infections (or, put another way, the efficacy was 44%) in the Truvada treatment group compared with the placebo group. However, when controlling for self-reported adherence and pill counts, the efficacy was 73% for those who reported 90% or higher adherence. Even more interestingly, the investigators found that even though participants reported high adherence, blood tests showed that actual adherence was much lower. Of those who became HIV-infected on the trial, only 9% had a detectable drug level of any nature, let alone one high enough to provide a protective effect. Thus not only were self-reported data unreliable, but also efficacy could have been at least 92%, and possibly as high as 95%, if participants had taken the study drug as prescribed. These data should be interpreted with caution, though, as the analytical approach of altering the 'intention to treat' cohort in a trial is controversial. As some argue, this goes against the whole premise of the randomised clinical trial (RCT) since adherence is a behavioural mediator, not a random factor with respect to outcomes. As we discuss in the final chapter, this is one reason why some suggest that the basic premises of clinical trials may need to be altered in the future.

Grant et al. (2010) also found efficacy was higher than the study average for men aged 25 and over (59%), the US cohort (which was older on average and had almost 100% reported adherence), those with secondary education or higher (54%), those reporting low alcohol intake (57%), men who were circumcised (77%), and those who did not have HSV-2 (54%). The study also reported a substantial decrease in high-risk behaviours after enrolment.

The Partners PrEP study (Baeten et al., 2012) aimed to test whether daily oral tenofovir and Truvada prevented HIV infection among East African heterosexual men and women in serodiscordant partnerships, and to determine which was more effective than the placebo treatment. It found that tenofovir had a 67% efficacy when compared to placebo, whereas Truvada had a 75% efficacy compared to placebo. When compared against each other, however, there was no significant difference in efficacy between the two intervention arms. As with the iPrEx study, adherence was an important factor in overall efficacy. Detectable tenofovir levels in participants were associated with a reduction in risk of infection of more than 85%.

According to the researchers conducting the Partners PrEP study, the results suggest that adherence, protection and resistance appear to be tightly intertwined and co-dependent in different ways. For example, low adherence provides little HIV-1 protection, but little risk of resistance if infection is acquired. High adherence blocks transmissions, but may bring a higher risk of drug resistance if seroconversion should occur, though the efficacy data suggest that with high adherence, seroconversion is unlikely (Baeten et al., 2012). These factors need to be carefully examined and unwound in order to make future decisions about prevention strategies.

The third clinical trial was the TDF2 study (Thigpen et al., 2012). It compared daily doses of Truvada with placebo in preventing HIV-1 infection among HIV-seronegative, sexually active men and women in Gabarone and Francistown, Botswana. There was low retention in the study so the trial had to close early as it became unfeasible to obtain the necessary statistical power to show efficacy. However, based on the findings that were obtained before the study was closed, the authors report an efficacy of 62.2% as compared to placebo. There were similar rates of adherence found in both arms of the TDF2 study,

but the protective effect of Truvada was higher when the analysis was limited to those who had reported taking the drug within the past 30 days. Unlike previous studies, the authors found an increased report of side effects, including nausea, dizziness and vomiting, among those receiving Truvada, but these symptoms lessened after the first month. They also found drug resistance in two of the individuals who became infected with HIV-1.

The final clinical study was of the FEM-PrEP trial, which took place in Kenya, South Africa and Tanzania, enrolling 2,120 HIV-negative women (Van Damme et al., 2012). This study did not show efficacy of Truvada compared to placebo and the study was halted early. Before the trial closed, 68 infections occurred, 33 in the treatment arm and 35 in the placebo arm. Less than 40% of the uninfected women had evidence of recent pill use when matched to the window during which women seroconverted on the study ; again, actual levels of Truvada in the blood were significantly lower than self-reported pill use. For example, among women who became infected with HIV, the level of Truvada in the blood that was needed in order to provide a preventative effect (10ng) was only seen in four out of 27 women at both of their visits to the clinic. Among uninfected control participants, numbers of women with the target level of the drug in their system were higher. Despite the closure of the trial, the authors observed that there was no evidence of increase in risk behaviours (as reported during counselling sessions) and there were modest yet significant reductions in the number of sexual partners women had during the study period.

Looking across the clinical trials, the efficacy of PrEP has been shown to be statistically significant when compared with placebo. A meta-analysis conducted in a recent systematic review (Okwundu et al., 2012) found that across all clinical trials there was an overall reduction in the risk of acquiring HIV infection of 51% when comparing Truvada against placebo and 38% when comparing tenofovir against placebo.

Modelling studies

The modelling papers we reviewed were all published in the last six years and investigate epidemiological outcomes, including impact of PrEP on transmission, risk of infection, number of infections averted, and/or prevalence. In addition, four of these studies examine the cost-effectiveness of PrEP. The majority of PrEP modelling studies focus on the developing world, primarily sub-Saharan Africa, although two studies focus on the effects among gay men and other MSM in developed countries. A selection of the main themes emerging from the articles is discussed here.

Several have modelled the lifetime infection risk, cost-effectiveness and reduction in transmission rate, but all use different underpinning data and assumptions. For example, Paltiel et al. (2009) modelled the lifetime infection risk and cost-effectiveness of PrEP for high-risk gay men and other MSM in the US, based on HIVNET data.[17] They found that for gay men and other MSM considered to be at high risk, PrEP could reduce lifetime HIV infection risk substantially (from 44% to 25%), and increase mean life expectancy by about one year, with greater improvements as higher PrEP efficacy was assumed. However, the associated cost-utility ratio of $298,000/quality adjusted life year (QALY) was high. The authors note that this ratio could be reduced by targeting younger populations with higher incidence of infection and by improving the efficacy and cost of PrEP. More recently, Juusuola et al. (2012) focused on the potential impact of PrEP on HIV transmission among US gay men and other MSM. Using efficacy levels based on data from the iPrEx study, the model predicts that, given coverage ranging from 20% to 100% of the population, PrEP could reduce the number of HIV infections by 13–51%, though the expected cost per QALY is also high, similar to that estimated by Paltiel et al. (2009) at $216,000/QALY. Juusola et al. (2012) go one step further in their model and estimate the costs of only target-

[17] The HIVNET Vaccine Preparedness study (HIVNET) cohort study was carried out between 1995 and 1997 among 4,892 persons at high risk of HIV infection in nine US cities, to determine whether testing of preventive HIV-1 vaccines is feasible in the US. In the study under consideration, these data were used to generate age-specific HIV estimates.

ing the 20% highest risk segment of gay men and other MSM. Here, the cost is only $50,000/QALY, but the up-front cost of even the targeted treatment remains substantial. The authors estimate that initiating PrEP in all high-risk gay men and other MSM carries an annual cost in excess of $4bn. Other modelling studies have also found reduction in transmission rates could be achieved, but there are uncertainties around the implications of increases in risk behaviour, resistant strains, or both (see, for example, Supervie et al., 2010).

In developing countries, modelling studies have looked at a range of populations including: the general population (Pretorius et al., 2010), young women (Van De Vijver, Derdelinckx and Boucher, 2009), sex workers and their clients, and sexually active adults (Vissers et al., 2008) in Botswana, Kenya, South Africa, Southern India and Zimbabwe. In the last year, modelling studies exploring the impact of PrEP in the developing country context have continued to focus on heterosexual populations (Abbas et al., 2011; Hallett et al., 2011). Overall, these models suggest that PrEP could decrease HIV transmission, particularly for women, but that this effect could be eroded or reversed if PrEP replaces condom use or results in behavioural disinhibition (Abbas, Anderson and Mellors, 2007; Vissers et al., 2008; Van De Vijver, Derdelinckx and Boucher, 2009).

In addition, while some studies have found that PrEP effectiveness may be reduced by a high number of drug-resistant HIV strains (Van De Vijver, Derdelinckx and Boucher, 2009) and a low level of adherence (Abbas, Anderson and Mellors, 2007), more recent modelling by Abbas and colleagues has shown that PrEP use could reduce cumulative HIV infection by 3–6.6%. In this study, the effect of PrEP on cumulative HIV infection and on viral resistance was simulated over a 10-year intervention horizon, yielding the reductions in cumulative rates. However, the proportion of cases with drug-resistant infections was estimated to increase by between 9% and 10% (Abbas et al., 2011). In addition, a study of PrEP in South Africa found that PrEP would become less cost-effective as the availability of ARV treatment increases (Pretorius et al., 2010), suggesting there are interesting synergies yet to be explored between different ARV-based prevention strategies.

Giving further support to the idea that interventions are not only dependent on efficacy, but also the wider social context, Hallett et al. (2011) compare the impact of early initiation of ARV treatment to PrEP on HIV transmission within serodiscordant couples in South Africa. The authors found that while both interventions yield significant reductions in the number of infections, PrEP is preferable where extra-partnership contacts are significant as PrEP reduces probability of infection from any infected person (not just the partner). PrEP is also associated with higher initial cost, but may be cost saving for policymakers over the medium term because of reductions in future spending on ARV treatments. In the realistic ('typical') case explored in the study, PrEP is more cost-effective than early ART initiation (ART at CD4 cells less than 500 per mm3) only if PrEP effectiveness exceeds 40%.

Interestingly, while earlier studies tended to consider the potential for increased drug-resistant strains in the population as a result of use of ARVs for prevention, in the later studies this has received less attention. This may be a result of the fact that the recent clinical trials and retrospective studies (Dolling et al., 2012) have not produced evidence of resistance following treatment, but these studies are not definitive on the issue and even a small increase in resistance in a high-risk segment of the population could have serious implications for efficacy in future. Therefore this issue should continue to receive serious focus.

Other intervention studies

Most of the studies reviewed in this category examined the use of PrEP and took a variety of approaches to assessing the factors associated with the effectiveness of PrEP as an ARV-based prevention strategy. Though nuances vary across the studies, all find that there is a high willingness to use PrEP across a range of conditions, but that there is a need for education campaigns, accurate reporting and a better understanding of the contexts in which different groups of individuals are inclined to use PrEP.

For example, the study by Mimiaga et al. (2009) on predictors of awareness of PrEP and willingness or likelihood of taking PrEP showed that overall 86% reported high willingness to use PrEP every day if

they thought it would prevent HIV infection, 85% reported they would use it before a 'hot date' and for 28 days after a risky encounter, and 89% would use it for all unprotected anal sex. However, there are gaps in knowledge and awareness of PrEP in the gay men and other MSM population and wider populations. Both Mimiaga et al. (2009) and Zhou et al. (2012) report low awareness levels, and a cross-sectional study in South Carolina assessing attitudes to PrEP of 405 sexually transmitted disease clinic attendees showed that gay men and other MSM participants were significantly more likely to have knowledge of PrEP than heterosexual participants, and male respondents were more likely to think that it would not be very difficult for themselves (or their partner) to use condoms and take daily pills to prevent HIV infection (Whiteside et al., 2011).

The factors associated with willingness to use PrEP also vary depending on context. While Zhou, et al. (2012) only found positive correlations with consistent condom use and knowledge of ARVs' side effects as a predictor of likelihood to use PrEP among Chinese men, Mimiaga et al. (2009) found a range of predictors among US gay men and other MSM in Boston, including lower education and income status and having fewer than ten partners in the 12 months before the study. Golub et al. (2010) explored the attitudes of MSM to condom use and PrEP and found that over 35% of those who would use PrEP reported that they would be likely to decrease condom use while on PrEP. In multivariate analyses, arousal and pleasure barriers to condom use significantly predicted likelihood of PrEP use, and risk perception motivations for condom use significantly predicted decreased condom use while on PrEP. This study showed that though there was an openness to use of PrEP, the interactions between PrEP and use of other prevention strategies would not be straightforward.

Brooks et al. (2012) identified factors related to the adoption of PrEP by gay and bisexual men in HIV-serodiscordant relationships. Motivators for adoption included protection against HIV infection, less concern and fear regarding HIV transmission, the opportunity to engage in unprotected sex, and endorsements of PrEP's effectiveness. Concerns and barriers to adoption included the cost of PrEP, short- and long-term side effects, adverse effects of intermittent use or discontinuing PrEP, and accessibility of PrEP. A survey conducted in Botswana, India, Kenya, Peru, South Africa, Uganda and Ukraine of 1,790 potential users showed a willingness to adopt PrEP if efficacious and affordable (Eisingerich et al., 2012). Another study focused on at-risk populations including female sex workers, male-to-female transgendered persons and gay men and other MSM in Peru and found there were concerns in using PrEP due to potential sexual risk disinhibition, stigma and discrimination associated with PrEP use, and mistrust of healthcare professionals (Galea et al., 2011).

Conclusion

Overall, all clinical studies of PrEP point to the crucial nature of the relationship(s) between behaviour, protection, adherence and resistance. All of these elements are intertwined and have complex feedback loops which are not yet entirely understood. A summary of the snapshots from the PrEP literature discussed above is presented in Table 2-4.

One of the clearest messages from the literature on PrEP is that efficacy is highly dependent on adherence. In the two trials that did not demonstrate statistically significant efficacy of the PrEP drug compared to placebo, adherence to the PrEP regimen was low (as demonstrated by low levels of the drug in blood samples) among participants. In the trials where efficacy was shown, it was even higher when findings were controlled for adherence, in some cases as much as 95% if medication was strictly adhered to. This gives rise to some caution when thinking about implementation of this strategy and has implications for our understanding effectiveness of PrEP in the 'real world'. We need careful consideration of how to ensure adherence to the medication and what kind of support mechanisms are required to achieve this.

This need is all the more pressing in light of the positive findings from the modelling studies, which suggest that implementation of PrEP can significantly reduce HIV transmission, albeit with only low to moderate cost-effectiveness. However, the results of the modelling studies explored in this review were highly sensitive to assumptions about PrEP cost, efficacy, adherence, impact on resistance,

Table 2-4
Summary of literature snapshots for PrEP

Type of literature review questions	Summary of findings
Efficacy	Strong evidence for efficacy of PrEP, though mixed clinical trial results suggest efficacy heavily dependent upon adherence
Effectiveness	Adherence critical to high efficacy Need for better understanding of interactions between adherence, behaviour, and drug resistance Need for better understanding of long-term side effects for individual, including implications for behaviour change and drug resistance
Cost-effectiveness	Some modelling studies show PrEP may not be cost-effective
Indirect outcomes	Little to no evidence present on externalities of PrEP
Epidemiological implications	Strong evidence that PrEP can reduce infection and transmission rates, but this is dependent upon no increase in high risk behaviours and no drug resistance emerging Evidence is needed on the interactions between different strategies
Framework conditions	Need for evidence on long-term safety, which would have implications for national and international public health

and effect on quality of life. Small changes in these dimensions change the estimates of the intervention's impact on transmission and cost-effectiveness. Further, the strategy will be implemented in a wider epidemiological and behavioural context, so embedded assumptions about these framework conditions are also important, if not critical to successful implementation. It also suggests that efforts to generalise modelling findings, even within one country, may be problematic.

There is a need for more studies in this area so that we can develop objective adherence measures; understand long-term safety implications, develop reliable, context-specific models to guide policy decisions; and improve our ability to generalise findings to different at-risk populations.

Snapshots from the literature on microbicides

Clinical studies

In the literature, there is only one fully completed clinical trial on the use of ARV-based microbicides to prevent HIV transmission which met our inclusion and quality criteria:the CAPRISA 004 trial in South Africa (Abdool Karim et al., 2010).[18] In this study a 1% vaginal gel formulation of tenofovir was compared against placebo. The study authors found

[18] Several clinical trials of microbicides that do not contain ARVs would have met our quality inclusion criteria, but as this literature review focused specifically on ARV-based prevention they were not summarised here.

that tenofovir gel reduced HIV infection by 39% more in the study arm than in the placebo (control) group. As with the PrEP studies discussed above, the higher the reported adherence, the higher the efficacy the tenofovir gel had in preventing transmission. For women reporting over 80% adherence, efficacy was 54% compared to placebo (Abdool Karim et al., 2010).

However, the researchers of the CAPRISA trial note that the small size of the trial and limited geographical scope limits generalisability and highlights the significant recruitment challenges they faced in enrolling high-risk women into the study (Williams et al., 2011). In addition, we note that future trials will need to develop improved measures for adherence and safety, effectiveness and cost. To this end, the VOICE trial is the most recent clinical trial to test the efficacy of tenofovir gel, although at the time of writing its results had not been published. The trial had three intervention arms, one testing the use of tenofovir gel and the other two testing the efficacy of Truvada and Viread, both taken orally. The tenofovir gel arm of the trial was suspended in November 2011 as it failed to show effectiveness (MTN, 2011), again demonstrating a need to develop our understanding in this area further.

One study examined the acceptability of tenofovir gel to heterosexual men enrolled in a Phase 1 clinical trial (Carballo-Diéguez et al., 2007). The majority of men in the study (16 out of 21) said they found the gel to be highly acceptable and liked its odourless and transparent qualities. They recognised a woman's right to determine her own HIV prevention strategies, but commented that they felt this was more appropriate for 'one-night stands' as opposed to long-term relationships. There were also interesting insights gained about men's condom preferences. The men complained about the trial protocol's requirement to wear condoms, leading the researchers to speculate that microbicides trials that do not require condom use may provide a more 'accurate assessment of acceptability', and likely effectiveness of the strategy (Carballo-Diéguez et al., 2007).

As noted above, several clinical trials of microbicides that do not contain ARVs would have met our quality inclusion criteria, but as this literature review focuses specifically on ARV-based prevention they are not summarised in detail here. We will point out though that even if they are not ARV-based, clinical trials testing microbicides such as Pro-2000, Buffer Gel and SAVVY gel have not demonstrated any effect (MTN, 2012). A clinical trial to determine the safety and effectiveness of BufferGel and 0.5% Pro-2000 showed no reduction in the incidence of HIV when using BufferGel and a modest 30% reduction in HIV acquisition with Pro-2000 (Abdool Karim et al., 2011). However, this result was not statistically significant and the HIV incidence rate between the placebo gel and no gel arms were similar. In general, microbicide trials have had difficulty demonstrating benefit – overall HIV infection rates among participants are too low to be informative. Some authors note this may be due to concurrent risk reduction activities that increase hand-in-hand with the trial, and that trial participants may not represent the larger community.

Modelling studies

Earlier papers on microbicides tended to focus more on the scientific aspects of the intervention, with more limited focus on the effects on HIV transmission in real world. However, perhaps reflecting the growing awareness of the need to base models in the reality of contexts on the ground, more recent modelling papers have shown much more emphasis on the potential practical impact of microbicides. Also, to date, more studies have focused on vaginal as opposed to rectal microbicides. This is likely because there have been more clinical trials conducted on the former type, thereby providing the efficacy and cost data required to parameterise the models. Thus the modelling studies have explored the potential effects on disease transmission in heterosexual couples whose assumed risk factor is unprotected vaginal intercourse. Papers also have tended to have a developing country focus.

Beginning with those papers which have modelled the scientific aspects, Tuckwell et al. (2008) included microbicides in a mathematical model of viral dynamics – specifically, the probability of infection of a new host – and found that microbicides could decrease the probability of infection, but only if the number of virus particles transferred is less than 105. Unfortunately, such a level is a

relatively common occurrence, implying that efficacy of microbicides would be limited in a large number of cases. Vickerman, Foss and Watts (2008) look at how microbicide's efficacy against sexually transmitted infections (STIs) contributes to its HIV effectiveness, and finds that if trials demonstrate moderate HIV effectiveness, they should not necessarily generalise these results to other settings since the result could be partially attributable to the gel's efficacy against a curable STI. Wilson et al. (2008) demonstrate that planned trial designs could mask resistance risks and enable high-risk microbicides to pass clinical testing, which could then result in high rates of resistance during wide-scale usage among the general heterosexual population.

Recently, studies have begun to focus on other issues, such as cost-effectiveness and long-term implications. Verguet and Walsh (2010) investigated the cost-effectiveness of vaginal microbicides in preventing male-to-female HIV transmission in South Africa and the US, assuming, inter alia, microbicide efficacy of 30–80% (55% in the base). They concluded that microbicides are likely to be very cost-effective in a country like South Africa with a generalised epidemic, but not in concentrated epidemics in developed countries like the US. Walensky et al. (2012) simulate the impact of ARV-based microbicides on lifetime HIV risk and life expectancy for South African women, and further examine the cost-effectiveness of such a strategy relative to provision of ART for infected persons. Using efficacy estimates based on CAPRISA 004 trial data, the model estimates a reduction in lifetime HIV risk from 40% to 27% and an increase in undiscounted life expectancy from 41.6 to 44.5 years associated with microbicides at the baseline. Given costs of ARV gel as per 2010 price lists, the cost per year of life saved (YLS) was estimated at $2,700, which compares favourably to the WHO suggested cost thresholds.

Williams et al. (2011) also explore the effect of tenofovir-based microbicides, parameterised along CAPRISA 004 data lines and on HIV acquisition in the South African context, but limit the analysis to a 5-year horizon. This model suggests that, within the range of coverage assumed, microbicide use could avert 0.5 to 2 million new infections and 0.29 to 1 million deaths over 20 years. Given model assumptions, the intervention would also be cost-effective, with cost per infection averted being around $1,701–2,392 and the cost per disability adjusted life year (DALY) around US$74–104, which is favourable compared with condom social marketing and sterile needle programme costs.

Finally, reflecting the growing need to use a 'toolkit' approach to address prevention, Cox et al. (2011) estimate the impact of male circumcision and use of vaginal microbicides, singly and in combination, on HIV incidence over a 20 year horizon. The model is parameterised using data from the Kyamulibwa General Population Cohost in Uganda. Results predict that while each separate intervention would have to attain extremely high levels of adherence before a significant reduction in HIV incidence was observed, combining the interventions could more realistically have a significant effect. They found that 91% and 96% coverage for female microbicides and male circumcision, respectively, would be required in order to lead to a 30% relative reduction in incidence over 15 years if each was implemented separately. If the interventions are combined, only 49% and 67% coverage, respectively, would be required to have the same effect.

Rectal microbicides

Some 10 to 15 years ago, the microbicide field was almost solely focused on the research and development of vaginal microbicides, and community engagement and advocacy aligned with this priority. If scientists and advocates considered rectal microbicides at all, it was strictly in the context of the need to test vaginal products for rectal safety, with the understanding that when a vaginal microbicide made it to market, it would likely be used in the rectum as well, or would migrate there during vaginal intercourse.

The realities of the HIV epidemic, though, point to anal intercourse as a practice that both men and women engage in, and as a significant factor in the spread of HIV and other STIs. The work of a growing number of scientists, advocates, funders and policymakers has led to new investigations in the role of rectal microbicides and related products as essential elements of HIV prevention. Our formal search strategy picked up very few published papers

about rectal microbicides, and none made it through our selection criteria. However, since it is a growing field with important considerations for future prevention, it is worth briefly reflecting on the state of rectal microbicide evidence.

Three Phase I rectal microbicide studies have been completed to date, and the first ever Phase II expanded safety and acceptability study of a rectal microbicide is set to launch in mid-2013. The MTN-017 trial will include sites in Peru, South Africa, Thailand and the US, including Puerto Rico. The 186 gay men, other MSM and transgender women who will be recruited into the study will more than double the total number of human beings who have participated in rectal microbicide clinical trials to date.

MTN-017 will investigate the safety and acceptability of a reduced glycerin ('rectal friendly') version of the same tenofovir gel tested in CAPRISA, and will directly compare acceptability and adherence to daily oral Truvada. The study features an open-label design with all trial volunteers following three different regimens, each lasting eight weeks. One regimen will consist of the participant applying gel to the rectum daily. A second regimen will ask participants to apply the gel rectally before and after anal intercourse, similar to the BAT 24 regimen utilised in CAPRISA. In the third regimen, participants will take a daily dose of Truvada. The order in which participants will follow the study regimens will be assigned randomly, with a rest period between each regimen.

The procedures carried out as part of MTN-017 will determine how much of each drug is absorbed in blood, rectal fluid and tissue, and will also look for changes in cells or tissues. Study participants will be asked about any side effects, what they like and dislike about using the gel either daily or with sex, and whether they would consider using the gel in the future. Gel acceptability and adherence will be directly compared to PrEP. This study could lead to another first – the launch of a large-scale trial to test whether a rectal microbicide actually works to prevent HIV infection among HIV-negative individuals.

Conclusion

Though not many articles on microbicides met the criteria for review, this should not be interpreted to mean that there is little ongoing research in this area. Indeed, many trials are under way around the world, as can be seen in the database of ongoing trials and findings (AVAC, 2013). It is a dynamic and interesting area to watch.

However, as can be seen in the summary in Table 2-5, there are still significant gaps in the empirical evidence base for microbicides.

Published modelling studies on microbicides are sparse, with no coherent strain of evidence thus far appearing to emerge. Earlier articles provide weak support for the strategy (implying that virion transference patterns are such that the intervention may only have a limited impact on reducing transmissions and that trials must be carefully designed), and later articles rely heavily on parameterisations linked to the CAPRISA 004 trial and therefore concentrate only on a very limited type of epidemiological environment. Nonetheless, the narrow set of research conducted so far does suggest that while microbicides may be appropriate only in those very limited settings experiencing a generalised epidemic, they nevertheless could prove a cost-effective method.

However, microbicides do offer an interesting alternative to other ARV-based prevention strategies, particularly as current models show them to be more cost-effective than PrEP. Moreover, though the current array of vaginal and rectal microbicide candidates are ARV-based and therefore HIV-focused, scientists are beginning to address the need for a variety of microbicides. For example, some women want microbicides that are also contraceptive, and both men and women want microbicides that protect against other STIs, not just HIV. People who are HIV-positive want microbicides, too, but here a new set of challenges emerges as microbicides based on ARV drugs should not be used by HIV-positive people, as the product could interfere with their own treatment.

In addition, some argue there is a strong need to have microbicides that work in both the vagina and the rectum. Having one 'dual use' product would allow women to apply the same microbicide vaginally or rectally as appropriate, and it would reduce

Table 2-5
Summary of literature snapshots on ARV-based microbicides

Type of literature review questions	Summary of findings
Efficacy	Efficacy data are weak, although CAPRISA 004 data are promising
Effectiveness	Adherence is crucial Attitudes show there is willingness to accept microbicides as a strategy Real-world effectiveness may be masked by clinical trials
Cost-effectiveness	Favourable cost effectiveness, if efficacy data from CAPRISA 004 are used
Indirect outcomes	Little to no evidence found
Epidemiological implications	Uncertainties about efficacy raise questions about parameters used in modelling When combined with other prevention strategies could have a significant effect on reducing incidence rates
Framework conditions	Need to consider multiple needs of different potential users of microbicides, including the need for a 'multi-compartment' microbicide

the stigma associated with anal sex. People may be afraid or ashamed to ask for a rectal microbicide because that could label them in an unfavourable way, and potentially cause discrimination and even harm. Asking for a multi-compartment microbicide reduces, if not removes, this concern. There are clearly many different avenues for development with this strategy, which could be pursued in the future.

Snapshots from the literature on PEP

Clinical studies

We discuss here studies focusing on occupational and non-occupational PEP. As summarised in Chapter 1, occupational PEP is the use of the prevention strategy for healthcare workers or others exposed as a result of their occupation. PEP for occupational exposures is considered an ethical imperative for healthcare workers exposed while on the job. PEP for non-occupational exposure (nPEP) is the use of the strategy for individuals exposed outside the healthcare setting through unprotected sexual intercourse or syringe sharing.

There are very few clinical trials of PEP because placebo tests for the efficacy of PEP as an HIV prevention strategy would be unethical. However, researchers have studied the efficacy of different PEP treatment regimes using other appropriate research designs. Two clinical trials using a non-placebo design (testing one PEP treatment regime against another) met our inclusion criteria, but there is only weak evidence of efficacy of the favourability of one drug regime over another. Mayer et al. (2008) tested tenofovir regimens combined with either lamivudine or emtricitabine for nPEP, against historical controls who used zidovudine-containing regimens. The trial was based in the US. While there were more new infections in the control group than in the treatment group, the difference was not statistically significant. The trial did show that the tenofovir regimens were more tolerable and had better adherence than the zidovudine-containing regimens.

Diaz-Brito et al. (2012) compared the rate of discontinuation and tolerability of two different PEP regimes. The trial was conducted in 255 individuals attending emergency rooms of six hospitals in Spain. Individuals received zidovudine or lamivudine plus either lopinavir (or ritonavir) or atazanavir. The primary end point of the study was the rate of PEP discontinuation before day 28 of follow-up. Secondary end points measured were incidence of side effects and rate of seroconversions. The rate of discontinuation of PEP before day 28 was similar with both regimens. Almost 50% of the patients in both arms suffered side effects, highlighting the need for strategies to improve tolerance of PEP in the future.

Modelling studies

Modelling studies for PEP generally focus on what regimen of PEP to use, or whether it is more cost-effective to avoid exposure in the first place. PEP for non-occupational exposure (nPEP) through unprotected sexual intercourse or syringe sharing is a topic of more debate, however. Studies of nPEP have tended to investigate relative cost-effectiveness. The results suggest that nPEP is most cost-effective for use with high-risk groups in developed countries, particularly for individuals exposed via receptive anal intercourse. No studies meeting our review criteria investigate the cost-effectiveness of nPEP in developing countries. Modelling studies pertaining to occupational PEP and nPEP are discussed in turn.

The earliest modelling study on the cost-effectiveness of occupational PEP, Scheid, Hamm and Stevens (2000), looked at the cost of three alternatives recommended under the US Public Health Service (USPHS) guidelines: triple drug therapy, zidovudine monotherapy or no prophylaxis. The USPHS guidelines were found to be marginally cost-effective (~$82,000/QALY), but more effective (and more expensive) triple drug combinations were found to be prohibitively non-cost-effective at almost $1 million/QALY. Another cost study (O'Malley et al., 2007) found that in general the costs of managing occupational exposure to blood and body fluids were high, and that health facilities would benefit by improving their efforts to prevent or reduce exposure rather than investing in different PEP regimes.

Goldberg et al. (2000) did not focus on costs, but instead used risk equations to model the risk of HIV transmission from patients to surgeons given the availability of PEP. The results affirm that while annual risk of acquiring HIV occupationally is extremely low, it can be reduced to completely negligible levels with the provision of PEP after exposure.

Early concerns that nPEP for sexual exposures would be prohibitively expensive spurred several studies on the costs and cost-effectiveness of nPEP programmes. Two short studies published as correspondence in the journal *AIDS* presented cost data for a nPEP programme in Vancouver, Canada. Both suggested that the programme was expensive, even for accidental exposure, and that providing nPEP for sexual and other non-occupational types of exposure should be approached cautiously (Low-Beer et al., 2000; Braitstein et al., 2001).

However, in 2004, Pinkerton and colleagues published two different studies examining the cost-effectiveness of nPEP in the US after sexual or injection drug exposure, suggesting that nPEP can in fact be cost-effective among key high-risk groups. One study (Pinkerton et al., 2004b) looked at the cost-effectiveness of the San Francisco nPEP programme and suggested that this programme prevented an estimated 1.26 HIV infections and loss of 11.74 QALYs at an average cost less than $15,000/QALY, much lower than accepted thresholds for cost-effective interventions in the US (which range from $50,000/QALY to $200,000/QALY). The second study (Pinkerton et al., 2004a) modelled the lifetime costs and benefits of one-time nPEP use for 96 metropolitan areas in the US, using data from the San Francisco PEP study (including completion rate, proportion of source partners known to be HIV-infected, and PEP programme costs). Results suggest that one course of nPEP would prevent most infections among both men and women reporting exposure via receptive anal intercourse. Overall, the intervention was found to be cost-effective in complementing existing HIV prevention efforts in most major metropolitan areas. The average cost-utility ratio was $12,567/QALY.

Guinot et al. (2009) examined the cost-effectiveness of nPEP provided in Australia between 1998 and 2004. At approximately A$176,000/QALY, nPEP

was not found to be cost-effective relative to Australia's commonly accepted threshold of A$50,000/QALY, though a targeted nPEP programme for patients exposed via unprotected receptive anal intercourse was cost-effective at approximately A$16,000, echoing earlier findings by Pinkerton et al. from a study in the US (Pinkerton et al., 2004b).

Herida et al. (2006) calculate the lifetime costs and benefits of a PEP programme which was implemented from 1999 to 2003 in the general French population for anyone with a possible HIV exposure incident – occupational or non-occupational. Results suggest that PEP prevented an estimated 7.7 new infections and saved 64.5 QALYs at a net cost of €5.7 million, resulting in a cost–utility ratio of approximately €89,000/QALY saved, which was considered only moderately cost-effective. The researchers conclude that PEP could improve its cost-effectiveness if high-risk exposures were better targeted.

Overall, results suggest that while universal PEP treatment (occupational or non-occupational) would not be cost-effective, more targeted approaches might be. However, the cost ranges presented in the studies above are estimates relative to a specific slate of assumptions. They should, therefore, all be viewed in light of the fact that practical implementation may produce quite different results.

Other intervention studies

Most studies of PEP are cross-sectional or longitudinal as these provide the easiest way to measure whether PEP is successful in preventing HIV infection after exposure. While many studies met our inclusion criteria, we will only highlight those here which help to illustrate the main themes from the literature as a whole.

The main focus of many PEP studies is on whether the course of ARV drugs provided post-exposure prevent seroconversion and whether the regimen of drugs is safe and tolerable for the individual. In addition to these outcome measures, researchers also focus on whether PEP has any effect on continued high-risk behaviours.[19]

Some early studies found overall that PEP was feasible as a prevention regimen, based on high completion rates and low side effects or toxicity (Kahn et al., 2001; Shoptaw et al., 2008). However, when we look further, we find there is actually mixed evidence on whether PEP successfully prevents infection. Roland et al. (2005) found that while PEP is not completely effective in preventing HIV infection, it was unclear if infections were due to exposures other than the one for which PEP was received. Nevertheless, the authors conclude that primary prevention remains essential. Other studies have reported effectiveness in terms of seroconversion. In most cases where there was seroconversion, the authors were unable to attribute this directly to failure of PEP as it could be the result of other factors such as continued high-risk behaviour (Sonder et al., 2010). In a recent study auditing 72 patients between 2003 and 2009 who were provided with PEP after sexual exposure, all patients who were followed up remained negative (McCarty et al., 2011). This is not to say that seroconversions don't occur, even when no differences in high-risk behaviour are reported (Schechter et al., 2004). Adverse side effects were reported across several studies (Quirino et al., 2000; Wang et al., 2000; Braitstein et al., 2001; Schechter et al., 2004).

Adherence has been a consistent theme across all the literature, and it is no different here. Variables affecting adherence include the type of drug regime and the nature of side effects and existing knowledge of the nature and type of exposure. In Sonder et al. (2010), which compares two different drug regimens, 91% of patients completed the 28-day regimen with no difference in adherence found between the two regimens. However, Garcia-Lerma et al. (2010) found that those on two drug regimens were more likely to complete treatment than those on three drug regimens. Tosini et al. (2010) looked at adherence and infections averted and found that 22 out of 188 cases stopped before the end of treatment, but no seroconversions occurred, providing support for the wider debate that the full 28–30 days treatment regimen may not be necessary.

Adherence may also vary by type of exposure. Sonder et al. (2007) found that out of a group of 245 persons requesting PEP, those who were victims of sexual assault were less likely to adhere to the

[19] See footnote 15 for a comment on the evolving meaning of this phrase.

regimen, though overall 85% of the study participants completed the course of treatment. Chacko et al. (2012) provide a systematic literature review and meta-analysis on the adherence of victims of sexual assault to PEP. The authors found that adherence to PEP was poor in all settings, and that further support to increase adherence is required. Effectiveness as indicated by adherence with the occupational health workers was also higher when the individuals knew the HIV status of the source and the exposure was high risk. In these cases, adherence was 78% (Garb, 2002). Bagley showed that HIV patients are more likely to complete their course of treatment if they have been given the information they want, underlining the importance of nurse prescribers having a sound knowledge of the drugs and their side effects, to relieve patients' anxiety (Bagley, 2012).

There is sometimes concern expressed that PEP might lead to increased sexual risk behaviours. Studies looking at behavioural risk factors during PEP as predictors of, and willingness to take, PEP yield interesting conclusions. Golub et al. (2008) found that engagement in sexual risk behaviours during nPEP was 21% and was linked to psychosocial factors such as high-risk sexual behaviour in the six months prior to nPEP, loss of loved ones to HIV, depression, prevention fatigue and engagement in the HIV care system. Kahn et al. (2001) also found that safe-sex behaviour lapsed during PEP. However, other studies seem to suggest that sexual risk behaviour did not increase as a result of PEP (Martin et al., 2004; Schechter et al., 2004; Shoptaw et al., 2008; Poynten et al., 2009) and a survey-based study before and after a PEP awareness campaign also suggested that fears that PEP would increase sexual risk behaviours may be unwarranted (Waldo, Stall and Coates, 2000).

One of the major barriers to increased use of PEP relates to the need to educate people and raise awareness of the strategy. Indeed, several studies discuss this. A survey of 230 staff at University of Abuja Teaching Hospital, Nigeria, showed that the majority (97.0%) have heard about PEP, but less than 31% could correctly identify the drugs used and duration of PEP and of the 13 respondents that were exposed to HIV-positive patients, only three (23.1%) received PEP while the remaining ten (76.9%) did not receive PEP despite their exposure to HIV-positive sources (Owolabi et al., 2012). Mehta et al. (2011) surveyed 554 gay men and other MSM on their awareness of nPEP or PrEP and found that only 36% were aware of the treatments. Overall, both examples show that knowledge among at-risk populations of the available treatment was low and that more could be done to disseminate information and raise awareness.

Conclusion

There are fewer clinical or modelling studies of PEP discussing its implications for prevention than there are longitudinal and cross-cutting studies. The latter provide strong evidence that PEP is an important component, but perhaps limited, of the ARV-based prevention tool kit. A summary of the literature is shown in Table 2-6.

Most studies showed that PEP was effective in preventing seroconversion and did not have an adverse effect on risk behaviours. Many of the studies were examining adherence under different conditions, including the nature of exposure (non-occupational, sexual assault, occupational) and the level of knowledge about that exposure. Overall, the evidence for effectiveness of PEP seems to be strong, although it is dependent on adherence and timing of treatment initiation. More studies should be performed under controlled conditions (though this poses its own challenges). The question of cost-effectiveness, however, continues to be an important one, as studies suggest the strategy is only likely to provide 'value for money' where the approach is appropriately targeted. This aspect of public health policy is likely to become even more important as fiscal austerity continues in most countries, and internationally, over the near to medium term.

Discussion

Looking across all the ARV-based prevention strategies and the empirical literature we reviewed, it is clear that strong evidence of *efficacy* exists for most of the strategies, particularly in the case of TLC+ and PrEP. However, the evidence is weaker and more mixed the further we allow for factors that affect *effectiveness* in real-world implementation settings to play a role. In particular, there is a strong message

Table 2-6
Summary of literature snapshots for PEP

Type of literature review questions	Summary of findings
Efficacy	Limited
Effectiveness	Most studies show prevention of sero-conversion, although this is highly dependent upon adherence, timing of PEP initiation, and risk reduction behaviours during course of treatment
Cost-effectiveness	Cost-effectiveness shown for nPEP
Indirect outcomes	Little to no evidence found in literature
Epidemiological implications	Good evidence showing that nPEP can avert new infections
Framework conditions	Little to no evidence; there should be more studies under controlled conditions to determine optimal treatment regimens

that adherence is critical for any ARV-based prevention strategy. While not necessarily surprising, this element is intertwined with efficacy, alongside other parameters that determine effectiveness, such as behaviour, drug resistance, side effects and the wider socio-political context. Though it is acknowledged in the literature presented here, we strongly believe that more research is needed about how these aspects interact, and importantly about what the long-term implications are independently and in combination over time. Some of the modelling studies discussed above begin to do this, and we comment below on how they can be further developed, and certainly a few clinical trial papers point to this as a pressing issue (notably Baeten et al., 2012). Thus, the strongly inter-dependent nature of the different variables that determine both efficacy and effectiveness needs to be a crucial aspect of any future research agenda.

The interactions between different kinds of strategies should be considered as well as these factors. The few studies we reviewed that looked at the interactions between different ARV-based and other biomedical prevention strategies had promising findings about the potential of a wider toolkit, not just the pursuit of one single strategy (see for example, Cox et al., 2011). However, this is crucially dependent on the wider health system and socio-political context in which any strategy would be implemented. It seems to us that the influence of these factors is not necessarily overlooked, but not systematically addressed in the literature to date. In addition, there is little to no data or evidence about the possible indirect outcomes of ARV-based prevention strategies. We believe these issues are crucial to support long-term decisionmaking about new prevention strategies, and that any evidence base might be considered incomplete if they are not taken into account.

One way this research agenda might be developed is through more nuanced modelling studies using techniques like agent-based modelling. This technique is a computational modelling strategy that assumes heterogeneous 'agents', such as individuals, patients, care providers or institutions, interact in communities in dynamic ways over time (Bobashev and Borshchev, 2009). Each agent is assigned relatively simple rules that govern its action as time progresses. Thus, agent-based modelling has

advantages over standard, equation-based strategies that are often data-intensive, and when modelling dynamic interactions between individuals can quickly become complex and intractable. Regardless of the method used, though, the challenge is in acknowledging both the strengths and the limitations of any modelling technique. As we saw in the discussions for each strategy, the results of the modelling studies often varied depending on the underlying assumptions, suggesting that any findings are likely to be highly context specific. As a result, it is essential that the methodology for such studies is appropriately couched in relevant data for the communities and contexts being analysed.

Finally, our review also highlighted a gap in the literature in understanding the framework conditions required for new innovations in treatment regimes to emerge, be evaluated, and be successfully implemented. This review seeks to take one step towards this, but it will require a concerted effort across the community, one which not only draws on the empirical literature, but synthesises across different types of knowledge and perspectives to understand how the different scientific, social, cultural and institutional elements interact to lead to effective and efficacious ARV-based prevention.

Conclusion

This chapter has attempted to synthesise lessons across a wide body of literature for the future ARV-based prevention research agenda. It also seeks to identify what, if any, overarching perspectives emerge from the empirical literature so that they can be considered alongside the other Mapping Pathways perspectives on the evidence base which are covered in the chapters of this book.

One of the perspectives that seems to emerge strongly is the central role clinical trial data play in the evidence base. This is not unexpected, but what is perhaps problematic in the long run is that if only clinical trial data drive the empirical evidence base for public health policy, then we risk missing important points that will drive effectiveness if these strategies are implemented. Though clinical trials allow us to observe the impact of proposed treatments in specific populations and provide the core efficacy data that allow things like epidemiological and cost-effectiveness models to be populated, our review and the previous discussion show that there is much more to consider than efficacy data. Research into effectiveness outside a clinical trial setting is an important part of implementation. Factors affecting effectiveness such as adherence and drug resistance, indirect outcomes on health systems, and context-dependent understanding of cultural influences on implementation all need to be addressed in a holistic manner. The evidence base must look beyond clinical trials as the context for delivery will vary. The areas highlighted in this review that are still the most uncertain are those which are likely to play the biggest role in determining real-world effectiveness.


3
SNAPSHOTS FROM
THE “GRASS ROOTS”
EVIDENCE BASE

The grassroots perspective: by grassroots we mean the views of those working with and directly alongside those living with HIV, delivering HIV services, or simply living in communities where people are living with HIV. They are on the front-line of prevention strategies and have a unique perspective on the contexts and cultures in which ARV-based prevention will be delivered.

Why the 'grassroots'?

While we know that ARV treatment has developed dramatically and greatly improved the lives and life expectancies of many people living with HIV, the implementation of ARV-based prevention strategies is new. In order to implement these strategies successfully we need to understand the issues 'on the ground'. These grassroots issues are those relating to the context that influences implementation including economic, political and social activities surrounding the implementation of ARV-based prevention strategies. This could potentially impact powerfully on implementation, so community voices are therefore significant. These voices represent people who will be on the front line of implementing ARV-based HIV prevention methods. Therefore, when we speak of grassroots perspectives, we mean the views of those working with and directly alongside those living with HIV, those delivering HIV services, those in communities where people are living with HIV, or people living with HIV themselves.

This part of the Mapping Pathways journey sought to highlight these community voices, bringing to the fore the critical perspectives of those at the front line of implementation. To do this, we explored what people at the grassroots in India, South Africa and the US thought about the implementation of ARV-based prevention methods in their respective countries. It was critical to survey those responsible for implementing prevention methods, as well as those affected by the implementation of prevention strategies. These stakeholders come with a wealth of knowledge and experience concerning the implementation of ARV treatment and relevant individual behaviours. This knowledge and experience is of fundamental practical importance in understanding how to map pathways to successful implementation of ARV prevention strategies.

Methodology

We asked participants to complete an online survey with 'closed' and 'open-ended' questions. By reaching out to individuals and organisation representatives who interact with their communities, we built an understanding of what these stakeholders thought about the practicalities and challenges of implementing ARV-based prevention strategies.

We ran the online survey using the Survey Monkey service and designed it to take no more than 20 minutes to complete. It was open for six months and was available to anyone who was interested in ARV-based prevention methods and could access the online survey. Members of the Mapping Pathways team and their respective organisations who were not involved in the survey design piloted the survey.

In order to increase response rates, Mapping Pathways project partners approached potential participants who performed roles in HIV prevention and treatment in their respective countries and contacted them via email or in person and gave them the web address where they could complete the survey. They were also invited to pass the survey on to anyone they thought might be interested.

Overview of survey questions

The survey consisted of a short demographics questionnaire, and closed (multiple-choice) and open-ended questions. The demographics questions allowed us to collect information on the individual's country, gender, sexuality, age, community context (rural, urban or suburban) and connection to HIV/AIDS work. These kinds of data not only allowed us to ensure that only individuals in our country of interest were able to complete the questionnaire (a routing feature in the survey did not allow them to proceed past the demographic information if they were not from India, South Africa or the US), but also allowed us to keep track of the types of individuals responding to our questionnaire so we could be confident that it included a diverse set of views and perspectives.

The closed-ended questions explored opinions about all four ARV-based prevention strategies in relation to what kind of information was, or should be, available about them, how important the individual felt they were, or should be, to the community, how accessible the prevention strategy was in their community (in the case of PEP), how much time they had spent thinking about the implementation challenges and other issues related to the kinds of dissemination of Mapping Pathways data they might like to see. These answers helped us to understand the scale of the pathways and barriers to promoting successful implementation.

The open-ended questions gave more scope for respondents to express their understanding of issues related to implementing ARV-based prevention strategies. The two main questions included discussing the types of information that would be useful to them or those they know and/or work with, as well as sharing any additional concerns or worries they had about ARV-based prevention strategies.

Survey analysis

In total, 1,069 people started the survey and completed its demographic section. Not everyone answered every single question on the survey, however, so the data could not be standardised across all questions. In India, 37 (36.6%) people completed the whole survey; in South Africa 255 (73.9%) people completed; and in the US 344 (67.5%) people completed the entire survey. Therefore the numbers of respondents per question varies and, consequently, comparability across questions was not always possible.

We conducted a simple quantitative analysis for the closed-ended multiple-choice questions. Because of the limitations of the data (incomplete surveys and small sample size in some countries) we did not feel a more detailed or complex analysis would have been robust and could have led to overstating findings from the survey. However, the point of the survey was to take a snapshot at a particular moment in time, which would give us a general sense of the level of awareness, and the concerns and views people might have, about ARV-based prevention strategies. The findings presented below, though given in quantitative terms, should thus be interpreted as a heuristic, which allowed us to reach our more qualitatively oriented analytical goals.

To that end, we examined the data for the qualitative, open-ended questions about participant concerns with the qualitative analysis software NVivo. We used a content analysis approach, going through all responses question by question to identify and code the issues raised, and then drew them together in a cross-cutting analysis in order to identify key themes and examine relationships between the different concerns raised by participants.

Findings from the grassroots survey – closed questions

Engagement and response rates

The majority of participants came from an urban setting, stating that they were advocates, people working for AIDS service organisations, doctors, people living with HIV, and non-governmental organisations (NGOs) with AIDS services. Two-thirds of respondents (69.5%) were mostly from urban settings, while the remainder were from suburban and rural settings. Demographics are shown in Figure 3-1.

The sample split by country was India 101 (10.6%), South Africa 345 (36.1%) and the US 510 (53.3%). Most respondents from India were from AIDS service organisations, NGOs or the government. Most were male (65.3%), followed by female (32.6%), male-to-female (1.1%) and transgender (1.1%) respondents. Respondents from South Africa tended to be doctors, people working in AIDS service organisations, NGOs or government. Most respondents were female (60.1%), followed by male (39.6%) and male-to-female transgender (0.3%) respondents. US respondents were mostly advocates or activists, people living with HIV, or people working in AIDS service organisations. Respondents defined themselves as male (61.4%), female (36.7%), 0.6% male-to-female transgender (0.6%), female to male transgender (0.6%) and transgender other (0.6%) (see Table 3-1).

In the full survey, data from 113 respondents were excluded because they were not from the countries where the research was taking place, leaving 956 respondents as part of the full analysis pre-

Figure 3-1
Participant demographics for the grassroots survey

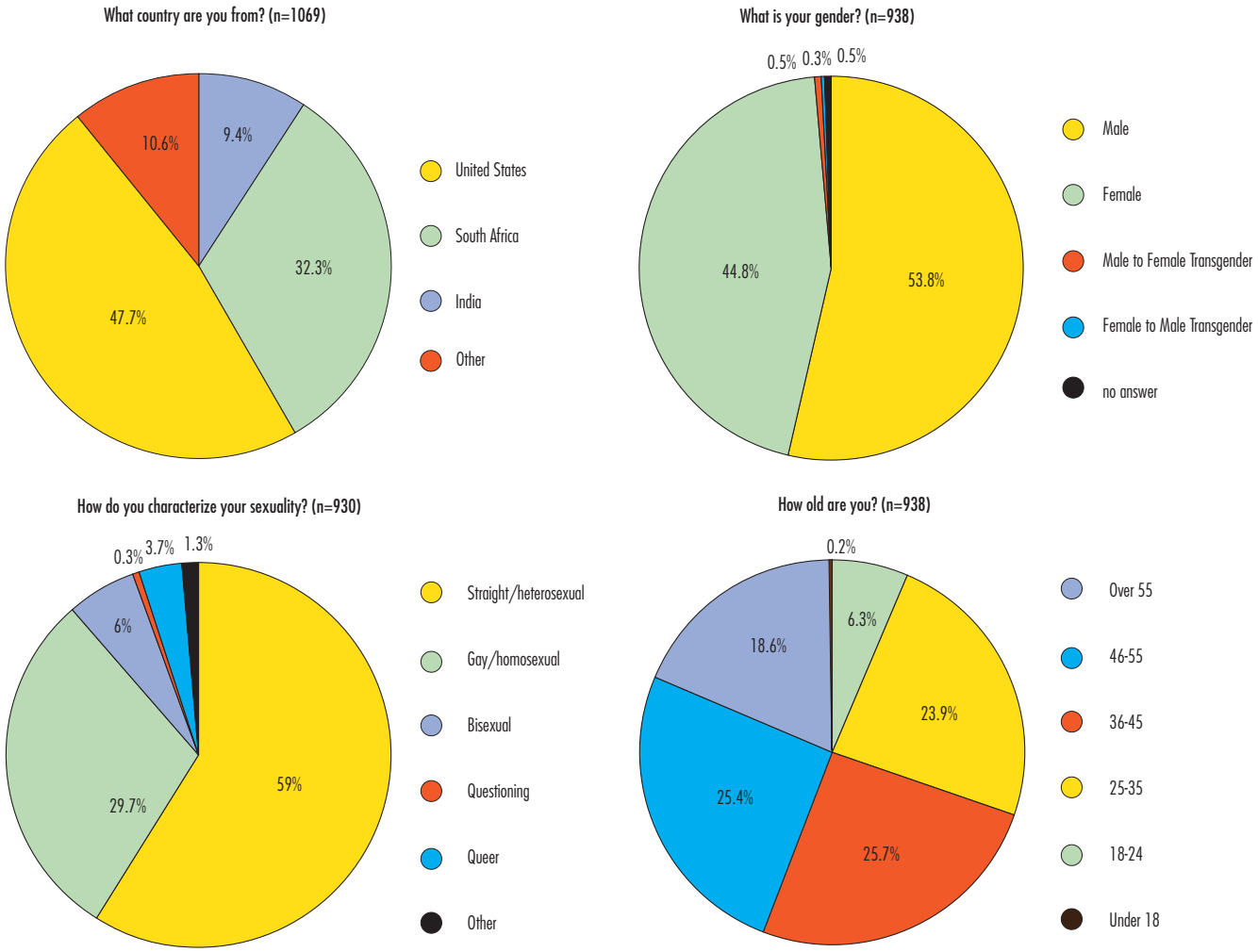
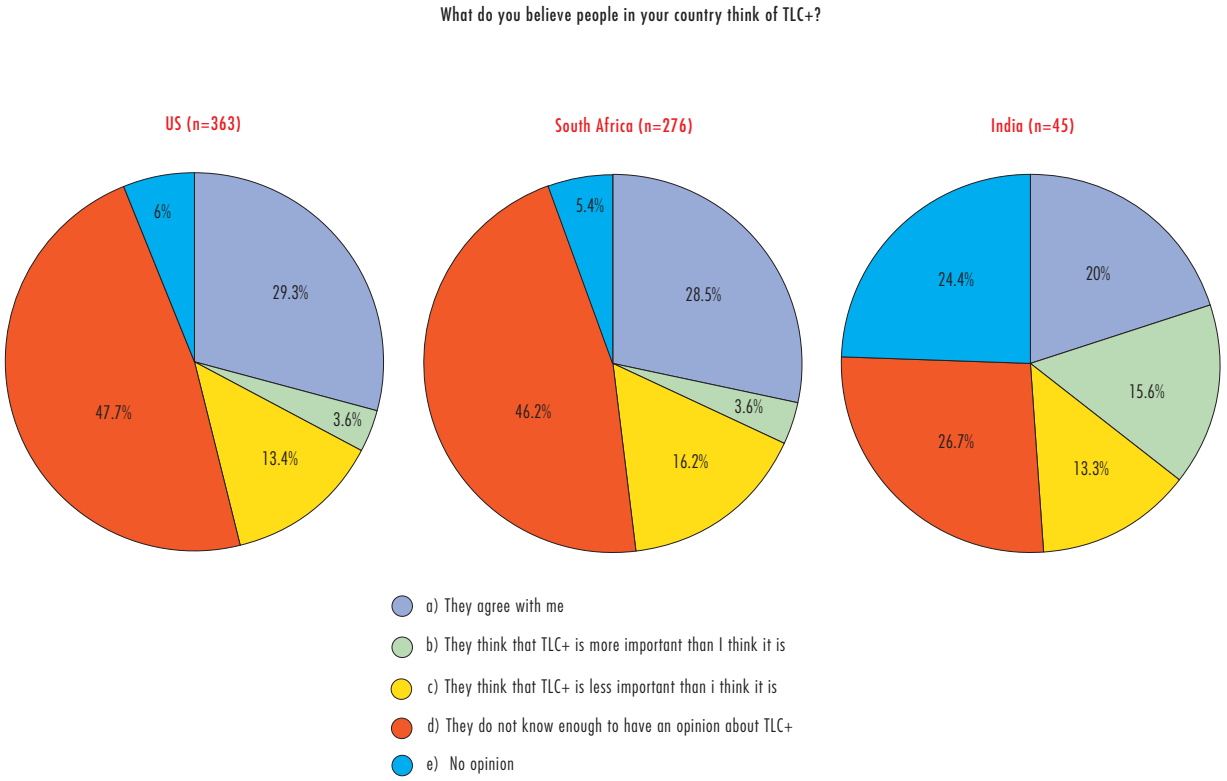


Table 3-1
Summary of survey respondents by country

	Predominant affiliation of sample individuals	Percentage of sample	Percentage male	Percentage female	Percentage other or transgender
India	AIDS service organisations, NGOs or the government	10.6%	65.3%	32.6%	2.1%
South Africa	Doctors, people working in AIDS service organisations, NGOs or the government	36.1%	39.6%	60.1%	0.3%
US	Advocates or activists, people living with HIV, or people working in AIDS service organisations	53.3%	61.4%	36.7%	1.9%

Figure 3-2
Stakeholders' views on what people believe others in their country think about TLC+, by country



sented below from the countries where the study was conducted (India, South Africa and the US). The demographic patterns did not vary with this group excluded. Overall, the survey is over-represented with US respondents and there was a significantly lower response rate in India.

Views from the grassroots about TLC+

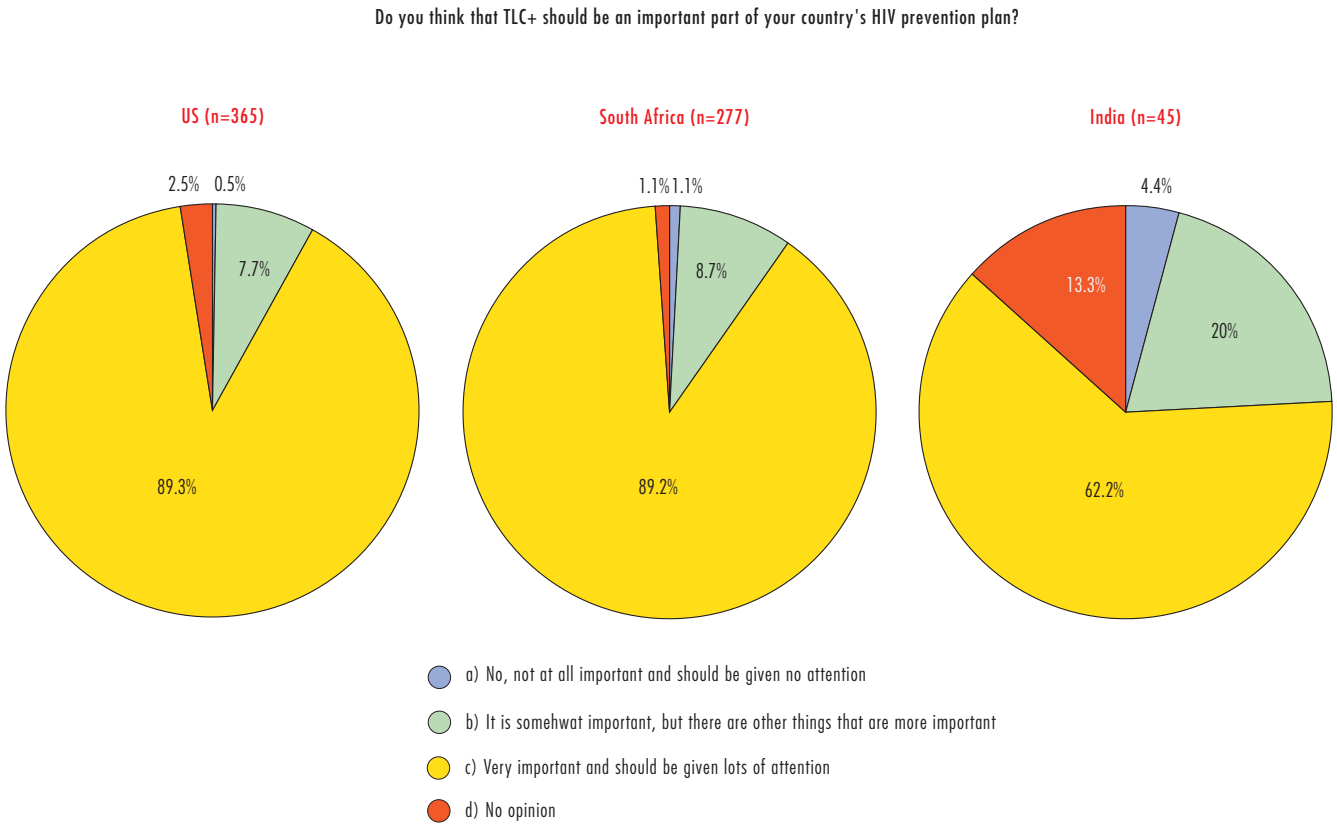
The first element to discuss relates to the awareness people believed others in their country had about the prevention strategy. Over a quarter of Indian respondents (26.7%) believed that others in their country did not have an opinion about TLC+, and a further quarter (24.4%) indicated they thought others did not know enough to have an opinion about TLC+. Conversely, 46.2% of South African and 47.7% of US respondents thought others in their community didn't know enough to have an opinion about TLC+ (see Figure 3-2). This suggests that in all countries there is a need for a concerted awareness raising campaign.[20]

Respondents had mixed views about whether people felt TLC+ should be a part of their community's prevention plan, as shown in Figure 3-3.

In India, approximately two-thirds of respondents (62.2%) reported that TLC+ was important and needed to be given a lot of attention. This figure is low when compared with the proportion of respondents in South Africa (89.2%) and the US (89.3%) who expressed a belief that TLC+ was very important and should be a part of the country's HIV

[20] All the analyses by country are broken down only at a country level and not, for example, by type of respondent (NGO, healthcare worker, etc) as respondents were able to select multiple affiliations, so there is not a one-to-one relationship between responses and respondent affiliation. Therefore any presentation and analysis of the data would risk distorting the figures.

Figure 3-3
Stakeholders' views on the importance of TLC+, by country



prevention plan. Comparatively, then, there was a difference between views in the two latter countries and India. Similarly, in comparison with the US and South Africa, more people in India said that TLC+ was an important prevention strategy but that there are more important issues to consider (22%), whereas only 7.7% of respondents in the US thought this. A small proportion of the Indian respondents (4.4%) said that TLC+ was not at all important and should not be given attention.

Views from the grassroots about PrEP

When asked about what others in their country thought about ARV-based prevention strategies, most participants (India 44.4%, South Africa 57.2%, the US 57.3%) believed that others in their country did not know enough to have an opinion (Figure 3-4). Some participants (India 26.7%, South Africa 11.2%, the US 10.7%) had no opinion about what others thought. In all three countries, the smallest number of respondents said that they thought others believed PrEP to be more important than the respondent did. It is worth noting that roughly similar proportions of relative importance of PrEP are seen across all three countries, indicating at the very least that awareness needs to be raised to address those respondents who think others don't know enough to have an opinion about PrEP.

When asked how important they believed PrEP should be to their country's HIV prevention plans, participants in each country were divided almost equally between believing that PrEP was very important and should be given significant attention (India 44.4%, South Africa 47.1%, the US 44.4%) versus answering that PrEP is important but that there were other strategies that are more important (India, 35.6%, South Africa 43.8%, the US 47.1%) (see Figure 3-5). For all three countries a relatively small proportion of respondents thought that PrEP was not important and should be given no attention (India

Figure 3-4
Stakeholders' views on what people believe others in their country think about PrEP, by country

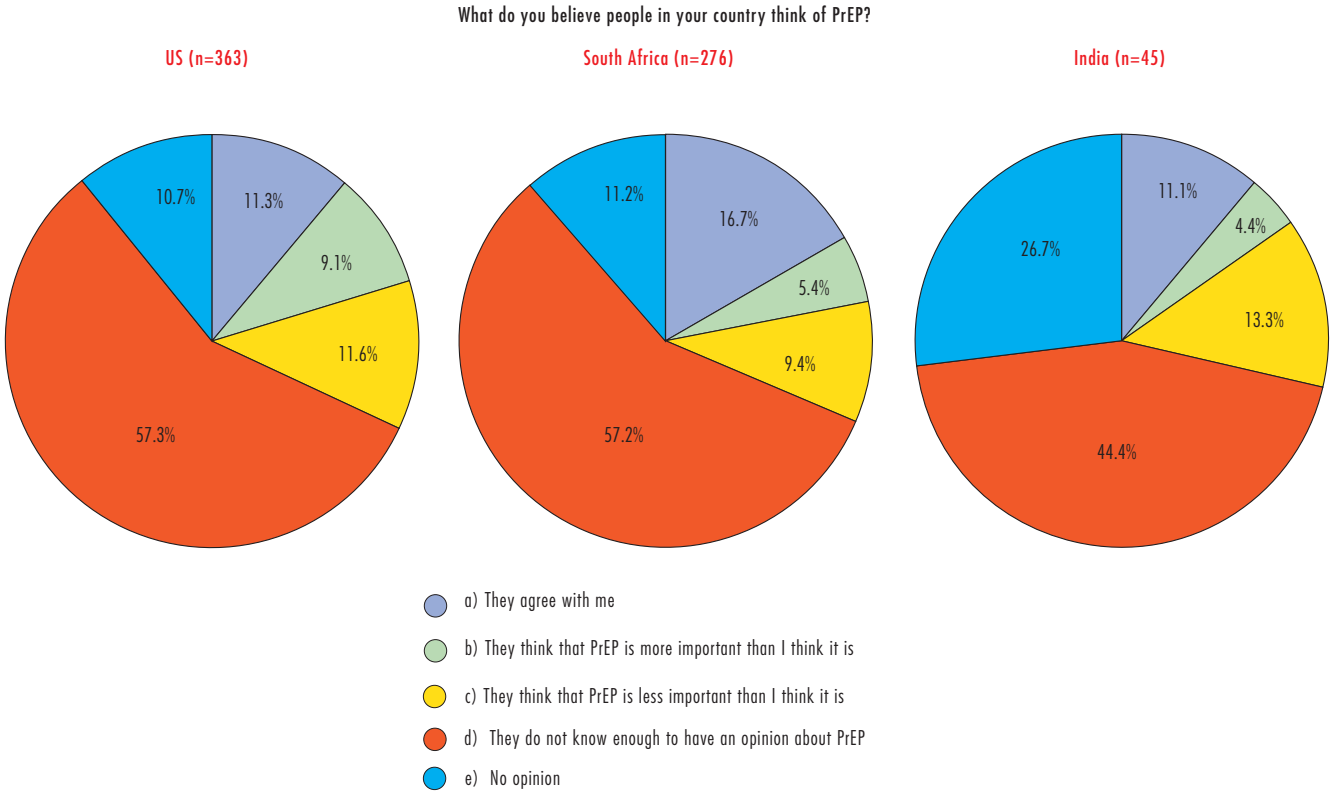


Figure 3-5
Stakeholders' views on importance of PrEP, by country

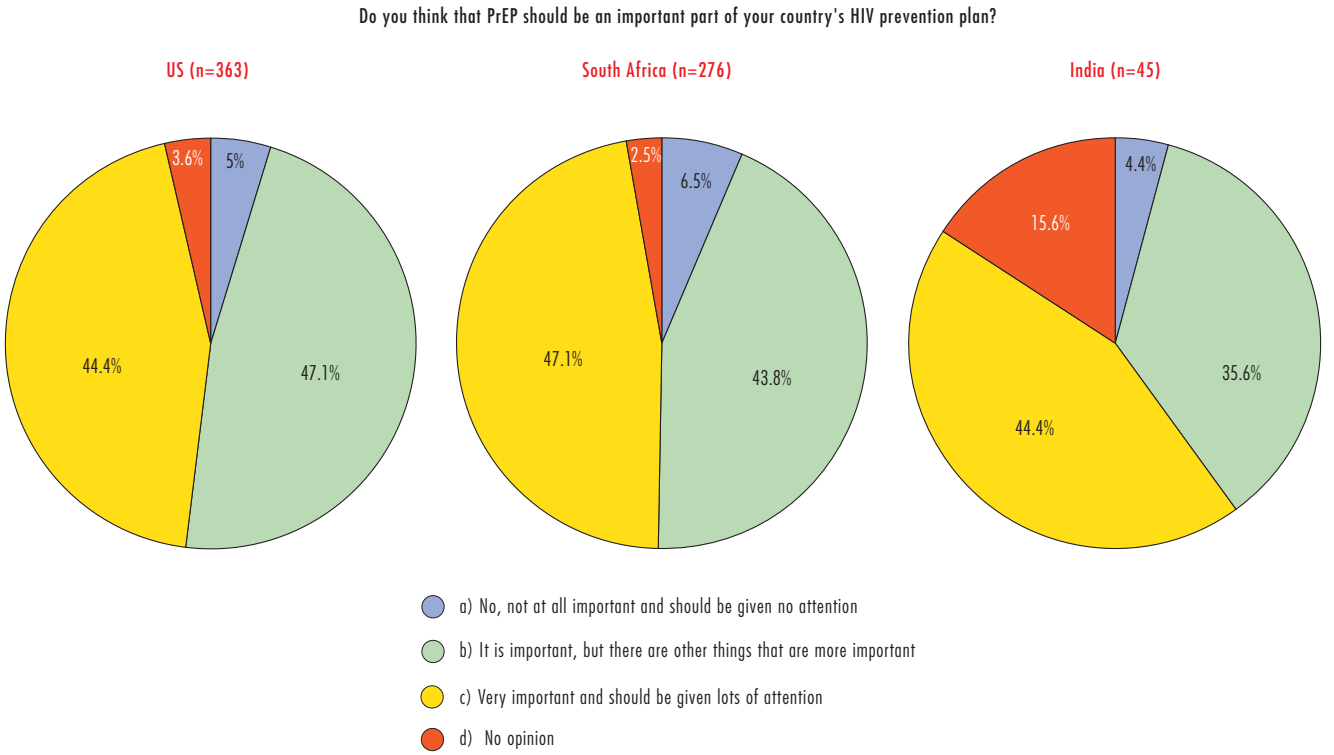
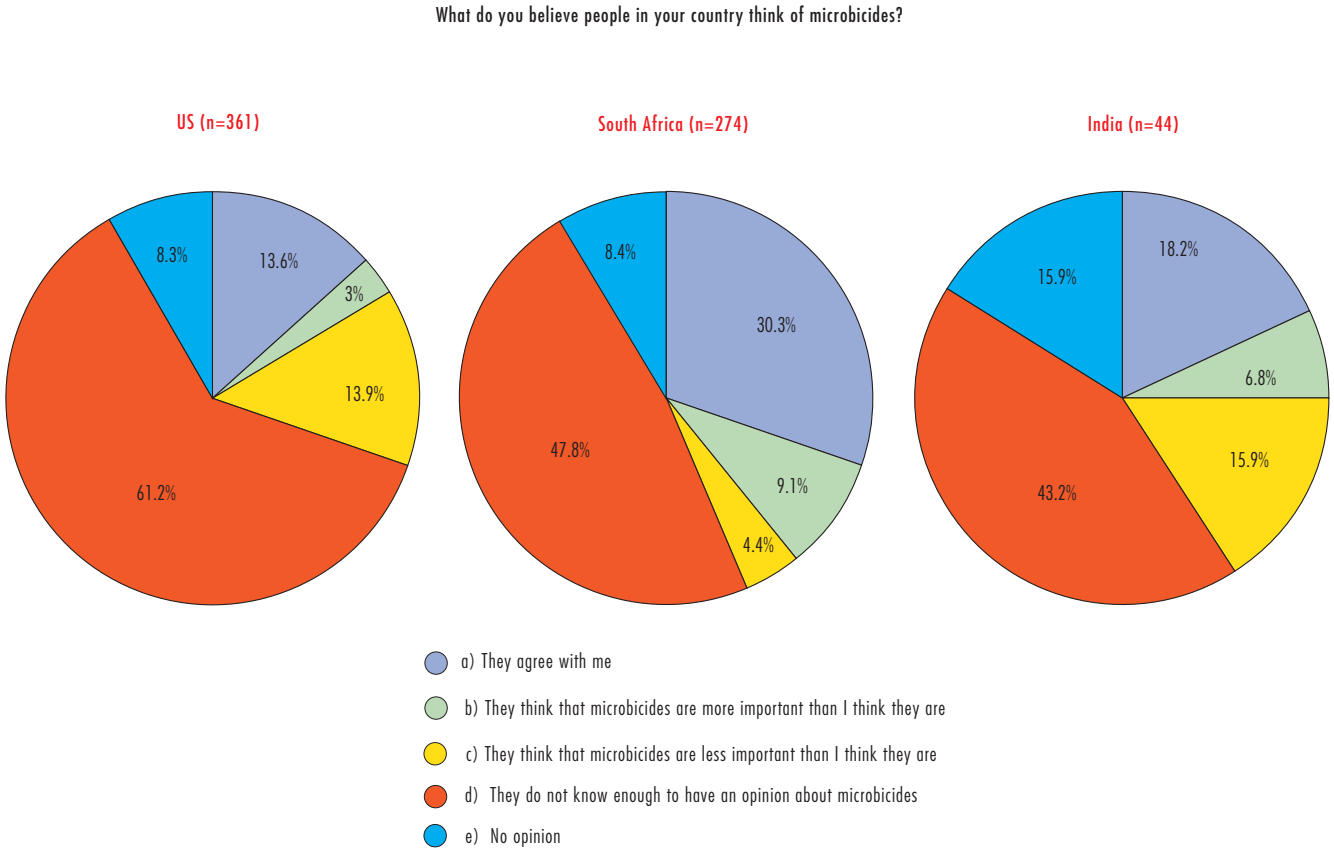


Figure 3-6
Stakeholders' views on what people believe others in their country think about microbicides, by country



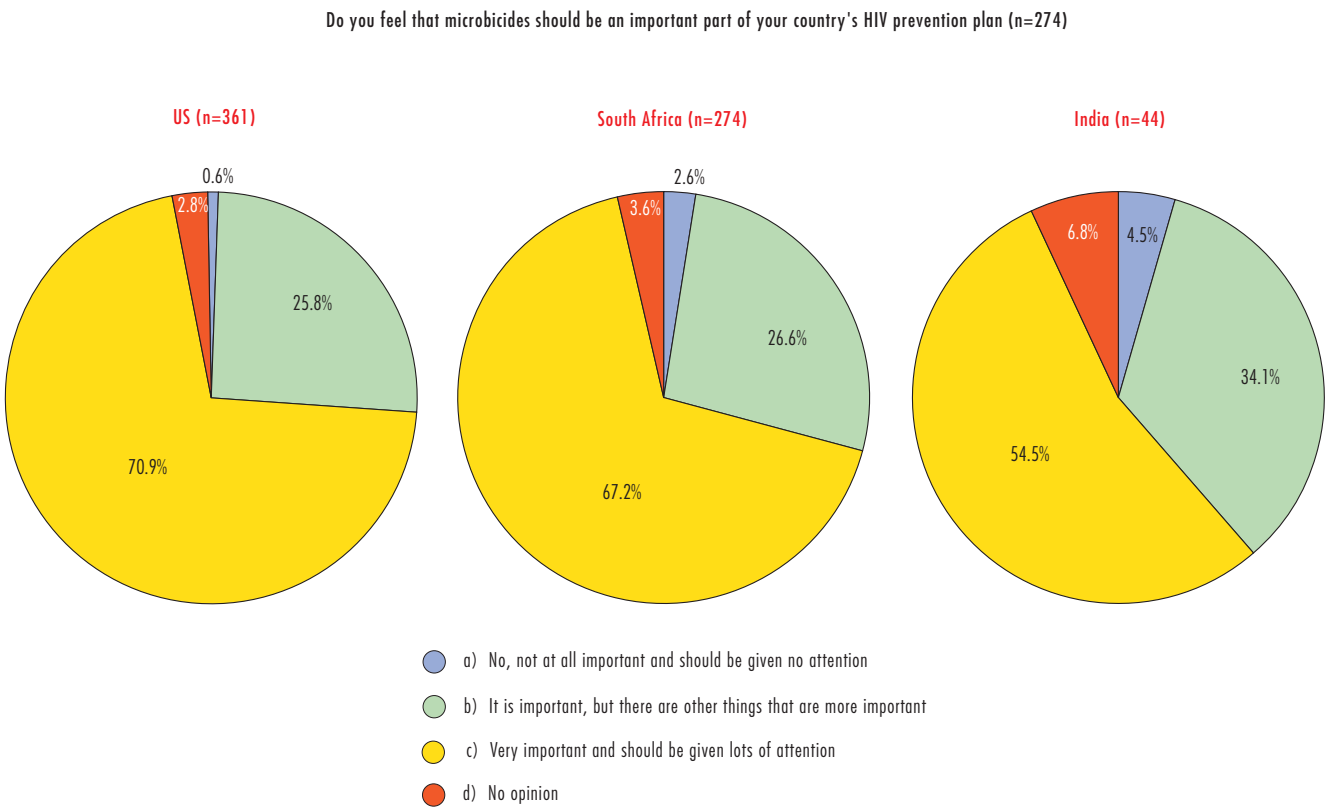
4.4%, South Africa 6.5%, the US 5%). It is interesting to note that whereas in South Africa and the US few people had no opinion about the importance of PrEP (South Africa 2.5%, the US 3.6%), in India 15.6% of the respondents had no opinion on the importance of PrEP. To a certain extent this correlates with the data presented above about the views they think others in their country have of PrEP – perhaps more so in India than other countries there is a lack of awareness and information about PrEP and what its benefits and implications might be for HIV prevention strategies.

Views from the grassroots about microbicides

When asked about what others in their country thought, many respondents in all three countries (India 43.2%, South Africa 47.8%, the US 61.2%) answered that people in their country did not know enough about microbicides to have an opinion (Figure 3-6). This view was most pronounced for US respondents, perhaps suggesting that there is the greatest need for awareness raising there. South African respondents were the most optimistic that others in their country agreed with them (30.3%) about microbicides, while fewer respondents from India (18.2%) and the US (13.6%) reported that they thought others would agree with them. It is worth noting that the respondents views for this question begin to vary across countries in a way not observed for the other countries. Though we still see the majority indicating that there is not enough awareness to have an opinion, there is more variation here across the three countries in response to the other options, suggesting that as an HIV prevention strategy, there is more variability than for other strategies in relative awareness.

When asked whether they thought microbicides should be an important part of a country's HIV pre-

Figure 3-7
Stakeholders' views on the relative importance of microbicides, by country



vention plan, the majority of participants across all three countries (India 54.5%, South Africa 67.2%, the US 70.9%) believed that microbicides were very important and needed to be given a lot of attention (see Figure 3-7). It is worth noting the higher figure for South African and US respondents, which perhaps suggests they have a strong belief in this type of prevention strategy as having great potential, whereas Indian respondents were slightly more sceptical. This finding sits in contrast to that described in the next chapter, which summarises the grasstops perspectives. Here, greater scepticism was expressed about microbicides by South African than by Indian and US interviewees. Most of the remainder of participants (India 34.1%, South Africa 26.6%, the US 25.8%) thought that microbicides were important, but that other issues were more important. Whereas for the earlier question we saw some variability in the response patterns across the countries, here we see that the pattern is very similar.

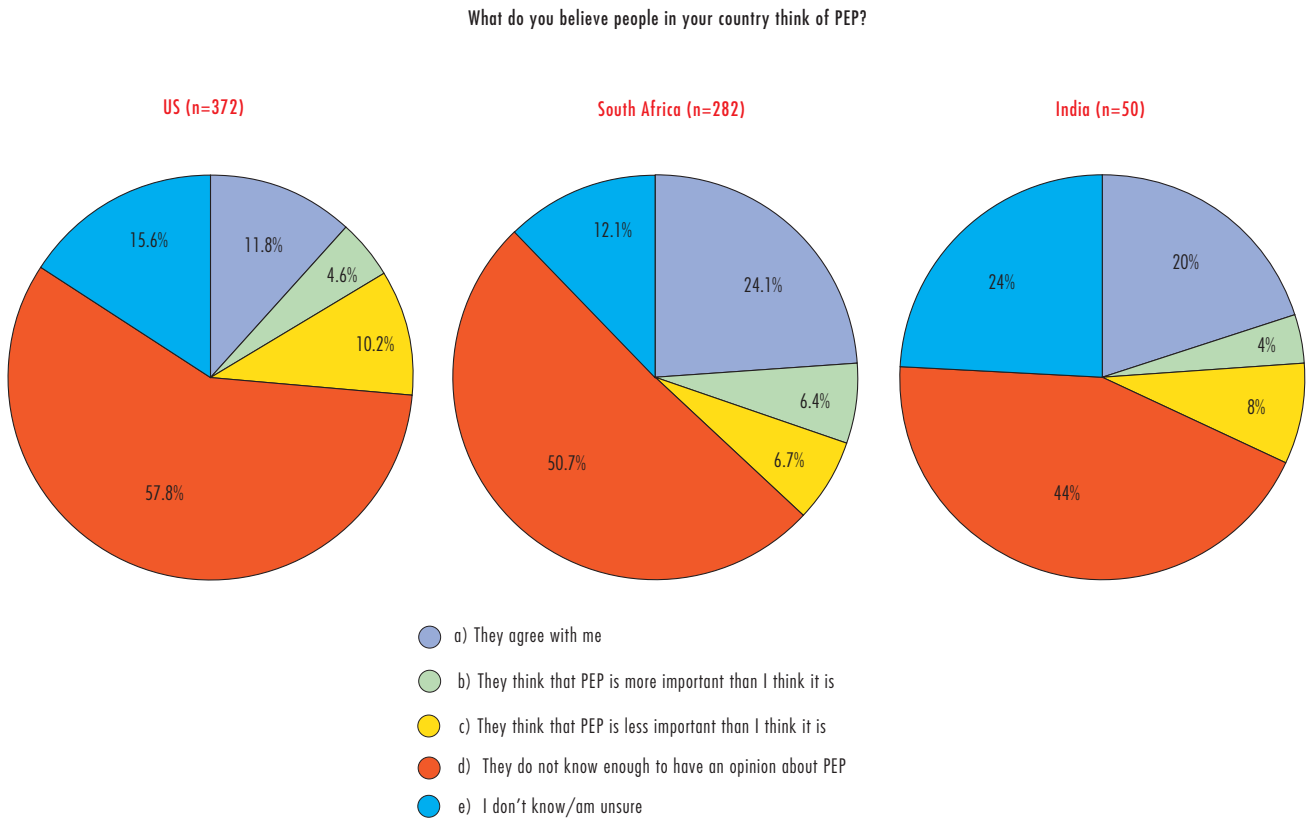
Views from the grassroots about PEP

One of the biggest challenges in the implementation of PEP, particularly non-occupational PEP, is its availability to those who may need it immediately after exposure (or at the latest within 72 hours). We therefore wanted to know how available respondents felt PEP was in their countries, as well as its relative importance as a prevention strategy and what the views of others were about it.

Respondents in the different countries had differing views about the availability of PEP. In India, 40% thought it was 'very easy' or 'easy' to get hold of and in the US a slightly larger, 47%, set of respondents thought it was 'very easy' or 'easy' to access. However, in South Africa 77.6% of respondents thought it was 'very easy' or 'easy' to get hold of, which is perhaps indicative of a much greater uptake of the strategy.

Further research might be warranted to explore the reasons for this. A small proportion of par-

Figure 3-8
Stakeholders' views on what people believe others in their country think about PEP, by country

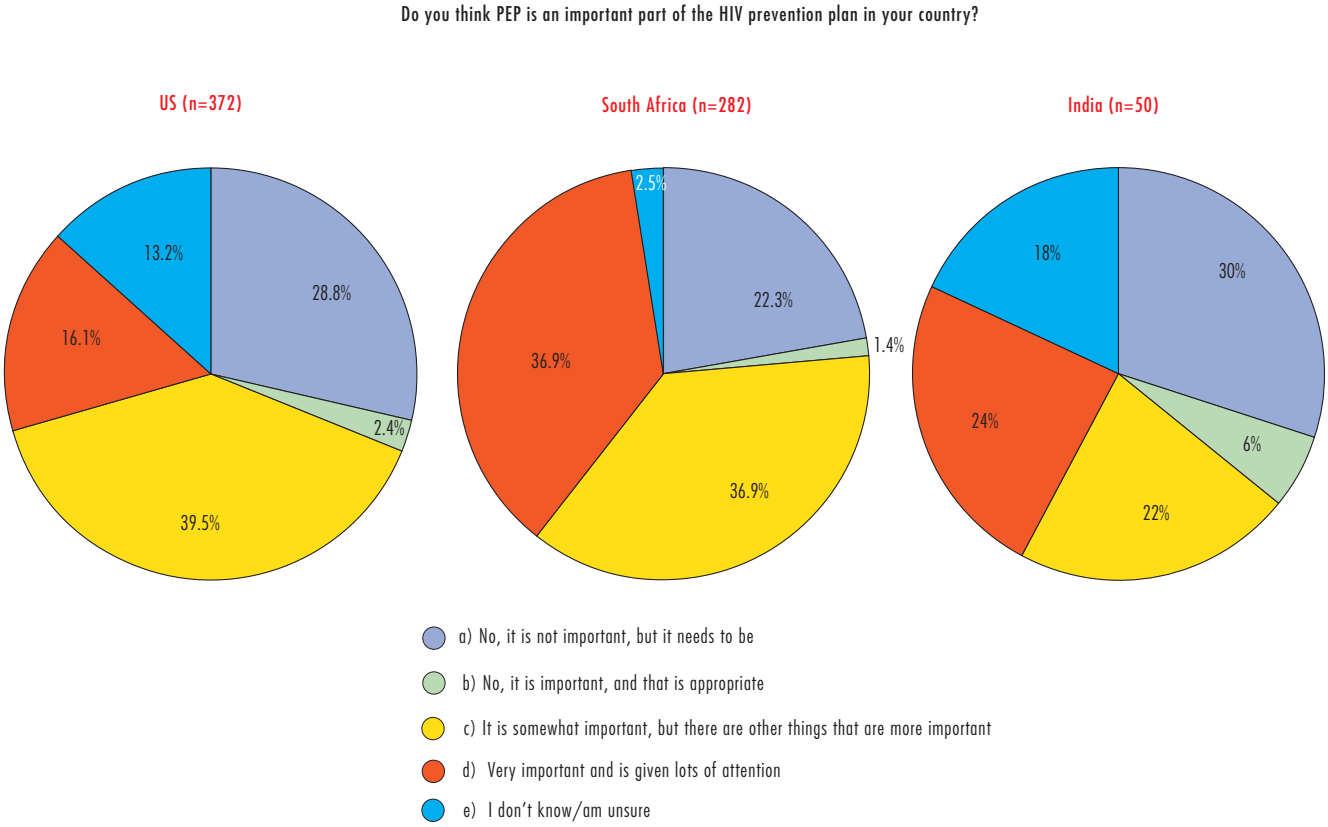


ticipants stated that PEP was unavailable in their country (India 6%, South Africa 0.4%, the US 2.4%), while almost a quarter in India (24%) and the US (24.2%) were unsure of the availability. Again in South Africa awareness and availability seemed to be strong (South Africa 5.3%) in comparison.

As with other strategies, when asked what others thought of PEP as a prevention strategy, the majority (India 44%, South Africa 50.7%, the US 57.8%) of respondents said that people in their country did not know enough about it to have an opinion (Figure 3-8). In all three countries the smallest proportion of respondents indicated they thought others felt PEP to be less important than they did (India 4%, South Africa 6.4%, the US, 4.6%). Again the data seem to suggest that there is a need for more information, which is particularly interesting in the case of South Africa given that so many people felt it was widely available.

When asked whether they thought PEP was an important part of the HIV prevention strategy in their country, the near majority of participants across the countries stated that it was either somewhat or very important as a prevention strategy (India 46%, South Africa 73.8%, the US 55.6%) (Figure 3-9). Consistent with other findings on this strategy, this view was most pronounced for South African respondents, seeming to indicate that for PEP, South African respondents felt most confident not only in its availability, but also in its importance and awareness among the public. In addition, across all three countries there were similar proportions of people suggesting that PEP was not important as presented, but it needed to be (India 30%, South Africa 22.3%, the US 28.8%). A small number of respondents stated that it had not been important in the HIV prevention strategy in their country and that that was appropriate (India 6%, South Africa 1.4%, the US 2.4%).

Figure 3-9
Stakeholders' views about the relative importance of PEP by country



Summary across all countries and strategies

On the face of it, respondents from all countries generally viewed all ARV-based prevention strategies as important in HIV prevention. TLC+ received the highest number of respondents saying that it was most important and needed the most attention, closely followed by microbicides. Respondents' views on PrEP were mixed: some respondents thought it was very important; others that there were more important strategies to consider. Again, views on PEP also differed somewhat with South African respondents rating it higher in importance than respondents from other countries, and proportionally more of them indicated it was easy to access. When comparing across countries, respondents from India rated TLC+ and microbicides as slightly less important than participants from South Africa and the US. In general, respondents from India rated ARV-based prevention strategies as slightly less important than other prevention strategies, while a greater proportion of participants said they thought there were other important issues in HIV prevention. There are parallels here with the views expressed in the grasstops interviews, which among other issues indicated that India was a long way from being able to implement ARV-based prevention strategies because there was still a significant amount of basic awareness raising, provision of testing services, and treatment of those already infected that needed to occur beforehand.

When we look at the open-ended responses to the questions, which cut across all the strategies, it was evident that many concerns about ARV-based prevention strategies were common across the countries, with the most frequently mentioned concern being the need to improve awareness around ARV-based prevention strategies. This correlated strongly with the response to what information would be most useful in their work: respondents gener-

ally thought that education and awareness of the strategies needed to be improved. This feeling was matched with responses to questions about what others in their country thought about ARV-based prevention strategies. Respondents indicated that people in their respective countries were not aware of and did not know enough about the strategies to have an opinion.

However, the way people wanted to approach information campaigns varied by country. In the US, our analysis suggested that raising awareness was less about lifting the profile of ARV-based prevention strategies and more targeted at elevating comparisons between the prevention strategies so that those working in the field could make more informed decisions. Conversely, the respondents from India and South Africa who discussed the issue wanted information that would help in raising the profile of ARV-based prevention strategies. For example, some commented that social marketing could be used to raise awareness of ARV-based prevention strategies.

Additionally, many respondents stated that they would appreciate information on drug resistance and side effects of taking the medication. Across all three countries, many respondents asked that information about the toxicity and side effects associated with an HIV-negative population taking ARVs be made available. There was also a concern expressed that the side effects of taking an ARV regimen may lead to problems with adherence, and disinhibition which could lead to sexual risk behaviours. Respondents wanted to understand how ARV-based prevention strategies and the associated toxicity would affect people in the long and short term.

Lastly, many respondents requested comparisons between the different strategies; the financial cost, including plans on how the strategies would be financed and implemented; and the epidemiological efficacy. This latter concern about cost and resource was articulated in several ways. In all three countries, respondents highlighted the need for information about the cost of implementing ARV-based prevention strategies, as well as wanting to know more about how implementing these prevention strategies might reduce the cost of providing ARV treatment post infection. There were shared concerns that implementing ARV-based prevention strategies may result in funds supporting treatment and other prevention methods being reduced.

Cross-cutting analysis of the grassroots survey responses

Respondents in the three surveyed countries generally leaned towards accepting that ARVs can be used in preventing new HIV infections. TLC+ was rated highest across all countries, and PEP rated lowest. Even though there was a largely positive response to using ARV-based prevention methods, respondents from all three countries expressed an interest in finding out more about the science. Specifically, respondents were concerned with non-adherence, the long-term effects of taking ARVs as prevention, and related behavioural disinhibition issues in people who are HIV-negative.

Looking across the data from all the ARV-based prevention strategies stakeholders were asked to consider and the countries, our analysis suggests that while stakeholders saw the benefits of using ARVs in preventing HIV infection, there were four main thematic concerns which emerged:

1. the need to minimise *drug resistance* and to *ensure adherence* in those who are not ill
2. the need to *communicate with*, *educate* and *raise awareness among* the general public, those who work in the field, and those in decisionmaking positions
3. the ability of *healthcare systems* to adapt to and manage the increased patient load
4. the need for implementation strategies that are *cost-effective* and *sustainable*.

We now consider the findings for each of these in more detail.

Drug resistance and adherence

Respondents in all three settings generally leaned towards accepting a role for ARVs in preventing new HIV infections. TLC+ was rated the most favourable across all countries, and PEP was rated lowest. The South African context is shared with India and other developing countries where a large proportion

of the population live in impoverished communities. Two South African respondents expressed concerns about the use of PrEP in resource-limited settings in the following ways:

> *A tricky subject in a community that is illiterate, poor and unemployed with little motivation or future to look forward to. In the public sector we are dealing with high rates of sexually transmitted disease and poor compliance to any treatment due to factors mentioned above. I'm just worried how many times a month an individual can take pre-exposure prophylaxis and how soon until the development of resistance to ARVs & what impact that is going to have when now the individual has to go onto HAART [highly active antiretroviral therapy] when indicated. (South African respondent)*

> *I am concerned about the widespread use of PrEP resulting in an increase in ART resistance, particularly to tenofovir which is a first-line medication. (South African respondent)*

While drug resistance was a major concern for PrEP, respondents from all countries also relayed a keen awareness of the possibility of drug resistance developing in relation to TLC+ and microbicide strategies. This led to some respondents requesting that ARV-based prevention strategies have a broader evidence base before being implemented. One asked for 'more evidence before any implementation. More research is needed with other drugs that are safe and have high barrier to resistance' (US respondent).

Communicating, educating and raising awareness

Communicating and raising awareness were important for the majority of respondents from all countries. However, while respondents from India tended towards rating ARV-based prevention strategies as slightly less important in preventing HIV infection than their counterparts in the other two countries (as shown in the survey data above), they expressed slightly more positive views about the strategies when asked whether they would be willing to spend their own time and resources to communicate and raise awareness of prevention methods. Some Indian respondents were concerned about a 'lack of proper public awareness and education', and there was an acute awareness about the need to fully think through the issues:

> *How could we devise advocacy and communications campaigns to raise awareness of these approaches, do media outreach to sensitize and educate media practitioners to ensure sound coverage, and in general use social marketing techniques to reach a wider population once these approaches are adopted? (Indian respondent)*

Many respondents from all three countries, particularly those from South Africa and the US, stated that information regarding implementation would be most useful to those working in advocacy positions.

Analysis of the open-ended questions also suggested that respondents from India and South Africa were most concerned with awareness about ARV-based prevention methods, as well as the cost of implementation in their country. The comment below by an Indian respondent expresses some of the barriers they are facing:

> *We are still grappling with raising awareness and trying to reduce stigma and discrimination. Ignorance and fear remain the barriers to 'learning'. Any and all information is welcome to help us learn. (Indian respondent)*

South Africans also thought that information about raising awareness would be most helpful in helping them think through the appropriateness of ARV-based prevention strategies in their communities. This mirrors responses in the closed question part of the survey where respondents indicated that many people in South Africa did not know enough to have an opinion of ARV-based prevention strategies and respondents offered several suggestions for how to overcome this. For example, one South African participant said that 'community education at the grassroots level is key', and another specifically stated that it is important to 'educate communities about the difference between ARV as treatment and ARV as prevention' (South African respondent). One person suggested an online databank where anyone could access information about all aspects of ARV-based prevention methods would be useful and that it

should contain information such as: 'Q&A [question and answer] for diagnosis, treatment, M&E [monitoring and evaluation] strategies, national clinic contact details and addresses, and drug interactions, dosing guidelines, [and] protocols, etcetera' (South African respondent).

Interestingly, information about how to raise awareness was not at the top of the list of the kind of information US-based respondents thought would be useful in relation to ARV-based prevention strategies, as it was in India and South Africa. Instead, respondents from the US wanted information comparing the different ARV-based prevention strategies and they were keen to quantify effectiveness of each prevention strategy and raise awareness about these cost issues, as opposed to issues about the nature of the ARV-based prevention strategies, themselves:

> *Need to take a cost-effectiveness point of view, namely, that the goal is to prevent as many new infections as possible within a given budget. Thus, targeting strategies is essential. (US respondent)*

> *I believe it is important to be specific about how effective each strategy is, what you mean by 'effective', and educate people, for example about what it really means to say that 'PREP is 65% effective'. (US respondent)*

Healthcare systems

Respondents across all three countries stated that knowing what those in decisionmaking positions thought, and having the backing of those working in advocacy, were important factors in implementing any ARV-based prevention strategy within a given healthcare system. For example, a respondent from India was concerned about 'resistance from some in the medical/HIV care and treatment field to these approaches and efforts to undermine these'.

In particular, respondents wanted to know that the people driving implementation would include healthcare workers, and people in advocacy, decisionmaking and leadership positions. They believed these factors would combine to impact on institutional variables and the success of implementing ARV-based prevention. US respondents stated that it was especially important to draw on the opinions of those communities affected, as well as healthcare workers, and to publicise these views in the media. Referring to healthcare workers, one respondent asked, 'What do people on the ground (so to speak) think of these strategies and how would they implement them?' (US respondent).

Financing

Lastly, while it was agreed that ARV-based prevention methods would help to reduce new infections, financing was a major concern for respondents across all three countries. Some noted that the cost of implementing ARV prevention strategies may be prohibitive and would impact on current treatment strategies: 'HIV-infected people needing ARVs are receiving it and adding more numbers to these will only strain the healthcare system in the country more' (South African respondent).

Other respondents indicated that while the cost was worrying, efforts should be undertaken to determine whether 'ARV-based prevention would actually reduce the final cost of providing ARVs post infection' (Indian respondent). Respondents were concerned about where the funding would come from, and whether funds would be diverted from other prevention options. A few respondents noted that ARV prevention might be in direct competition with prevention methods and treatment: 'There will be [such] a shift away from behavioral interventions, and from treatment, that individuals get lost in population interventions' (US respondent).

Discussion of the grassroots perspective

The perspectives from the grassroots highlight for us several factors which will be important to consider in any future assessment of ARV-based prevention strategies. First and foremost, a clear message from the survey data is the lack of information and awareness people have of any ARV-based prevention strategy. This is not to be overlooked as a message for the entire community of people who might be involved in implementing future strategies. Not only do we need more information about the contexts within which implementation will occur, but the people whom the prevention strategy will be tar-

geted at also need this information. Grassroots opinions are important because they are the perspectives of people who are on the front line of implementation. Funders and policymakers need to understand the issues raised by those at the grassroots by taking into account the economic, political and social variables. Understanding this will help to forecast the relative success of implementing ARV-based prevention strategies. In light of this, there are several additional issues for consideration which emerge from our findings.

Respondents were generally positive about using ARVs to prevent new infections, with TLC+ and microbicides being most highly rated, and PrEP and PEP garnering slightly less optimism. However, respondents from South Africa differed, as they were more enthusiastic about PEP being used to prevent new infections than those from other countries. Respondents from India reported the lowest levels of awareness of ARV-based prevention. In contrast, these participants were more enthusiastic about using their own time and resource in lifting the profile of ARV prevention strategies.

In addition, ARV resistance was clearly a high priority for respondents. There were a number of issues associated with resistance, including concerns about the ethics of the broad scale dissemination of ARVs to healthy people, the toxicity and side effects generated, resistance to the medications with poor adherence, and the long-term effects of taking ARVs.

Although all countries were interested in raising awareness and receiving information that would help them to do so, respondents from the US raised a unique concern. They suggested that raising awareness should involve presenting people with information that would help them compare ARV strategies with each other, and with non-ARV-based strategies. In other words, they should be enabled and empowered to make their own decisions about what prevention strategies were right for them. This specific point highlights a more general one: information and education needs vary by community and country. Responding to them in a targeted way, and informing these responses through additional, comprehensive and targeted surveys which seek to build up a detailed picture of respondents' views, will be an important part of this campaign.

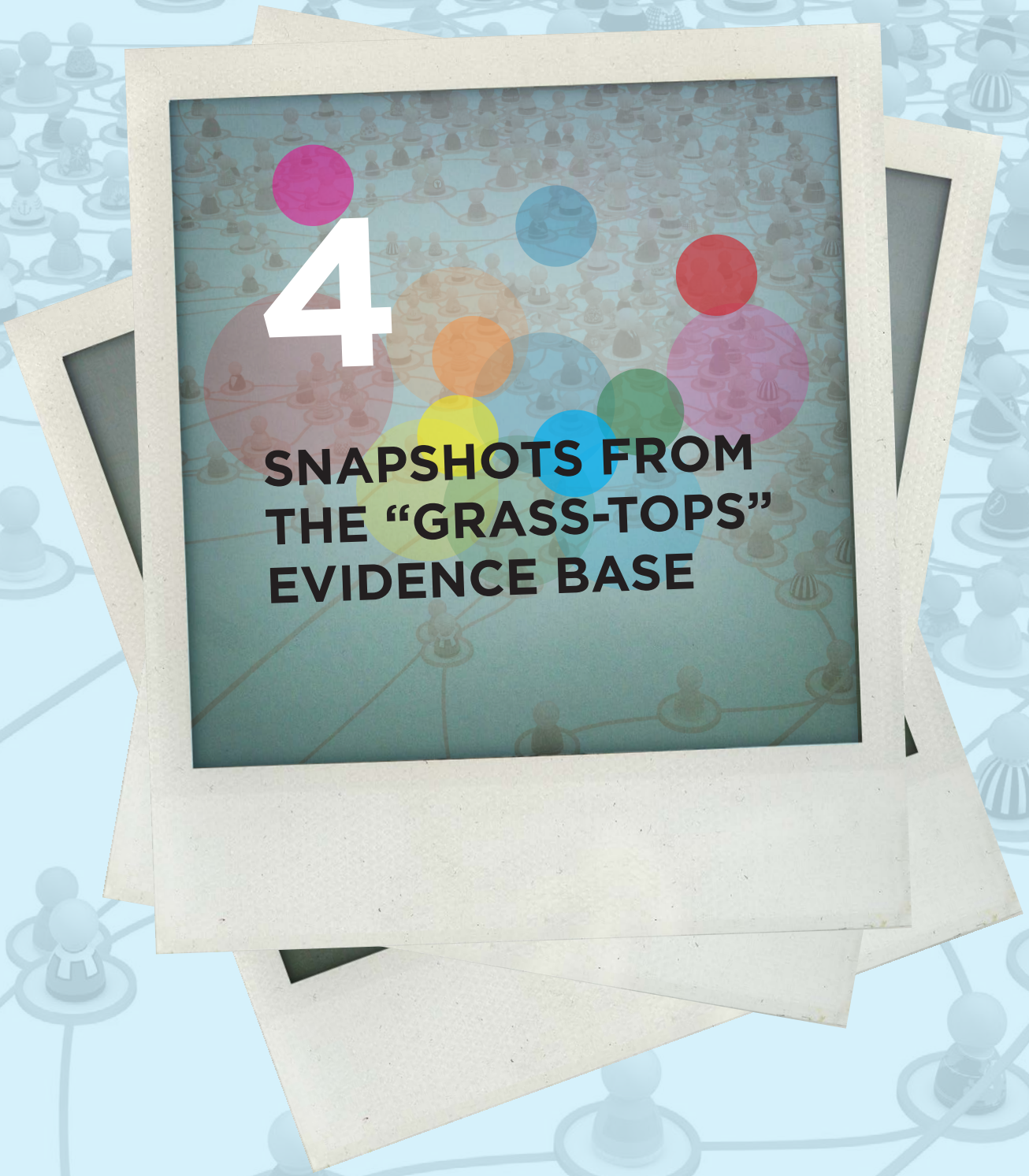
Following from this, respondents in all three countries raised concerns about how any implementation would be financed, and how healthcare systems would cope with the increase in patients, especially in contexts where healthcare professionals may not necessarily be involved. It was therefore important for respondents that they receive information about the opinions of people in leadership positions, including policymakers and decisionmakers.

Finally, before concluding it is worth offering a few comments on the limitations of the approach we present here. First, obviously a survey sent out to a broad base identified by the Mapping Pathways team risks a certain selection bias. However, as we are just trying to capture a snapshot of grassroots views as a means to illustrate some of the concerns of the communities in which ARV-based prevention might be implemented, this is less of an issue for this project than it might be for others. Our aim was to be illustrative, not fully representative. This applies also to the fact that not all survey respondents answered the survey. We wanted the survey to be as flexible as possible and for stakeholders to feel comfortable answering only those questions they held a view on. Nonetheless, the poor survey completion rates did limit the extent to which a more sophisticated and detailed analysis could be undertaken. Of greater limitation was the lower response rate in India, in particular, and we comment on this more fully in Chapter 5, as we experienced this also with the Delphi ExpertLens, another web-based consultative tool. There may be limits to the extent Indian communities can be engaged in this way and we believe this should be considered when building on this research in future, as it has methodological implications. Despite this, the views captured by our survey do provide a strong indication that there is an important agenda to be developed and a broader series of engagements that needs to take place. This will enable a fuller understanding of the potential opportunities and challenges posed by ARV-based prevention when considered from the point of view of those in the communities in which it will be delivered.

Concluding thoughts and looking forward

All of the concerns highlighted by grassroots respondents should be considered seriously if funders are to implement ARV-based prevention successfully. They stress the importance of the perspective of those who are involved in day-to-day issues related to HIV prevention and treatment, including, if implemented, ARV-based prevention. Thus, the views reflect subtle issues of context, which might not otherwise be apparent to those viewing the problem from a different perspective.

In addition, these concerns demonstrate that the views of the community are not to be taken lightly or disregarded, as they will be crucial to not only helping with implementation, but also accepting whatever strategy is pursued. They show us that despite clinical trials showing efficacy, legitimate concerns still exist about whether these strategies will work and be accepted. This 'social' side of the strategies and the institutional and organisational systems in which they will be implemented is just as important to these community voices as the clinical trial p-values seen in the previous chapter.


4
SNAPSHOTS FROM THE "GRASS-TOPS" EVIDENCE BASE

The grasstops perspective: by grasstops we mean stakeholders who are at the forefront of policy discussions about local, regional and national HIV/AIDS strategies and who have the ability to set the 'scene' for which strategies receive wider discussion, and which do not. They play prominent roles in shaping or responding to their respective country's policies on HIV/AIDS prevention and included clinicians, advocates, policy advisors, policymakers and researchers.

Why the 'grasstops'?

The third perspective we solicited on our journey was from the grasstops, the key stakeholders including policymakers and advocates, who are often at the forefront of national policy discussions about different HIV/AIDS strategies. Owing to the rapidly changing, complicated background presented by advances in ARV-based prevention strategies these grasstops leaders have had to shift their focus and re-examine their approaches, often with little evidence to base their decisions on. Our aim was to capture the views of this group as they were starting to grapple with these decisions, in order to provide a snapshot of the kinds of questions they were asking and the evidence they found themselves requiring. This would enable us to identify what additional research and evidence was needed, as well as provide a view into their perspectives on what the relative importance of different pieces of evidence were for making policy decisions about ARV-based prevention.

Thus, involving decisionmakers and stakeholders from the policy community helped to assure policy relevance and contextualise the research needs in relation to current issues, such as the funding environment, technical difficulties (such as human resource bottlenecks) and other implementation challenges that should be considered alongside the scientific data. This contextualisation was critically dependent on other elements of the evidence base and there was a continuous feedback loop through our methodologies.

Methodology for eliciting the grasstops perspectives

We conducted semi-structured interviews with selected policy stakeholders in India, South Africa and the US. These exposed respondents to the emerging findings and issues around ARV-based prevention strategies; assessed attitudes to the strategies, including relative levels of optimism or pessimism and resistance to or acceptance of this new kind of prevention; asked whether more or different information is needed; solicited the respondents' ideas on unanswered questions; and asked how the findings should be delivered so that they are most useful for the communities involved. In total, we interviewed 41 stakeholders (9 in India; 13 in South Africa; 19 in the US) and held two small focus groups of six people in the US to help us understand the decisionmaking needs of leaders. We held all interviews under the condition that responses would be treated anonymously and confidentially. We conducted them using a topic guide and asked all stakeholders questions that focused on the four ARV-based prevention strategies the Mapping Pathways study explored and several inter-related areas within them, including existing ARV-based prevention strategies, implementation challenges, socio-economic effectiveness, comparative cost-effectiveness and expected 'spill-over' effects. In addition, the interviews contained questions on the following more specific issues:

- general impressions of the Mapping Pathways project and aims
- the implications and local applicability of the results of the HPTN 052 trial[21]
- the usefulness of a number of possible outputs from the Mapping Pathways project by which HIV/AIDS prevention study findings can be disseminated to communities and policymakers for the purpose of advocacy and developing evidence-based policies.

[21] See Chapter 2 for a discussion of this trial.

Individual semi-structured interviews

We collectively and purposively identified stakeholders across a range of policy areas who play prominent roles in shaping or responding to their respective country's policies on HIV/AIDS prevention. After contacting this broad range of stakeholders, 41 individuals accepted our invitation for a discussion. The interviewed stakeholders were sometimes directly involved with persons affected by HIV/AIDS, either through clinical work, advocacy or research, and sometimes functioned in a policy-level, administrative role. Regardless of their level of involvement, all participating stakeholders exerted some degree of influence on HIV/AIDS prevention policy in their country by virtue of their position and experience. In addition and also by virtue of their position and experience, each selected stakeholder could meaningfully reflect on the extent to which recent research findings on the potential use of ARVs for preventing the spread of HIV/AIDS likely would or would not result in a change in existing policy; the primary barriers to policy change; and the projected usefulness of various 'tools' to promote the use of current and future scientific findings for shaping HIV/AIDS prevention policy in their country.

The stakeholders came from various disciplines but could generally be distilled into one of five categories: clinical, advocacy, research or academic, political, or administrative. These categories were not mutually exclusive and many if not most of those interviewed held multiple roles. For example, a stakeholder in one country was a physician as well as an agency administrator and a public health specialist. In another, a stakeholder was a social service agency administrator, a policy adviser and an advocate. Because of the high rate of role crossover, it did not seem reasonable to present findings based on stakeholder role in the analysis. Moreover, assigning many of the stakeholders to a single role would be a clear oversimplification and mischaracterisation of their mixed responsibilities and perspectives.

Focus group discussions

In addition to the individual interviews with 41 stakeholders, members of the Mapping Pathways project team led two group-based discussions with participants attending the US conferences on HIV/AIDS prevention: the National HIV Prevention Conference in August 2011 in Atlanta Georgia and the Southern Reach (Regional Capacity to Address HIV/AIDS in the South) Conference in Charlotte, NC, in October 2011. There were six participants at each group discussion. The people interviewed at these conferences did not overlap with those interviewed individually.

Project team members used a subset of the questions asked of individual stakeholders to guide the discussions. The subset consisted of 11 questions and included the same questions on each of the four ARV-based prevention strategies and the questions on the usefulness of different tools for promoting the use of scientific findings. Questions on the implications of the HPTN 052 trial and on current involvement in discussions about and plans for using and promoting any of the four ARV-based interventions were not included in the group discussions. For the purposes of the analysis, we examined the responses from each group for key themes in the same way the discussions from each individual interview were, which we then factored into the qualitative analysis alongside the individual interviews. For the purposes of the quantitative, heuristic charts presented below (Figure 4-1 to Figure 4-9), each focus group was treated as one data point so as not to disproportionately weight the views, bringing the total number of interview data points for the questions in common for the US to 21.

Analysis

We then studied the qualitative interviews thematically using a qualitative software analysis programme, which allowed for systematic and structured thematic coding of the interview findings.[22] The thematic analysis proceeded in a hypothesis-driven way whereby the interview documents were critically reviewed to develop a set of analytical codes for each main theme in response to the questions. Themes were refined and sub-themes identified in an iterative process until diminishing returns set in and no new codes could be identified. This

[22] The programme was Text Analysis Markup System (TAMS) Analyzer.

left us with a critical and sufficient level of analytical depth and breadth.[23]

It is worth noting that for most questions the number of codable responses was less than 43. This is because some interviewees did not wish to answer certain questions in the way they were asked. For example, in India, one interviewee strongly objected to the fact that Mapping Pathways was sponsored by a pharmaceutical company and declined to answer almost all of the questions. This interviewee nevertheless offered opinions on their concerns about the use of ARVs for HIV/AIDS prevention and these responses were coded and included in the analyses and findings where applicable. In other cases time constraints on the part of the interviewee led to the interview being terminated early. Given that the study was qualitative in nature and that the interviews proceeded using a topic guide, we do not believe the validity of the findings and the conclusions drawn from them were adversely affected.

The findings are presented in quantitative and qualitative formats. The quantitative assessment of views are presented as a heuristic guide for the reader and the analyst as indicative of some of the broader themes that emerged from thematic analysis. Patterns in these themes could then be explored in more depth where merited by the data. This provides a structured and fully transparent way of presenting and evaluating qualitative data (Morgan Jones, 2010; Wooding et al., 2012).

Findings

Before going into the more detailed findings about individual ARV-based prevention strategies, it is worth briefly reflecting on some of the stakeholder views in response to our more general, overarching questions. First, stakeholders were generally positive across the three countries about the Mapping Pathways study and the four ARV-based prevention strategies. Interviewed stakeholders in the US had the most positive overall response to Mapping Pathways with 47% giving a solely positive opinion about the study, while stakeholders in India were the most sceptical with only 11% expressing a positive response. However, the reasons for scepticism were more to do with the strategies themselves, and during the discussions much of the uncertainty about them began to surface. Concerns included effectiveness or efficacy of the strategy, local circumstances or politics being an obstacle to implementation, and cost or resource constraints. This last area was of great concern to more than half the US interviewees (52%), and to about one-third of interviewees in India:

> *This research [the Mapping Pathways project], because of its biases, does not work in the context of India. Behavioural change and education is key, not treatment as prevention. Treatment as prevention focuses on being provided to people at high risk of getting HIV/AIDS, but concerns are present already here. It is an assumption that MSM and sex workers are at high risk of getting HIV/AIDS, but women in monogamous relationships are also at high risk. Nobody can be excluded completely from being at risk. (Indian respondent)*

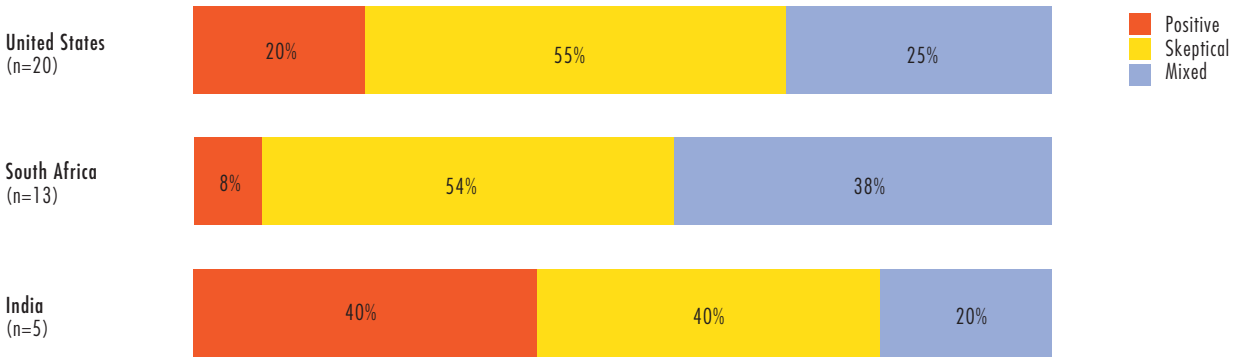
> *This is the first time [the stakeholder] has heard of an HIV prevention project with this level of involvement and collaboration. [The stakeholder] likes that we are 'pulling multiple viewpoints together' and thinks this is truly the 'only way forward', and the only way we can possibly deal properly with the evidence. (US respondent)*

When it came to sceptical or negative views about Mapping Pathways itself, almost every interviewee in India was concerned about the project being sponsored by a pharmaceutical company:

> *Why is Merck funding this and what is their interest in this project? I'm not suspicious of it, I know they do fantastic work, but I can see how the medicalization of HIV will be highly profitable for pharma companies. But will this sacrifice the benefit [to] marginalized communities? (Indian respondent)*

[23] This is a standard approach to analysing qualitative data, drawing on methods such as those described by Yin, 2003; Flick, 2009; and Silverman, 2001.

Figure 4-1
The likely programmatic and policy impacts of TLC+



South African stakeholders were generally positive about the study, but often expressed concerns such as the following:

> *[Mapping Pathways] captures everything that's going on at the moment' in the HIV prevention field.... [but I am] concerned that we are not including other African, and particularly sub-Saharan African, countries in this analysis. (South African respondent)*

Overall, the respondents supported our efforts, but were quick to point out the challenges associated with a project that was trying to capture feedback in such a dynamic and fast-moving environment. As one US stakeholder put it,

> *Things are going to move quite fast and the Mapping Pathways team may find ourselves chasing events, since the field will 'carry on growing and growing'. (US respondent)*

The stakeholder mentioned that two significant results will be coming out shortly – the Thai trial expected out later this year, and the VOICE trial possibly coming out later this year: 'it would be best if we got this done as fast as possible, and then it's done' (US respondent).

Thus, it seems that despite some scepticism and concerns, stakeholders were positive about the types of questions we were asking and the approach being taken. After these initial questions, we asked interviewees questions about what the programmatic and policy impacts of each of the four ARV-based prevention strategies would be and, where relevant, what their interpretation of recent clinical trial data was in relation to likely implications for policymaking.[24]

Views from the grasstops about TLC+

The overall response pattern for TLC+ discussions is shown in Figure 4-1. Somewhat surprisingly, given the sceptical tenor of their general reaction to Mapping Pathways, stakeholders in India had the highest percentage of purely positive responses (40%) compared with US (20%) and South African (8%) respondents. However, respondents in all countries were sceptical about how TLC+ might impact on programmes and policy. Sizable proportions of the interviewees had sceptical or mixed responses to questions on the likely impact of TLC+ on programmes and policy in the near term, and expressed more negative responses about the likely success of the strategy given other factors at play.

In all countries, the main reason for positive responses was the established efficacy of the drugs in the clinical trials. This statement by a stakeholder interviewed in the US exemplifies the thinking expressed by many others as to the proven efficacy of starting TLC+ treatment earlier:

[24] See Chapter 2 for a full discussion of the literature.

> *Treating people with ARVs impacts prevention by decreasing the community viral load. If this strategy were complemented with PrEP, infection rates could decrease and help towards long-term eradication of HIV in communities. (US respondent)*

In India, respondents said they thought that TLC+ would produce side benefits for the health system and enable HIV-infected people to start treatment earlier. This latter issue was important to South African stakeholders, as was the idea that TLC+ could be a good return on investment as it would lead to more people being given ARV treatment.

Despite the optimism over the efficacy of TLC+, there was also an equal measure of scepticism across all three countries about this intervention, as well as related concerns about people taking these drugs for a long period of time. The main reason for the scepticism was the costs and resources that would be needed to pay for expanding ARV-based treatment to implement TLC+, but stakeholders' apprehension had country-specific nuances. In India, for instance, one stakeholder noted how expanding treatment to such an extent would require reducing or eliminating almost the entire prevention budget. South African respondents' unease about resources was more influenced by the logistical support necessary to increase ARV-based treatment as well as the political support needed to budget in the future for the increased numbers of people who would be on ARVs long term, potentially for the rest of their lives:

> *This forces politicians to think beyond normal political timelines... it's easy to get stuck in the discourse of 'this is difficult to do within next year's budget' but we need to accept the reality that we're going to have a staggering number of people on treatment for a very long time, regardless of what CD4 is stipulated in the guidelines. (South African respondent)*

> *We need to ask ourselves, 'Do we have the capacity to do this?' (South African respondent)*

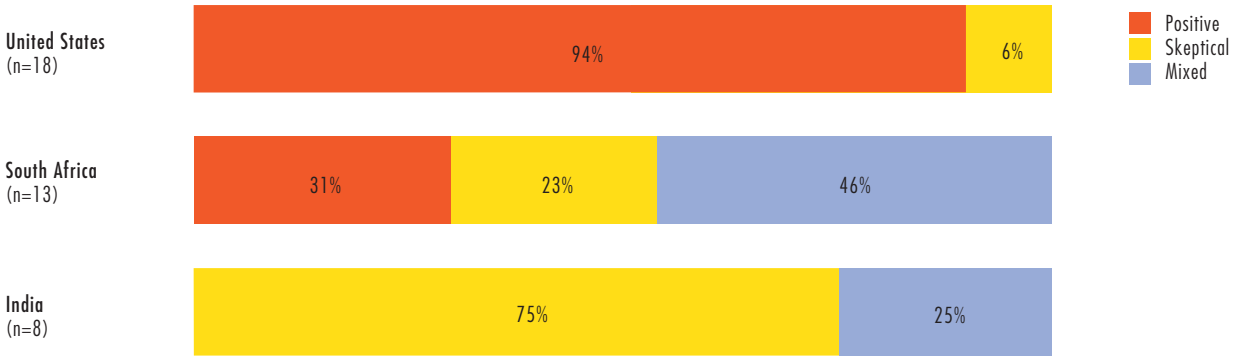
Among US stakeholders, issues around resources for implementing TLC+ as a prevention strategy were directly related to funding and to the already noted concern that the inability to identify and treat a majority of those who are HIV-positive under current guidelines and practices casts doubt on the ability to fund the expansion of ARV-based treatment to those with lower CD4 levels or those who are HIV-negative.

Interestingly, given the tendency towards scepticism and mixed responses about the likely impacts of TLC+, the overwhelming majority of US stakeholders thought that the recent HPTN 052 data supported changing treatment guidelines, while the majority of Indian stakeholders felt exactly the opposite (Figure 4-2). In effect, these views were given in relation to the question of whether people should be started on ARV-based treatment at a higher CD4 cell count (approximately 500 cells/mm3) as opposed to waiting for the CD4 count to drop lower as is current practice.

In India, the large degree of scepticism about the implications of the HPTN 052 trial results was evenly spread together with concerns that risk behaviours would increase, costs and resource issues, and local circumstances that would make implementation difficult. In one sense, these views seem to contradict those from the previous question, which suggested that respondents in India were generally positive about the potential programmatic implications of TLC+. However, close analysis of their responses to the question about the HPTN 052 trial shows they had real concerns about the generalisability of these findings to their context and the nature of the epidemic and problems in India. It is a striking example of how people may support the idea of TLC+ in principle, but when presented with evidence from one context, they come to strongly question whether it will translate across to their own situation:

> *[HPTN 052] provides strong evidence, because of what it has done in a very controlled condition. 96% is strong evidence of giving ART to people, but it has only been done to couples with counts that are not below 350. In India people don't come in for diagnosis early, so the question is if you want to use it as a prevention strategy: how do you get them in earlier? (Indian respondent)*

Figure 4-2
Stakeholders' views about whether the HPTN052 trial findings supported changing treatment guidelines



However, mixed with this scepticism were some positive views from the Indian stakeholders, including the idea that if successful, the strategy could really help reduce the stigma of HIV:

> *This evidence would have huge implications for guidelines for people living with HIV. Currently, guidelines define parameters for when people are put on ARVs depending on viral loads and CD4 counts. However, this evidence would imply that all people should be put on ARVs. If there were a large decrease in transmission rates, the stigma towards HIV could be reduced. (Indian respondent)*

Positive South African stakeholder responses were driven largely by optimism that the HPTN 052 trial provided strong evidence for the efficacy and effectiveness of starting TLC+ earlier than prescribed by current guidelines, but as the high percentage of mixed responses indicate, this was balanced by concerns related to issues that could mitigate effectiveness, in particular the challenges faced in the South African context and healthcare system, as was noted by these two respondents:

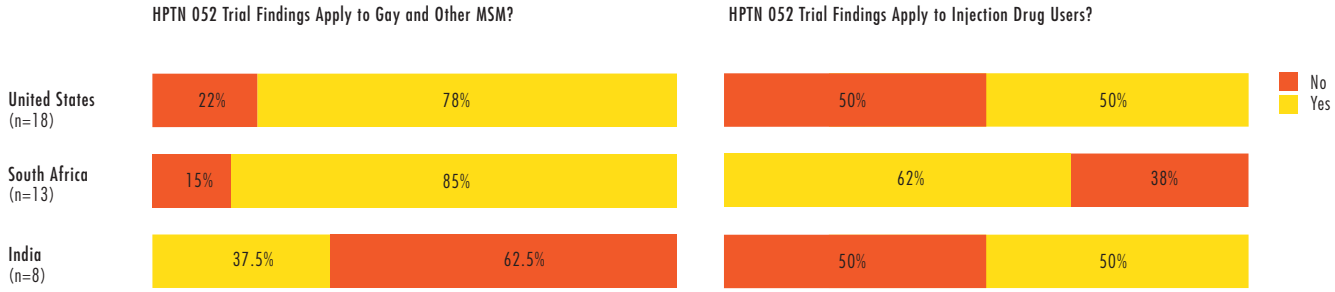
> *Before a prevention intervention can be successfully implemented in South Africa, one needs to understand the South African HIV epidemic. The bulk of infections in the country occur between older men and younger women, which is the driving force behind transmission. South Africa doesn't have large numbers of stable, long-term relationships – if we did, treating a positive partner in a serodiscordant couple would work. – It only works if the negative partner is not having sex outside of the relationship, but they are! For the strategy to work, we'd need a high uptake of testing, which is not the case in South Africa. For this to be successful, we'd need everyone to test. (South African respondent)*

> *This is a resource question. The South African health system is struggling to cope with 1 million people on treatment, so how will it cope with 5 million? (South African respondent)*

Finally, US stakeholders were the most optimistic group of those interviewed. Many US stakeholders pointed to efficacy and effectiveness as the main selling point of the HPTN 052 trial results. The quotes from three individuals in the US below show that these stakeholders were often uneasy about the perception that the study findings supported a public health benefit, but not necessarily an individual benefit (because of the potentially negative and long-term effects of taking the drugs):

> *Yes, I think it provides evidence, I don't think it can be the only evidence but I think it definitely supports the growing concern that treatment should be initiated at the time of diagnosis and*

Figure 4-3
Applicability of the HPTN 052 trial findings to gay men and other MSM populations, and injection drug users



it's not dependent on the degrees of damage. It is complicated because it's lifelong treatment. It shouldn't imply it's the only study and now everyone gets treated early, but it does imply we should start treatment sooner. (US respondent)

The evidence provides a strong case for having an introduction section in treatment guidelines for treatment as prevention. We need to be clear that HPTN 052 doesn't necessarily provide evidence for a treatment benefit but rather as a public health benefit. That is something that people with HIV want. We need to be clear about the benefits and risks involved particularly in early stages of treatment. (US respondent)

That is one of the main concerns, there's no indication that as good [an] idea as it is, that implementation is feasible due to a lack of resources. (US respondent)

These results, perhaps more emphatically than any others, indicate the degree of divergence which can exist after reviewing the same scientific findings. Though there were common concerns, analysis shows that the divergences appear to turn on the local conditions and policies that are unique to each country and suggest that a one-size-fits-all approach to advocacy for the adoption of an evidence-based practice would not be a successful strategy; local contexts and concerns must be first understood and addressed. This is a key finding of this study and we will be returning to this issue later.

Another important issue raised during the interviews in relation to TLC+ and the HPTN 052 trial, in particular, was the broader applicability of the findings to groups not featured in the trials, such as gay men and other MSM individuals, and injection drug users. As was discussed in the literature review (see Chapter 2), one of the major evidence gaps for TLC+ is the lack of knowledge about how applicable the study is to those outside the trial group (primarily composed of heterosexual, serodiscordant couples). Generally, there was reasonable concurrence among stakeholders in the three countries that the findings were more applicable to gay men and other MSM than they were to injection drug users (Figure 4-3).

Central in the determination of whether a stakeholder believed the HPTN 052 results were generalisable was whether they believed the transmission dynamics (how infection occurred or how the chance of infection could be lowered) were the same or different for groups at high risk because of varying behaviours. If the stakeholder believed that lowering the level of HIV in the blood was necessary and sufficient for lowering HIV risk and the route of transmission was relatively less important, they also believed the HPTN 052 findings applied to gay men and other MSM, as exemplified by this response from a US stakeholder:

I haven't seen anything that suggests that there would be any reason why the finding would be different among gay men if this study were replicated in that population... I think there has been a street knowledge for a long time that if you are HIV-positive you could dramatically

reduce risk of transmission with treatment and people have been acting on that within the gay community... On the street the logic of this has already filtered out based on modeling studies and people were already being motivated by this type of information. (US respondent)

If, however, the stakeholder gave relatively more weight to the importance of distinctions owing to the route of infection (vaginal versus anal intercourse versus intravenous drug use) they were more likely to believe that the HPTN 052 results did not generalise across populations, to be uncertain about the generalisability, or to believe the results could be generalised, but with qualifications. Those believing the results applied to injection drug users hinged their optimism on the overall efficacy of the HPTN 052 findings, particularly in the US. In fact, US stakeholders were also unique in the extent to which they believed the transmission dynamics were the same despite the different routes of infection. The following quote from a US stakeholder reflects both the belief that ARV-based prevention would be an effective strategy for injection drug users and that lowering viral load is the most important issue to consider:

It's interesting you are asking the questions this way because I'm not sure that the evidence is suggesting it would be different for other groups of people. If you are transferring through a dirty needle it would be about transmission of the virus. Of the unanswered questions coming out, I don't think this is the area that needs to be focused on. If it decreased the viral load in some it seems like it would work for everyone. (US respondent)

Other stakeholders, such as the two quoted below from India and South Africa, were simply not convinced that the infection route should be discounted and that it could limit the effectiveness and applicability of ARVs as prevention for injection drug users:

There is not enough evidence to relate the same correlations regarding sexual transmission rates with blood transmission rates. (Indian respondent)

[The stakeholder] expressed strong concern about IDUs' [injection drug users'] ability to adhere since there is a 'non-rational component' to their decisionmaking processes. We would need an adherence program like DOT [directly observed therapy] to compensate.[25] A daily prevention strategy may be 'impractical' in this group and would 'probably not produce the same result'. Since IDU is an illegal practice, there may be practical and ethical roll-out challenges. (South African respondent)

Finally, we also asked stakeholders about their views on a *Lancet* editorial that had been published before we argued that HIV/AIDS prevention funds should be shifted from less effective interventions to evidence-based prevention interventions such as the use of ARV-based treatment as prevention. Despite expressing concerns that funding of such an expansion could prove difficult, the editorial states:

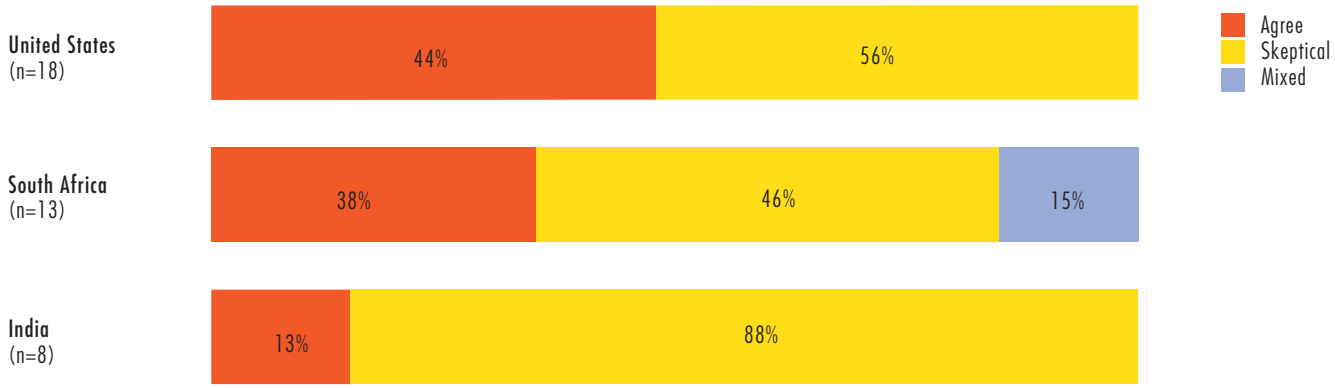
Findings now need to be translated into policy and action. Agencies such as President's Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis and Malaria need to reassess their prevention portfolios and consider diverting funds from programmes with poor evidence (such as behavioural change communication) to treatment for prevention. (Lancet, 2011)

We asked stakeholders if they agreed with this opinion in light of the HPTN 052 trial findings. Their replies are shown in Figure 4-4.

Not surprisingly, given the previous findings, stakeholders in India disagreed the most (88%) followed by 61% of stakeholders in South Africa who disagreed or had mixed opinions on the matter. Even in the US, the country where the stakeholders had the highest level of agreement, the majority (56%) still disagreed with the *Lancet* editorial. The main reasons across countries for disagreeing with funding reallocation was a perceived need for a balanced strategy, the likelihood that the demonstrated effectiveness would not carry over to local contexts, and the need to consider cost-effectiveness as well as clinical effectiveness when determining funding allocations:

[25] This is when trained health care workers or other designated individuals (excluding a family member) provide the medication and watch the patient swallow each dose.

Figure 4-4
Level of agreement with the Lancet article advocating the transfer of funds to TLC+ strategies



Note: Categories with no (0%) responses for stakeholders in a given country are not represented.

We are in a prevention revolution, and the strategic pooling of funds is important. Prevention is a continuum, with types ranging from before infection, during infection, post infection, and others. A combination of strategies and a comprehensive toolbox is imperative for effective prevention. (Indian respondent)

We need to save lives and treat who needs treatment as a first priority. This needs to be balanced with prevention efforts though, because 'if we focus only on treating people, we won't be able to keep up with new infections'. In terms of which prevention strategies to focus on, the decision needs to be based on 1) evidence, and 2) setting – a one-size-fits-all approach won't work – for instance, circumcision may be best in one setting, another intervention in another setting. (South African respondent)

As we develop more knowledge, we always have to assess our investments. We don't continue to use AZT [azidothymidine] as our primary treatment. Why would we continue to use prevention strategies that aren't as effective? (US respondent)

This is ridiculous. Only 2–3% of the AIDS portfolio is spent on prevention. Prevention money continues to go down. Switching funds would result in total elimination of prevention funds. We would go back on prevention successes. (US respondent)

This is the biggest mistake that we can make! Only 3% is prevention. Most HMOs [health maintenance organisations] are working to re-focus prevention efforts. Costs will go up if we pull money from prevention for treatment. Prevention is cheaper. (US respondent)

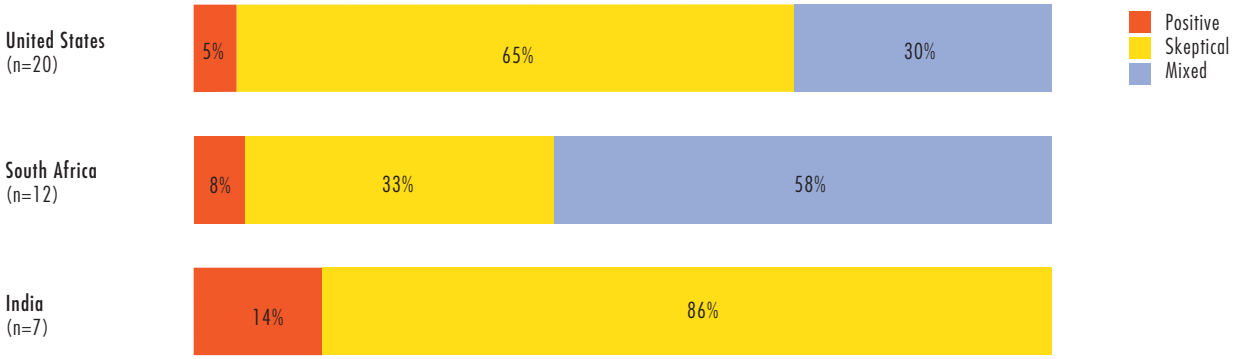
Though there are clearly different views and reasons for them among stakeholders in all three countries, our findings suggest that overall there is not strong support in these countries for switching prevention funding priorities on the basis of this one clinical trial, as persuasive or as striking as the findings might be.

Views from the grasstops about PrEP

Before presenting the findings for this section, it is worth noting that as with many aspects of this study, the evidence changed in the midst of conducting the interviews. Partners PrEP and TDF2 both reported findings in July 2011 and arguably changed the way people thought about the evidence for PrEP and corresponding information needs. Nevertheless, our data present a useful snapshot in time during this dynamic and tumultuous phase in HIV prevention science.

The use of ARVs as primary prevention (TLC+ is considered secondary prevention or 'prevention for positives'), particularly in the case of PrEP, provoked a stronger sceptical and/or negative reaction among stakeholders than did the use of TLC+. Of the 39

Figure 4-5
Stakeholders' views on the likely programmatic and policy impacts of PrEP



Note: Categories with no (0%) responses for stakeholders in a given country are not represented.

stakeholders who replied to the question about the likely policy and programmatic implications of PrEP, only 3 (8%) stated that PrEP would have beneficial policy and programmatic implications (Figure 4-5). The majority of the remaining 36 stakeholders (23 or 64%) were sceptical. While Indian stakeholders were sceptical and pessimistic about any positive impacts of this strategy, US stakeholders began to express more scepticism as well. As with the previous question, South African stakeholders gave the highest rate of mixed responses.

Those who felt that PrEP had a positive role to play – including those who offered a mixed response – suggested that it had demonstrated efficacy or effectiveness. But this view was also often tempered by the belief that the main use of PrEP, in fact the only appropriate use, would be in high-risk populations and that it would be hard to identify such populations with certainty. As one South African stakeholder in favour of PrEP but also leery of implementation issues put it:

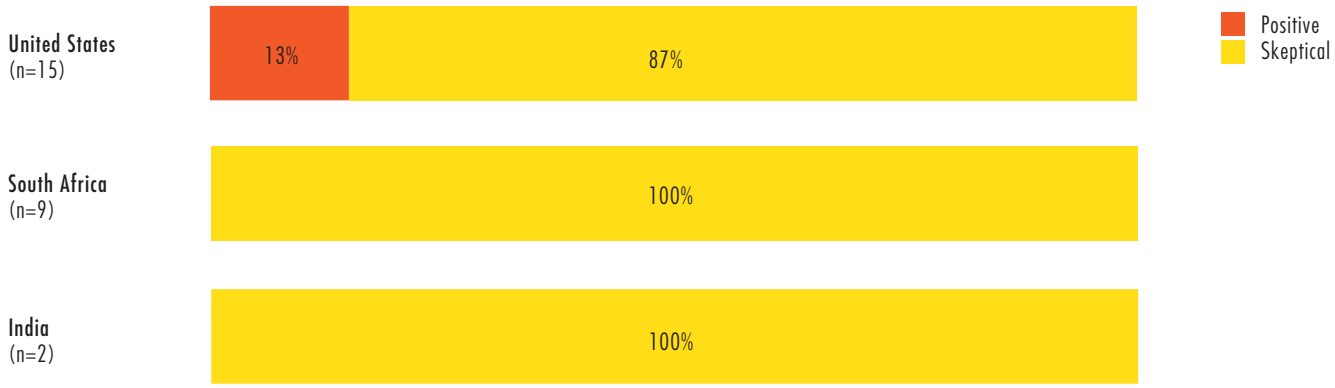
> *I can see a justification for implementing PrEP in high-risk groups [such as] MSM… However, in the South African context there are social/contextual issues that would make even this difficult [and could result in] greater stigmatization of MSM and criminalisation of sex workers. Ultimately, I think we can look at targeted PrEP use in high-risk groups, but that it won't necessarily be easy. (South African respondent)*

Although all stakeholders shared a large degree of scepticism, the underlying reasons for it diverged by country. The sole Indian stakeholder who expressed a positive opinion about PrEP based his view on its established efficacy and effectiveness. The remaining six Indian stakeholders offered multiple reasons for their scepticism, including that local circumstances and politics would be obstacles to implementation, fear that PrEP would increase risk behaviours, concerns about costs and resources, difficulty in identifying high-risk groups, and uncertainty about the effectiveness of PrEP outside the context of a clinical trial. Various local circumstances and cultural factors were cited as limiting factors, particularly to acceptance:

> *In an Indian culture that still struggles to accept condoms, it would be difficult to get the general population to accept PrEP. While risk categories based on global norms are feasible to define and accept, it will be hard for an individual to accept that he or she is 'high risk' and should take this treatment. (Indian respondent)*

Concerns about costs resources were common across all countries and were couched in the observation that the current inability to afford ART for the priority population of people already infected underscores the unlikelihood of using scarce resources to fund HIV prevention on a broad scale. US stakeholders were by far the most sceptical about costs and resources. One US stakeholder questioned

Figure 4-6
Stakeholders' views on whether the evidence for PrEP supported changing prevention policy



Note: Categories with no (0%) responses for stakeholders in a given country are not represented.

whether PrEP would be most useful for high-risk populations and its cost-effectiveness:

> *Cost-effectiveness is important. HIV-positive couples that aren't monogamous are more likely to get HIV from their main partner. Realistically there are way too many couples to put all negative partners on treatment. We need to reach the people who are so vulnerable they can't negotiate condom usage regularly… It's a great tool, but how to use it as sparingly as possible and how many resources should we devote to it [is the question]. (US respondent)*

A higher proportion of South African stakeholders than Indian and US stakeholders believed PrEP would be useful, particularly for high-risk populations, but shared the same concerns as their Indian and US counterparts about the difficulty of identifying such populations. In particular they were not convinced that the efficacy of PrEP had been established sufficiently to warrant using it widely. One South African stakeholder couched this in the context of a study – FEM-PrEP – that had been carried out in a South African locale and failed to demonstrate efficacy:

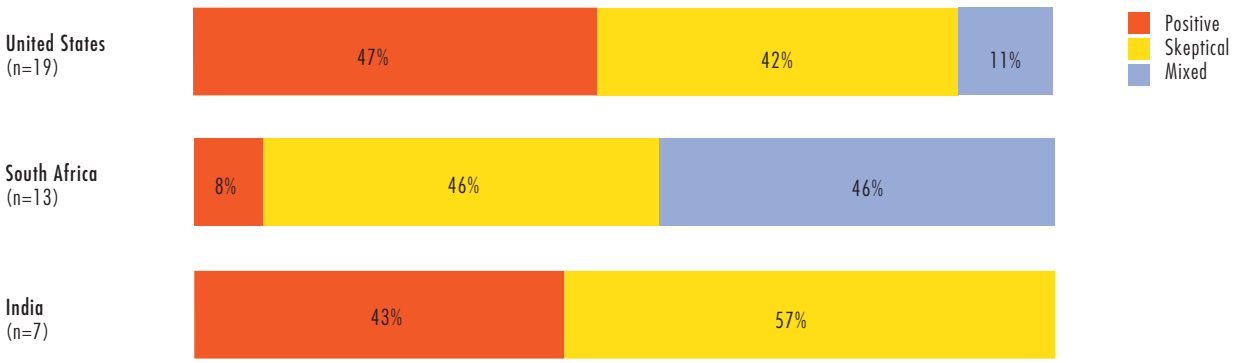
> *We already have a shortage of resources. There are currently 6–7 million people on treatment globally, and the prediction is that we'll be initiating around 30 million people globally over the next 10 years or so. And now we're talking about a massive roll-out in negatives? [I've been] one of the people who was centrally involved in arguing the case for the affordability of ARVs in South African in the 2000s, but even [I] think there just aren't the resources – it's inconceivable. (South African respondent)*

Given the degree of scepticism over implementing PrEP in circumstances beyond just that of high-risk populations – a proposition viewed as being fraught with its own difficulties – it is not surprising that the verdict on changing prevention policy in the face of the PrEP findings was a resounding, emphatic and near unanimous no (Figure 4-6).

Although they did not want to change existing guidelines, many respondents were open to changing them in the future pending the results of further study. Here are examples of statements given by stakeholders in each of the three countries of their reasons for not changing existing prevention guidelines to accommodate the PrEP findings:

> *I did not think we are ready for it now. As for the future it will depend on how effective it is. It is important to give an option to a couple, and counseling is the better and safer option than ARV. (Indian respondent)*

Figure 4-7
Stakeholders' views on the programmatic and policy impacts of microbicides



> *I am skeptical about how to use the PrEP results. I think the guidelines could be modified to include the examples above (abused women, sex workers, couples wanting to conceive, MSM who self-identify as high risk) – but how do you put that in the guidelines – at the discretion of the clinician? (South African respondent)*

> *I don't think so yet. There is still a lot we don't know. What we do with heterosexual men and women and MSM, we have some tricky evidence right now. VOICE and FEM-PrEP – we don't have good science to tell us what this means for heterosexual, HIV-negative women. We need to know a lot more. Until we do, we can't make such decisions. (US respondent)*

These results suggest that there is still more to do to ensure that PrEP is both efficacious and effective in real-world settings. This again points to the importance of considering not just whether the drugs work technically, but social and organisational factors of their implementation and effect.

Views from the grasstops about microbicides

Interestingly, though the science is least developed for microbicides, stakeholders were the most positive about the policy impact of microbicides relative to their views on TLC+ and PrEP.[26] Stakeholders in the US (47%) and India (43%) were the most positive about the likely programmatic and policy impact of microbicides (Figure 4-7).

In contrast, South African stakeholders, who usually occupied the middle position on the subjects we raised, were the most sceptical: 82% had a mixed response to questions about the impact of microbicides. Their pessimism about their efficacy and effectiveness was based on a number of different factors and as a result is hard to characterise, though it seems to be rooted in the recurring tension between efficacy shown in a trial, and effectiveness outside the clinical trial setting. Several South African respondents mentioned the results from the CAPRISA trial of vaginally applied tenofovir gel. Though some thought the results were promising because they provided the first evidence of potential efficacy of ARV-based microbicides, others believed that the infection rate among the women using the tenofovir gel in that trial was still too high, even though it was significantly lower than in the placebo condition:

> *[I am] not convinced by the efficacy of microbicides. [I think] the CAPRISA results showed the effect to wane with time. [I also think] the CAPRISA interventional arm [which received active microbicides] received additional safe-sex practices counselling and wonder how much of an impact [that had]. (South African respondent)*

> *There is clear evidence of efficacy. However, the incidence in the CAPRISA trial was mind-boggling and we need to work out what's going on. [I am] concerned about risk compensation and the*

[26] See literature review of the microbicide science in Chapter 2.

sociological consequences of a gel that people are told is protective... I wonder how the efficacy result could be translated into guidance and policy: I don't know. (South African respondent)

Among the underlying reasons for the positive opinions of stakeholders about the potential impact of microbicides was the rationale that vaginal microbicides were empowering, particularly for women, who would not necessarily have to negotiate with male partners before applying a microbicide before sex (as she would with a condom). This consideration was the main reason Indian stakeholders were more positive about microbicides than about TLC+ and PrEP. Most of the reasons for scepticism were similar to those given previously: doubts about efficacy and effectiveness, costs and resources, and mitigating local circumstances (mainly for Indian stakeholders). In addition, and uniquely among the stakeholders, South Africans were concerned about whether women would accept topical microbicides, for the same reasons as their failure to use condoms:

The only way there will be more of a chance of them ever being taken up by communities is if they are marketed as a sex toy or lubricant. If you call them microbicides, you'll sell 3 in 20 years; if you call them applicators, you'll sell 2 in 20 years… they now need to be handed over to a marketing company to consider how to advertise them as a sex toy. But [I] wonder how this could ever be done in practice. Grumpy old nurses are funny about condoms so [they] would struggle with marketing a product as sex enhancing. (South African respondent)

While sharing concerns about the effectiveness and efficacy of microbicides with their South African and US counterparts, Indian stakeholders again spoke of mitigating local circumstances or politics as major obstacles to the adoption of microbicides. These were usually related to the lack of relevant data and whether the clinical trial findings from other countries would apply to India, which could also be construed as a matter of generalisability and effectiveness. A more unique perspective on the mitigating local circumstances came from an Indian stakeholder who thought that by 'medicalising' HIV transmission, the gains realised in getting families to discuss and react to HIV/AIDS as a social issue would be reversed:

What might happen if you tell rural women to use microbicides to be safe? One must factor in family systems that are not conducive for using a female condom. Because HIV is transmitted sexually, there has to be a conversation about these topics. Anecdotally, she has seen families that don't want HIV and therefore are changing their family systems. This has led to more maternal families responding to women who report sexual harassment and domestic violence. The extreme medicalization of HIV transmission will go back on these social gains. (Indian respondent)

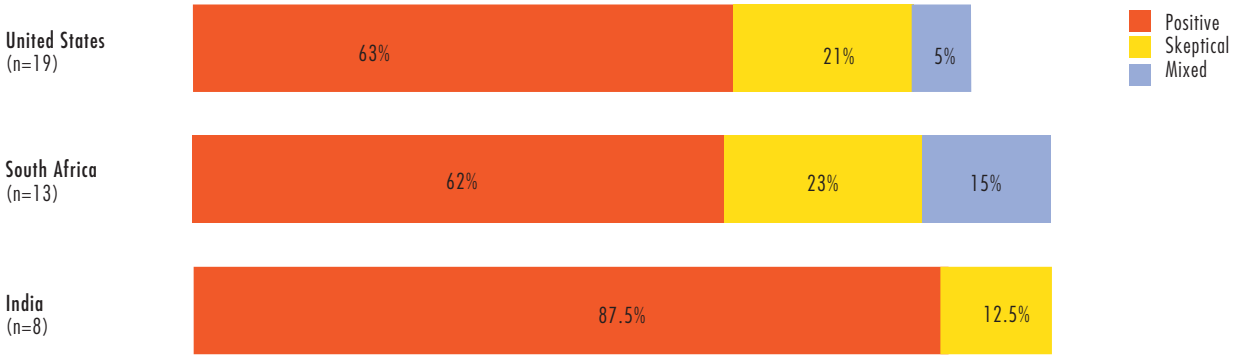
The most optimistic of all three groups of stakeholders interviewed were those in the US. They were most concerned about efficacy and effectiveness (though to a much less significant extent than the South African stakeholders) and to a lesser extent about costs and resources. One US stakeholder used the CAPRISA trial as a reference point for considering how important it would be to understand how those findings translated into different cultural and national settings:

I think it's certainly a promising development; it's just a different [means of] delivery from PrEP. We need to think about CAPRISA... we need to improve on it and we need to see if we can use rectal microbicides as well as vaginal microbicides. When CAPRISA came out, there were research questions to ask about straight women in the US. In broader studies, in multiple studies, it's challenging to figure out the US perspective on how to deploy it but it's still exciting. (US respondent)

Another US stakeholder reflected on the role of microbicides in the context of the other forms of ARV-based treatments as prevention:

I think we know less about microbicides; the concept study is very exciting. It's not as high efficacy as the other treatments but it's definitely worth supporting further exploration before policy is changed. I think, again, it would require

Figure 4-8
Stakeholders' views on whether PEP is an important part of a country's prevention strategy



careful thought about which population is this best appropriate for. We know that vaginal microbicides have been effective, not a lot of information on rectal microbicides. The issue with these three preventions (TLC+, PrEP, and microbicides) is they don't exist in isolation from each other. They are three new powerful tools, but you can't think about them alone. How do they work in the real world, individually and together? There is more that needs to be assessed. (US respondent)

Views from the grasstops about PEP

The last set of questions about ARVs as prevention were related to PEP, which, as previously described, entails taking an ARV as soon as possible after an incident whereby there has been possible exposure to HIV. PEP has been available for much longer than TLC+, PrEP and microbicides – since the early 1990s for occupational exposures and since 2005 for non-occupational exposures. Therefore, we asked respondents separate questions about whether PEP *was already an important part* of a country's prevention strategy and then *whether it should be an important part* of the prevention strategy. As similar proportions of those we interviewed reported that PEP *is* and that PEP *should be* important, and for similar reasons, we present only the findings for our question about the current status of PEP in each country (Figure 4-8).

Many stakeholders qualified their positive observations on PEP by noting that its availability was limited, mainly to occupational exposures; it was scarcely used for non-occupational exposures. One Indian stakeholder noted the limited extent to which PEP was used and then suggested that this was not a bad thing as more widespread use of PEP could encourage risk taking:

Yes, for injuries it's ok and it is used. As care providers you can re-ensure that people's interests have been taken care of. But it should not encourage risk behaviour such as unprotected sex. It should not become the same way as with other sexually transmitted diseases. It should not be that you can just go take a shot after unprotected sex and then people think everything is taken care of and [they] don't have to worry about it. It should not become anything like that. (Indian respondent)

South African stakeholders were concerned about the lack of availability of PEP, particularly for non-occupational exposures, and saw this as a fundamenal barrier that would need to be overcome before it could be part of the country's prevention strategy:

[PEP is] not efficiently implemented generally and not well implemented for rape survivors [because of] poor knowledge, poor health systems, poor monitoring, and lack of political will to protect victims of sexual violence. (South African respondent)

PEP is only available – if you're lucky – as a healthcare worker (occupational exposure) and if you're raped and report it. It is essential for PEP to be available in both of these situations. I'm not sure if it's available through any other way. (South African respondent)

Understanding the information that would be needed to map pathways

Finally, as part of determing what would be needed in order to make future policies and decisions about ARV-based prevention strategies, to 'map pathways' we asked the stakeholders which kinds of information would be most useful to them as they considered their future strategies and policies. Interviewers asked about the potential usefuleness and relative importance of seven specific types of evidence:

- discounted cost based on the cost of making HIV/AIDS a rare disease relative to money saved in treatment and lost economic output
- cost-per-case-averted (cost of preventing a new HIV infection)
- identification of main barriers to successful implementation of treatment
- experts' views on the social, economic, and clinical impact of treatment as prevention
- a calculation of health system spillovers from increased investment in treatment initiatives (eg, infrastructure benefits)
- provision of research tools and models that allow for testing the effects of different assumptions, scenarios and policies
- a clear idea of community, expert and government views of the acceptability and significance of treatment as prevention strategies.

Indian stakeholders indicated that the three most useful types of evidence would be the 'identification of main barriers', 'calculation of health system spillovers' and 'cost-per-case-averted'. They thought 'experts' views of impacts' the least useful. They made little distinction among the seven potential outputs when asked whether they would use the evidence in regional or national advocacy. Policymakers clearly thought 'identification of main barriers' most useful, followed by 'calculation of health system spillovers', but recognised this had to be made context specific. One stakeholder commented:

> *[I] presume the tool would help me ask the right questions about a new prevention strategy? But, the tools need to be specific to different kinds of experts and researchers. An epidemiologist would need different questions from a clinical/medical expert. (Indian respondent)*

South African stakeholders identified 'cost-per-case-averted', 'discounted costs' and 'experts' views of impacts' as the most useful types of evidence for their work. As 'experts' views of impacts' was rated lowest by the Indian stakeholders, this finding highlights the distinctions between the countries on their perceptions of how information can best be used to have a programmatic and policy impact. A more enthusiastic South African stakeholder described how she would benefit from this evidence:

> *[This output would] absolutely [be] of interest me. I'd love to see [it because I could] look at these views very carefully [and see if they were] novel and interesting [and] weigh them up against [my own]. (South African respondent)*

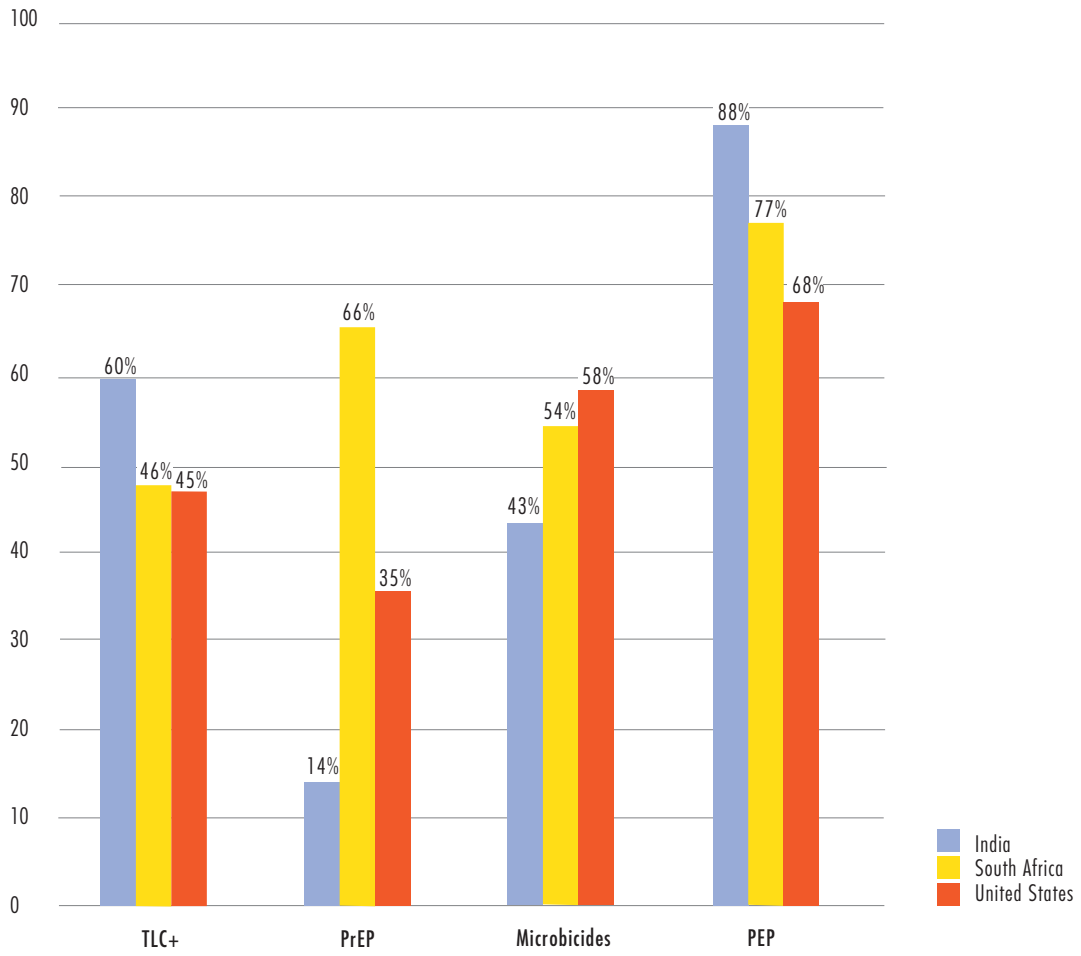
Given that one of the chief concerns of US stakeholders about implementing ARV-based prevention strategies was cost and resources, it is not surprising that one of the types of evidence they valued most for their own work would be information on how much money could be saved by making HIV/AIDS a rare disease. Many US stakeholders were enthusiastic about the prospects of identifying cost savings as a way of lobbying for resources for which there is considerable competition during a protracted economic recession, and felt the tool would broadly be useful:

> *I think that this is a critically important calculation across all three venues especially from an educational (eg AETC [AIDS education and training centre]) standpoint. It has the potential of changing people's opinions and would be powerful in helping to ask for funding from bureaucracies. (US respondent)*

Interestingly, 'calculation of health system spillovers' was chosen least by the stakeholders, although our literature review suggested it is one of the biggest gaps in the evidence base. However, one US stakeholder explained her lack of enthusiasm for this kind of evidence in the following way:

> *I'm laughing because I can see the value in so many fields the advances derived from HIV/AIDS and it's never appreciated nor truly brought to the attention of public or policymaker. Substantial gains in immune systems, rheumatology, arthritis,*

Figure 4-9
Cross-country comparison of favourable views on the strategies



psoriasis – These areas made huge strides and no one has ever appreciated that spillover. I don't think that's going to change this year, next year or the year after. People are only interested in resources. So I don't think this will be helpful unless someone can make it more attractive than it already has been. (US respondent)

Cross-country and cross-strategy comparison

Before discussing the implications of the findings presented in this chapter for the broader study, we briefly examine the relative acceptance of the four ARV-based prevention strategies covered in the interviews. Figure 4-9 provides a summary and shows the percentages of stakeholders in each country who had either a positive or a mixed opinion – indicating at least some favourable support – for each ARV-based intervention. PEP, the prevention intervention with the longest track record, consistently garnished the most support from stakeholders in all countries. But this finding is somewhat deceptive because most of those backing PEP pointed out that it is likely always to occupy a niche role in prevention and be limited mainly to use after occupational exposure. The strategies that received the next highest level of support were microbicides and TLC+. Indian stakeholders tended to favour TLC+, while US stakeholders tended to favour microbicides. South African stakeholders were divided between the two.

PrEP had the least support overall, though South African stakeholders tended to view it much more favourably than stakeholders in India and the US, though they had mixed opinions. The South African stakeholders believed that PrEP could be important, but had many reservations; moreover, not a single South African stakeholder felt that existing guidelines (which at the time of the study did not recommend PrEP use) should be changed on the basis of existing scientific data. This difference of opinion among South African stakeholders – being impressed with the research findings and yet maintaining strong reservations about changing prevention guidelines – is one of the clearest illustrations of why there need to be projects that provide pathways between research and policy to address and identify such concerns. What is perhaps even more striking is that it is in the US, where there was only 35% support for PrEP, where the policy has actually been changed to allow for it to be prescribed to individuals. Indeed, in July 2012, Truvada became the first drug to be approved for PrEP in the US, after its efficacy and safety was demonstrated in two large RCTs (iPrEx and Partners PrEP). To be taken daily and by individuals at high risk of HIV infection, Truvada must be used with other prevention methods and can only be prescribed to confirmed sero-negative individuals (FDA, 2012). This policy decision was taken after we had completed our interviews, and is yet another example of how the policy and scientific context is dynamic and constantly shifting, posing even more challenges than those that already exist for decisionmakers.

Discussion of the grasstops perspectives

The findings presented in the preceding sections support a number of general conclusions relevant to how scientific information is presently interpreted in the field of HIV prevention and how that information can be developed and disseminated to increase its use in shaping policy and programmes. The most significant conclusion is that scientific data alone are necessary but not sufficient to bring about policy change, no matter how compelling the findings. In other words, it is not just the physical technology that matters – the social arrangements and institutional and organisational contexts are important, too. Take, for example, the discussions about the HPTN 052 clinical trial where there was a 96% reduction in the rate of HIV infection for serodiscordant couples started earlier on ARVs. This is a very striking scientific finding, and yet the US was the only country in which a majority of stakeholders thought that treatment guidelines should be changed as a result. Not a single stakeholder in India believed this and many South Africans were sceptical or had a mixed opinion on the matter.

While part of the scepticism simply reflects caution and a reluctance to change course without multiple studies supporting that change, there is perhaps merit in the view that wholesale policy and programmatic changes that could affect millions of lives should not be made in response to a single study, especially when that study was carried out in a different country. Moreover, as discussed in our review of the literature (see Chapter 2), the HPTN 052 study mostly enrolled heterosexual couples engaged in vaginal intercourse. We don't know what the efficacy would be for different populations, such as unstable couples; gay men and other MSM, and transgender individuals; sex workers; and so on. Differences in local circumstances, particularly sociocultural differences in the make-up and nature of sexual relationships and liaisons, were often important mitigating factors for the more sceptical stakeholders. Context matters and those conducting replication studies with local population(s) of interest need to do more than prove the efficacy of the strategy, and whether the technology or drug works; they need to explore how the strategy would be implemented in a local context and what social arrangements are needed to support it in order to make it more than just efficacious, but also effective.

A second observation is that the stakeholders from the different countries had different opinions, so specific insights cannot be generalised across countries. Although we can say that many stakeholders in every country were sceptical about the immediate impact of the scientific data on ARV-based prevention strategies, they had different reasons for their scepticism. Looking at the exact same data and reports, stakeholders in India, South Africa

and the US often came to very different conclusions about the implications of the findings and their relevance for HIV prevention and treatment policies in their countries.

These divergences were driven less by unique concerns – all stakeholders cared about issues such as costs, resources, efficacy, effectiveness, adherence and resistance – than by the weight or priority given to any one of them. Hence, arguments that might be persuasive in one country, such as the cost-effectiveness of ARV-based prevention in the US, might have little impact in another where stakeholders placed more importance on the possibility that a particular form of ARV-based prevention could increase risk behaviours or be ineffective because women have less power than men to negotiate the parameters of sexual relationships.

A third observation is that although stakeholders' views on adopting a policy of using ARV-based prevention varied, as described above, their opinions on some matters were consistent, most notably that of costs and resources. Because many people who are already infected with HIV and should be treated under current guidelines cannot get the drugs they need because of lack of access and/or insufficient funding, it was hard for many stakeholders to justify delivering ARVs to HIV-negative people, even those at high risk. Moreover, it was also difficult for some stakeholders to accept that cheaper prevention mechanisms, such as condoms, would not be sufficient.

Cost and resource concerns also came into play when stakeholders considered whether funds should be shifted to ARV-based prevention from other prevention strategies, such as behavioural counselling and condom distribution. Since ARV-based prevention strategies are likely to be significantly more expensive than others, the funding for other prevention activities would likely be affected. Therefore those expressing this concern argued that clinical effectiveness should not be the sole determinant of policy; cost-effectiveness is an important consideration as well. US stakeholders in particular pointed out that studies aiming to influence policy would be more persuasive if they included measures of cost-effectiveness and cost-per-case-averted, especially if comparable measures for existing interventions were also provided.

Conclusions and looking forward

The key stakeholders – the grasstops – were concerned about costs and resources, strength of data on efficacy and effectiveness, the importance of local circumstances, and the need for details about changes to priorities, and these issues are all interrelated. Indeed local circumstances can be viewed as a special case of the efficacy–effectiveness dichotomy as stakeholders were sceptical that the findings could be generalised to different types of epidemics. And although many could envision changing priorities to broaden the limited use of ARVs as prevention for high-risk groups, they had important questions about how to determine exactly who would be at high risk. Would it be all gay men and other MSM, for instance, or just some? Would it depend on the local population or on transmission patterns?

None of these issues will be fully addressed without implementation studies which can show the interplay between efficacy and effectiveness and indicate what additional resources and support from local organisations and institutions will be required. Our findings suggest that much of this will be culturally and context specific and that further research and evidence is needed in order to understand what is going to be most useful for each community.


5
SNAPSHOTS FROM
THE EXPERTLENS

Complex policy decisions require input from experts from a wide range of disciplines and backgrounds. ExpertLens is an online methodology for harnessing the wisdom and insights of a large number of geographically dispersed individuals with different sets of knowledge and levels of expertise.

Introduction

The purpose of using an ExpertLens survey in Mapping Pathways was to understand the perspective of a diverse group of research stakeholders on the 'fault-lines' in the evidence base for the use of ARV-based prevention strategies. By fault-lines, we mean critical perspectives from researchers in the field about where they agreed about the relative strength of the evidence base, and where they felt it needed further strengthening. In contrast to the grassroots and grasstops, which primarily highlighted the information people in communities or making decisions still needed, the ExpertLens provided specific information about which kinds of conditions could be crucial to the success of the strategy, and what kinds of evidence experts were already using to make those distinctions. By bringing together experts from three different countries, we sought to identify whether, how and why different perspectives on the evidence might differ across different types of experts in different communities.

We asked 32 experts from South Africa, India and the US a series of questions about the patient-related, social, economic and clinical delivery conditions that may affect the relative success of any of the four ARV-based prevention strategies. Participants included health clinicians, epidemiologists, AIDS policy advocates and policymakers. What distinguished this group from the grasstops was the participants' strong focus on research and evidence. In this chapter we will briefly outline the ExpertLens process and why this approach was suited to the Mapping Pathways project. We then discuss the findings and insights gained from the ExpertLens and draw out the implications for our project as a whole.

ExpertLens methodology

ExpertLens is an online variant of the traditional Delphi approach

ExpertLens is an online variant of the Delphi approach (Dalal et al., 2011), which was developed over 60 years ago (Dalkey and Helmer, 1963).[27] In a traditional Delphi process, participants respond to a survey anonymously, the results of which are combined and fed back to the group. Participants discuss the combined group results and compare them to their own individual responses. After discussion, the participants have the opportunity to refine their responses through a second survey. This process can be repeated until a conclusion is reached (Van de Ven and Delbecq, 1974). The Delphi process can be used to achieve consensus, and can also yield insight into where the major points of agreement and disagreement lie.

A traditional Delphi is recommended for 5–20 participants, but the ExpertLens can incorporate more than 100 participants who may be geographically dispersed. Thus we could engage a diverse, multi-disciplinary panel of leading experts in the field of HIV/AIDS research and policy analysis from around the world in a meaningful and productive way. Moreover, we were able to provide a forum where these experts could engage with each other. ExpertLens therefore allowed for both a structured way to find out *what* the experts in our study thought about ARV-based prevention strategies and provide an interactive way to find out *why* they thought about things in the way they did. It is their expertise and the diversity of their opinions which drove the analysis and emergent insights into their views.

Overview of ExpertLens approach

ExpertLens proceeds over three rounds (Figure 5-1). In Round 1 participants respond to a set of predetermined questions. In Round 2 participants familiarise themselves with the answers given by others and discuss the group responses via anonymous online discussion boards. Finally, in Round 3 participants

[27] ExpertLens was developed by the RAND Corporation.

Figure 5-1
The Mapping Pathways ExpertLens process

respond to the questions again, and have the opportunity to modify their original answers in light of the group discussion.

The group's final answer is determined statistically by analysing the last set of responses provided by each individual. For Mapping Pathways, the aim of Round 1 was to elicit the individual views of the experts on the different strategies and the different types of conditions which could affect the ultimate 'success' of the given strategy. Experts were given nine days to complete Round 1.[28]

In Round 2, experts were provided with a summary comparing their own answers with those of the entire group. Over a 12-day period they could engage in anonymous online discussions about the questions with the entire group of experts. The Mapping Pathways project team monitored and facilitated the discussion during this round. The discussion in Round 2 allowed them to explore issues in a way that is not possible within a structured question set. For example, diverging views on strategies were identified in real time, and by directing attention to points of divergence within the group, we were able to explore why particular views were held.

Finally, in Round 3, lasting 10 days, experts were asked to answer the same set of questions as those in Round 1, but this time they were free to amend any responses in light of discussions or further reflections made during Round 3.

Developing the ExpertLens survey

The framework for the question set was ultimately designed to explore the importance of various sets of conditions to the success of the four prevention strategies. The sets of conditions reflect the factors which the research team thought were important to the policy decisionmaking process based on their prior expertise and other emerging streams of work in the Mapping Pathways project (preliminary literature reviews, interviews and survey data).[29] The five conditions were:

- individual or patient-related conditions
- individual groups for which the strategy would be most successful
- socio-economic factors
- delivery conditions
- (un)intended outcomes most likely to arise as a result of the strategy.

[28] We initially planned to have each round running for one week, straight after each other (Round 1 on 20 September 2011, Round 2 on 27 September 2011, Round 3 on 4 October 2011), but as we had low response rates at the end of each week, we extended each round (Round 1 on 20 September, Round 2 on 29 September, Round 3 on 11 October). The ExpertLens closed on 21 October 2011.

[29] Careful deliberation between the Mapping Pathways partners resulted in at least 20 versions in order to achieve a tone, style and substance of the question set which would frame the analysis appropriately.

Box 5-1
Example of questions for TLC+

1. If an individual tests positive for HIV and is immediately linked to care, including being put on ARV drugs, which of the following related to the patient's condition and ongoing care are important to ensure the patient does not transmit HIV to others (onward transmission)?
   (Please rate the importance of each option, where 1 is not important and 6 is extremely important)
   - clinical and biological reliability of ARV drugs to reduce onward transmission
   - high patient compliance and adherence to ARV drug regimen
   - patient avoiding HIV high-risk behaviours (disinhibition, unprotected intercourse, injection drug use, etc).
2. For which group of individuals would a TLC+ strategy be effective in preventing onward transmission?
   (Please rate the importance of each option, where 1 is not effective and 6 is extremely effective)
   - heterosexual individuals
   - intravenous drug users
   - gay men and other men who have sex with men (MSM)
   - serodiscordant, heterosexual couples
   - serodiscordant, gay men and other MSM couples
   - sex workers (male, female or transgender).
3. Overall, which set of conditions do you think are most important for the effectiveness of TLC+ in preventing onward transmission of HIV?
   (Please rank in order of importance where 1 is least important and 3 is most important.)
   - clinical and delivery conditions (eg counselling services, testing kits, suitable clinical guidelines, and presence of skilled medical and clinical staff)
   - patient-related conditions (eg reliability of drugs, patient compliance, decreased risk behaviours, individual profiles)
   - social and economic conditions (eg strong healthcare system, committed finance, cultural acceptance, and co-implementation with other strategies).
4. When implemented as policy, different ARV-based prevention strategies are likely to have indirect and unintended outcomes. How likely are the following indirect outcomes to occur as a result of a TLC+ prevention programme being implemented at a national, regional and/or local level?
   (Please rate the likelihood of each option, where 1 is not likely and 6 is extremely likely)
   - changed family and community structures and dynamics (eg intimacy, conception practice, community cohesion)
   - greater health inequality and disparity in access to health resources
   - improved infrastructure and healthcare system benefits
   - increase in population-level HIV risk behaviours
   - increased likelihood of drug resistance emerging at a population level
   - rise in unintended side effects across the population (eg damage to liver as a result of long-term ARV use).

The question set probed these conditions for each of the four prevention strategies. An example of the type of questions asked about the patient-related conditions is given in Box 5-1.[30]

[30] Careful thought was given as to whether the questions were rating (participants rating the options discretely between 1 and 6), or ranking questions (participants ranking the options against each other). We used ranking questions when we wanted to push respondents into making choices between a set of options, and rating questions when we wanted to accord respondents the freedom to state that all of the options presented were important or unimportant.

Identifying a wide range of stakeholders for recruitment into the ExpertLens survey

In order to identify participants for the ExpertLens survey, the project partners each identified several stakeholders from the following overarching groups: clinicians, researchers, policymakers, people from industry, and patient advocacy and coalition groups. Drawing on our collective contacts and knowledge of the field, we identified 45 potential participants from the US, 29 from South Africa and 31 from India (a total potential list of 105).

Table 5-1
Breakdown of ExpertLens participant invitations and response rates

	US	South Africa	India
Clinicians	1 invited	8 invited	4 invited
Researchers	19 invited	9 invited	7 invited
Policymakers	12 invited	5 invited	7 invited
Patient advocacy and coalition groups	11 invited	5 invited	10 invited
Industry employees	2 invited	2 invited	0 invited
Total invitations sent	45 invited	29 invited	31 invited
Total 'acceptances' positive responses)	26 accepted	15 accepted	6 accepted

Table 5-2
Response rates from the ExpertLens survey[32 33 34]

	Round 1	Round 2	Round 3
Response rate	30 (32) respondents[37]	27 'accesses'; 17 respondents made at least one comment[38]	17 respondents[39]

1. One participant only answered 3 three questions, and another answered only 11 out of 36 questions.

2. 13 accessed more than once

3. One person only answered 1 question, and another only 11 questions, one 17, one 28 questions. Thirteen respondents answered more than 30 questions. The responses of these 13 respondents were used in the analysis, and although not all of them answered every question, averages were calculated to incorporate the number of respondents per question individually.

We invited these 105 people to become participants, and 47 accepted (see Table 5-1). Those 47 were enrolled in the study and assigned a confidential ExpertLens User ID to allow us to track individual responses, discussion posts and logins.[31] Of the 47 enrolled, 32 participants engaged in some way in the exercise. This was a very high response rate compared with the rates of response most experienced survey researchers are accustomed to. The response rates for each round are summarised in Table 5-2.

Despite the attrition over the course of the exercise, as the reader will see in the findings, it is the expertise of the participants and the nature of their interactions that give rise to the insights offered by ExpertLens – not just the number of participants.

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31 This unique reference was unknown to the study team, but allowed us to track individual survey responses, discussion posts and number of logins.

32 One participant only answered three questions, and another answered only 11 out of 36 questions.

33 There were 13 'accesses' more than once.

34 One person only answered one question, another only 11 questions, one 17 and one 28 questions; 13 answered more than 30 questions. The responses of these 13 respondents were used in the analysis, and although not all of them answered every question, averages were calculated to incorporate the number of respondents per question individually.

A note about the analysis

Before discussing the findings from the ExpertLens survey it is worth summarising the different types of analysis that will be presented in the subsequent pages. First, we used both 'median' and 'average' ratings and rankings to understand what the overall group thought. We calculated median scores for the entire group for each question and reported back to everyone at the end of Round 1. Respondents could then reflect on the group's median score in relation to the score they provided as individuals. This helped them to contribute to discussions in Round 2. We also used average scores, which are more sensitive to extreme responses than median scores, and noted the distribution of the scores, for example whether they were uniformly distributed with equal numbers of all scores for a given question (eg three 1s, three 2s), or a skewed distribution with more of one score than any other. We used the results in the analysis to draw additional insight.

Second, when we discuss the results of the survey we refer to levels of 'agreement' or 'disagreement' among the group. This is the extent to which participants respond with similar answers, indicating agreement, or give a range of different answers with none emerging more frequently than another, indicating disagreement. [35, 36]

Finally, we will also refer to 'convergence' or 'divergence' of answers. This is where the group's responses differ in the degree of agreement they show between rounds. So, if the group's Round 1 answer shows disagreement, but by Round 3 the group's answer shows agreement, we might say there is some convergence, or even that the group reached consensus on that point.

Findings from the ExpertLens survey

Unlike the other chapters and 'snapshots' of evidence throughout this book, we will not present the findings here by type of ARV-based prevention strategy. The purpose of the ExpertLens survey was to understand the fault-lines in the debate as a whole, exploring where these differed by type of strategy, and where they cut across strategies, as in reality none of these strategies would likely be implemented in isolation. Thus, the findings are presented by the type of implementation issue and condition we explored.

The importance of individual conditions to prevention strategies

The individual conditions examined covered issues related to how ARVs work biologically within the individual, as well as factors related to the individual's characteristics and behaviours:

- clinical and biological reliability of ARV drugs to reduce onward transmission
- high individual compliance and adherence to ARV drug regimen
- individual avoiding HIV high-risk behaviours (eg, disinhibition, unprotected intercourse, injection drug use)[37]
- heterosexual individuals
- intravenous drug users
- gay men and other MSM
- occupational health workers
- serodiscordant, heterosexual couples
- serodiscordant, gay men and other MSM
- sex workers (male, female or transgender)
- victims of sexual assault.

There were five headline findings from this section of the survey. First, for all the prevention strategies, there was agreement on the importance of adherence and biological reliability of ARVs, but disagreement on risk behaviour. When asked to rate the importance of reducing onward transmission of HIV to others, 70–80% of experts thought individual compliance and the underlying biological reliability of transmission reduction were very important to the

[35] Thus the distribution of the responses was unimodal, with one unique score, or mode, emerging from the responses.

[36] This is indicated by a uniform or bimodal distribution.

[37] As mentioned earlier in this book, the very idea of 'risk behaviour' is constantly evolving and changing, much like the dynamic nature of ARV-based prevention strategy research. Thus, we present our findings here, and the comments people made about them, in the context in which they were made, fully recognising that they were snapshots in time and may not reflect the more nuanced understanding of the risk and prevention behaviours emerging today.

Figure 5-2
The relative importance of individual-related conditions for all strategies (median scores)

success of a prevention strategy. However, they were divided about the importance of risk behaviours of the individual. This finding held for all of the four prevention strategies and there were no discernible differences in the level of agreement across strategies (Figure 5-2). Experts questioned who would monitor adherence and resistance, and how to do this accurately. Two participants commented that this is an uncertain issue. For example, adherence in the iPrEX trial was noted as a cause for concern with regards to PrEP strategies:

> *When iPrEx asked people if they took the medication virtually everyone said they did, but in fact half did not, as measured with blood levels. (South African respondent)*

One expert was not troubled about the public health implications of individual compliance:

> *If the patient chooses not to take their medication, that is different, but I would not hesitate to prescribe the treatment. (South African respondent)*

The views about the importance of adherence and drug resistance were consistent over all rounds, and there appeared to be growing convergence about how important compliance and the biological reliability of ARVs are to prevention strategies. It seems that the interaction process led the group to stronger consensus.

Second, we found that disagreement regarding risk behaviour reflected uncertainty about the impact of a prevention strategy on individual behaviour. We found risk behaviour and its effect on any given strategy to be a contested issue and it attracted a high number of posts and comments. Some felt that there was little evidence that risk behaviours would increase:

> *In addition to iPrEx, in the trials of VMMC [voluntary medical male circumcision], there has been little evidence of behavioral disinhibition. (US respondent)*

> *It is clearly how we do the messaging and there is no evidence that effective HIV prevention options have increased risky behaviour. (US respondent)*

Another participant suggested that behaviour may differ for some population groups:

> *iPrEx actually showed possible reductions in risk behaviour – expressed desire for fewer partners and increased desire for monogamy among MSM. (Indian respondent)*

One participant felt that risk behaviours would be encouraged by implementing a prevention strategy:

> *You run the risk that the most risk adverse will get the idea that they don't need to protect themselves because they can just pop a pill, particularly after the slick marketing and sales campaigns that Gilead would do if they get FDA [Food and Drug Administration] approval of a prevention indication*[38]*… It has been well documented for decades that condom use can be adversely affected by anything that gives people a false sense of security or the thought that they are not part of the at-risk group. (South African respondent)*

Another participant offered a portrayal of real-world behaviour that is not readily captured in clinical trial research:

> *Men don't like condoms. They don't need much justification for not using them. If they take a serious medication everyday it is because they don't intend to use condoms. (South African respondent)*

Many commenting on this issue pointed out that risk behaviour was hard to measure, and often our data on the matter are inaccurate:

> *Self-reporting about sexual matters is flawed based on the shame-based culture we live in. People tell the study monitors or their doctors what they think they want to hear, particularly when they are being paid to do so.*[39] *(South African respondent)*

In addition, the nature of clinical trials lends itself to recruiting risk-averse individuals, making it harder to generalise about behaviour in the general population:

> *In regards to prevention strategies, it tends to be more risk adverse individuals who embrace these strategies and remain risk adverse even with the use of a new strategy. (US respondent)*

> *A major challenge for implementation of any biomedical prevention strategy is to engage the least risk-averse individuals [as well as the most risk-averse]. (US respondent)*

This uncertainty and disagreement grew over the course of the ExpertLens, particularly in relation to PrEP. In Round 3 we saw even greater disagreement, suggesting that the discussions summarised above had led to participants becoming even more entrenched in their differing views (and thus expressing more extreme perspectives).

Our third fininding was that there was high disagreement about the usefulness of the strategies for individual groups. The exception was for the following groups, about which there was strong agreement among participants when we looked at the average scores:

- TLC+ would be useful for serodiscordant couples.
- PEP would be useful for health workers and assault victims.
- Microbicides would be useful for heterosexual individuals and serodiscordant, heterosexual couples.

Expert opinion about other population groups was divided, but generally the experts felt that prevention strategies would be effective for most of them (as shown in Figure 5-3). The cautionary note offered by our analysis is that while the median scores shown in Figure 5-3 are high, the disagreement among experts is also high (which is not shown in the figure). There was particularly little agreement about how effective the PrEP strategy could be for any of the groups listed.

Fourth, we found that the experts valued clinical trial evidence but noted difficulties in generalising

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38 Since this exercise was conducted, Gilead has received FDA approval for Truvada, but to date Gilead has appeared rather reticent to market Truvada and there has been very little uptake of it. The company is also providing a drug access programme for people who don't have health insurance to get Truvada as PrEP for free – and to access free HIV testing and free condoms as well; see https://start.truvada.com/.

39 This respondent pointed out that this could be mitigated to some extent in the clinical trial protocol: 'Situations when the counsellor or doctor interacts in confidence and people can trust the counsellor/doctor, responses are more likely to be true.' The respondent gave no reference point for the view that people will be more truthful with a trusted doctor, as studies elsewhere have shown this is not always the case.

Figure 5-3
The relative likelihood of effectiveness of different strategies for individual groups (median scores)

to other populations. We observed that the nature of the discussions regarding the relative effectiveness of a prevention strategy for individual groups depended on the prevention strategy being discussed. Overall, it was noted that it is difficult to generalise data for ARV-based prevention strategies beyond the populations that were enrolled in the clinical trials because 'it is unknown how generalizable these interventions may be to a variety of at-risk populations, yet' (US respondent). Two participants referred to the HPTN 052 data in this regard, while there was considerable discussion on how PEP might be effective for different groups. In particular, some experts emphasised that though it is a proven strategy for healthcare workers, it might not be effective for victims of sexual assault as there were wider uncertainties that could affect its effectiveness, in particular issues like the mistreatment of rape survivors, which could be a barrier to its use:

> *Access to PEP is limited by the way in which the system (mis)treats rape survivors. (South African respondent)*

> *Many rape survivors [are unwilling] to risk reporting rape (even to health services). (South African respondent)*

One expert noted that PEP would be beneficial for all population groups as 'most HIV transmission occurs during consensual sex' (Indian respondent). But another one commented that it is 'unlikely to be an effective response to reduce overall HIV incidence' (US respondent), as it has not been studied as a public health measure and there is no evidence of its expanded coverage. As one expert noted, 'implementation for public health impact hasn't been trialled' (US respondent).

Finally, three participants noted that PrEP may be useful for gay men and other MSM, and they based this view on the iPrEx trial results, but were cautious about interpreting them: 'iPrEX recruited only MSM. It is unknown how generalisable these interventions may be' (US respondent). It was also generally agreed that more data are needed for women for PrEP. Two participants pointed out that data limitations aside, we can still make some pre-

liminary judgements about PrEP and microbicides, and the populations they will be most useful for. One pointed out:

> *Even after we have all the data and (if) we get approval, PrEP will not be for everyone, it should only be used for specific high-risk individuals or serodiscordant couples, when all other prevention messages and modalities have failed. (US respondent)*

Finally, although there was disagreement about the effectiveness of TLC+ for individual groups, there was increased agreement, and hence a tendency towards convergence, about the effectiveness of TLC+ for serodiscordant couples after the discussions in Round 3. This is interesting as the discussion highlighted the importance of the strategy for heterosexual couples on the basis of the HPTN 052 trial results. In particular, the difficulty of generalising the findings of clinical trials beyond those groups measured was emphasised, perhaps leading to more convergence of views in Round 3 and higher scores.

There was more agreement in Round 3 about the lesser importance of PEP as a strategy for gay men and other MSM and serodiscordant couples. The discussions were dominated by the usefulness of PEP for occupational health workers and victims of sexual assault (groups which scored higher), and the broader social and cultural barriers to PEP's successful uptake among a more generalised population group. Finally, there was a slight convergence about the importance of PrEP and microbicides for serodiscordant couples.

The importance of socio-economic conditions to ARV-based prevention strategies

We examined the following socio-economic conditions:

- the effect of a strong healthcare system
- co-implementation of other prevention strategies in the community
- committed financing in place for long-term delivery of TLC+
- cultural acceptance of ARVs and the removal of stigma surrounding HIV.

Given that resources, time and effort are finite, we wanted to ascertain which areas should be accorded priority. In this vein, we asked experts to rank rather than rate the options. Therefore options given a low ranking may not necessarily be unimportant, just of less importance than the other conditions put forward.

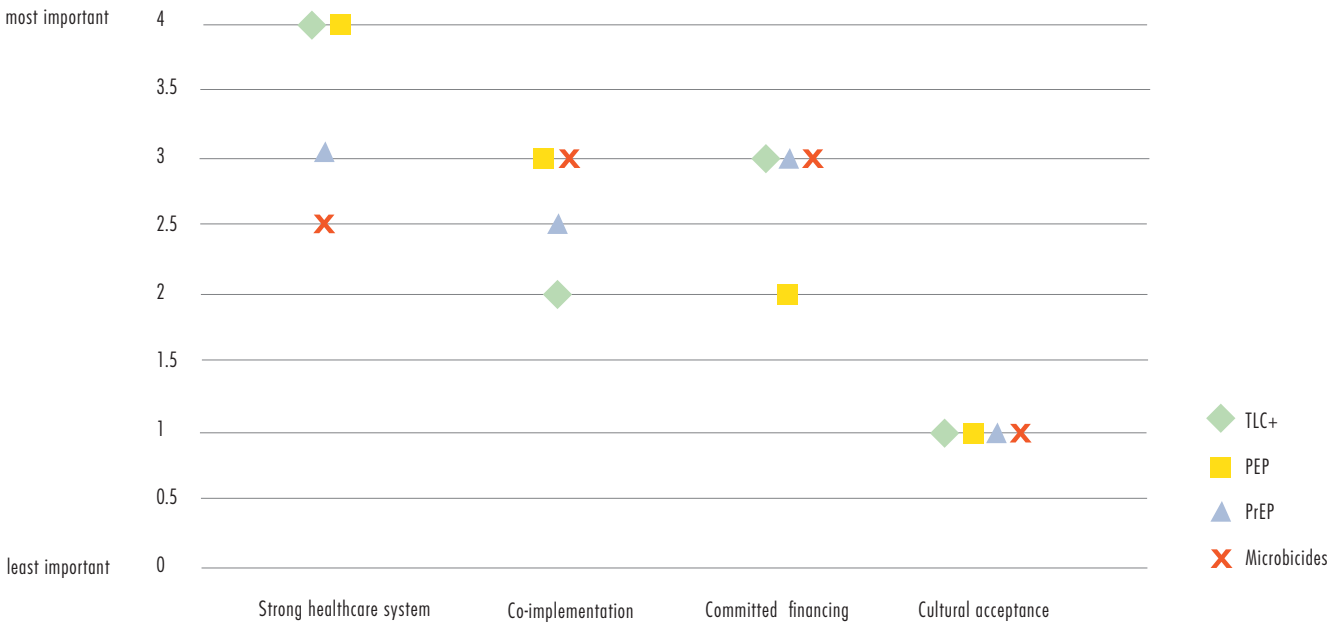
We found that cultural acceptance was least important for all strategies, and the healthcare system was agreed to be important for some strategies. Across all four strategies, cultural acceptance of ARVs and the removal of the stigma surrounding HIV was ranked as the least important condition and there was widespread agreement among the experts on this point (see Figure 5-4). However, the low ranking of cultural acceptance does not necessarily mean it is unimportant; rather that experts consider it of less importance than the other socio-economic conditions put forward. There was little change in participants' views on this in Round 3, suggesting that they were fairly well established.

In contrast, the existence of a strong healthcare system scored higher than other socio-economic conditions. A strong healthcare system was ranked most important by most experts for TLC+ and PEP prevention strategies in particular. For PrEP and microbicides, responses were more widely distributed, indicating that expert opinion was more divided over what was most important for these prevention strategies. However, in the discussions it emerged that committed finance was seen as particularly important for these strategies.

When looking at the reasons why a strong healthcare system was ranked as important, there were different points of view. One participant felt it was important in order to 'support drug monitoring', but others felt that a strong healthcare system was not pivotal to the successful implementation of strategies. For example, one said:

> *ART is being given to millions of people in countries with highly dysfunctional/weak healthcare systems. You can offer ART in the context of weaker healthcare systems, it's just harder to do, but we **have** done it (US respondent). [emphasis in the original]*

Figure 5-4
The relative ranked importance of socio-economic conditions across the strategies (median scores)



Related to the issues of a strong healthcare system is the co-implementation of other strategies alongside ARV-based prevention. It emerged in the discussion that this was considered fundamentally necessary and any future set of strategies should be mindful of the consequences of pursuing any one strategy at the expense of others:

> *Letting our guard down on condom use could do serious harm. (South African respondent)*

> *We need to ensure that we implement both in ways that complement each other. (South African respondent)*

> *We have seen how political and other barriers that limit access to ART are the very same barriers that limit access to prevention services. (South African respondent)*

We also found that other issues emerged as important socio-economic conditions for some respondents, including policy and legal contexts, better education, and engagement and community participation. The political climate and the legal context were also cited by five experts as an additional area of importance. One participant said, 'There are numerous barriers, including the law and its interpretation (reporting requirements to police officials)' (South African respondent). Another specified that 'laws that criminalize sex work, same sex and injecting drug use' (US respondent) needed to be changed; another went further: 'we must include legal reforms' (US respondent).

Although cultural acceptance and stigma removal was ranked low, its importance as a condition that should not be overlooked was highlighted in the discussions. For example:

> *We need much better leadership in prevention coming directly from the affected communities themselves. It is not up to drug companies, the CDC [Centers for Disease Control and Prevention] or academia to try to dictate this. (South African respondent)*

> ***Messaging** will play a key role in influencing perceptions about specific prevention options (US respondent) [emphasis in the original]*

Perhaps most noteworthy was the emphasis on community engagement and community participation, rather than acceptance per se. This has implications for scaling up programmes, since community-led efforts are likely to be more differentiated, and some communities may not want to pursue the pathway at all. Education and awareness was considered important for the success of PEP in particular:

> *Knowledge about PEP was so minimal and at times incorrect. This forms a barrier to access as many people are uninformed about the merits of PEP. (US respondent)*

> *Increasing awareness in [the] general population on PEP with [the] right messaging will yield results. (US respondent)*

Finally, many experts noted the low ranking of cultural acceptance and the removal of stigma about PEP, which prompted them to emphasise how important it is to take sensitivities into account:

> *Engaging communities **with dignity** is so important at all levels of HIV programming and is seldom reflected in spirit. (US respondent) [emphasis in the original]*

The importance of execution and delivery conditions to prevention strategies

There was considerable contention about the importance of delivery conditions for the success of each prevention strategy. By delivery conditions we mean the way in which the strategy is implemented and the associated conditions that might affect its relative success, such as access to follow-up services, diagnostic availability, and presence of suitable guidelines for healthcare staff and the presence of skilled medical staff. The specific clinical and delivery conditions examined were:

- the availability and access to follow-up or other counselling services
- the availability of rapid and reliable testing kits and joint screening and treatment programmes
- the presence of suitable clinical guidelines and appropriate implementation
- the presence of skilled medical and clinical staff.

Again, we asked experts to rank the options, rather than rate them. The experts did not necessarily consider those with a low rank unimportant, they just deemed them less important than the other options put forward.

We found that there was no clear consensus among respondents about which delivery conditions were more important than others for the different strategies. There were few similarities in the results across the strategies, and we report results relating to each one in turn. The median scores are shown in Figure 5-5.

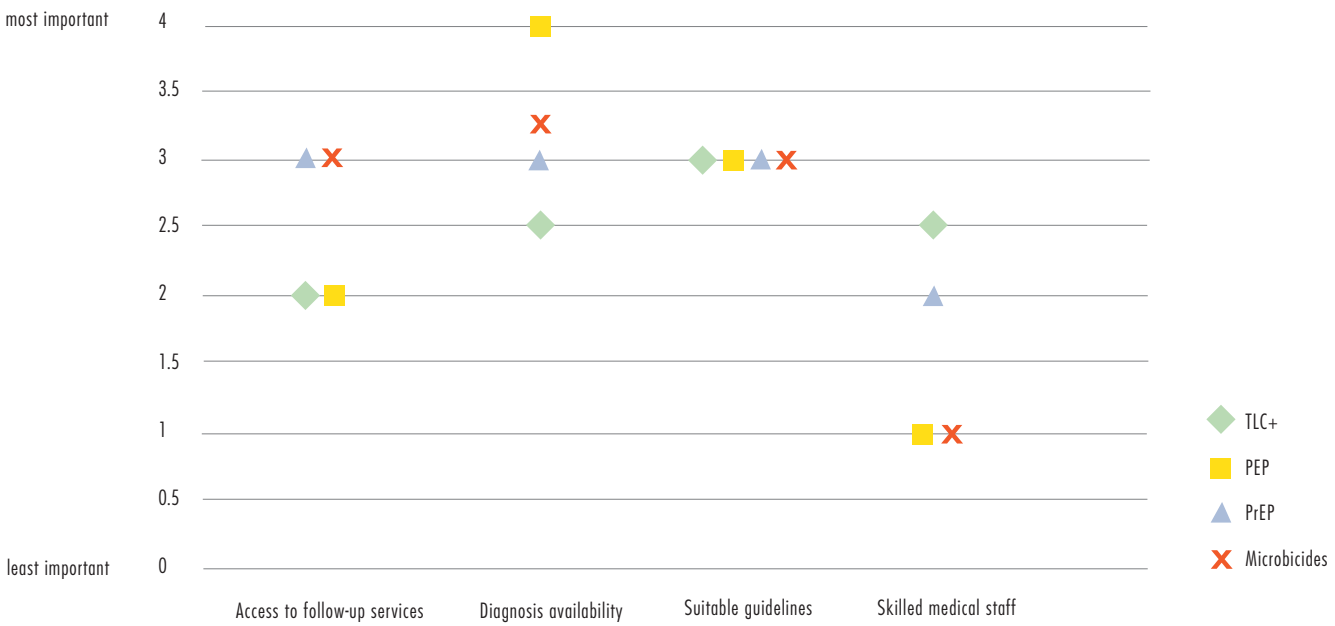
Experts tended to rank the conditions for TLC+ in the following order: presence of skilled staff, suitable guidelines, testing availability, and access to follow-up. However, within this overall ranking, there was a high level of disagreement. The distribution of responses was uneven, especially on the need for skilled staff: half the group ranked it as the most important and the other half ranked it least important. The need for skilled staff to make TLC+ strategy a success (in reducing onward transmission) was therefore highly contentious.

Of all the strategies, expert opinion was most divided over what was important for PrEP, but there was some limited agreement that the presence of skilled staff was least significant. In contrast, there was strong agreement on the most and least important conditions for delivering PEP. Availability of PEP and access to diagnostics was the most important, while the presence of skilled staff was ranked least important, though there was weak agreement on this point.

Expert opinion was divided over what was most important for microbicides; as with PrEP, respondents agreed that the presence of skilled staff was not significant. Overall, the presence of skilled staff did not seem as important as other issues, though expert opinion was highly polarised on this matter in relation to TLC+.

It is worth noting that although the presence of skilled medical and clinical staff was ranked lower than other issues, some of the disagreement about this ranking was aired and clarified in the discussion. There was a general view that while clinical and medical staff may not be essential, training of healthcare workers, front-line staff and counsellors is nevertheless very important. As one participant

Figure 5-5
The relative ranked importance of the delivery conditions across all strategies (median scores)



noted, 'we must not underestimate the need to train front-line health workers [and] volunteer counsellors' (US respondent). But others pointed out that the availability of services only at designated service delivery points is already a barrier to delivering PEP; moreover, healthcare workers' 'knowledge about PEP was... minimal and at times incorrect' (US respondent), so it was not always helpful.

In addition, and bringing out issues related to the type of trained healthcare staff needed, the importance of developing stronger regulation and better guidelines, was also noted in relation to PrEP. This was illustrated by one participant who commented: 'the concern is in countries where ARVs can be bought from a drug store without a prescription; [this] may lead to misuse' (US respondent). There were also unease about the amount of monitoring required for PrEP based on the iPrEx trial data:

> *The intensity of clinical monitoring required at present (HIV testing, etc) for a non-medical intervention makes it, at present, impractical in many resource-limited settings. (US respondent)*

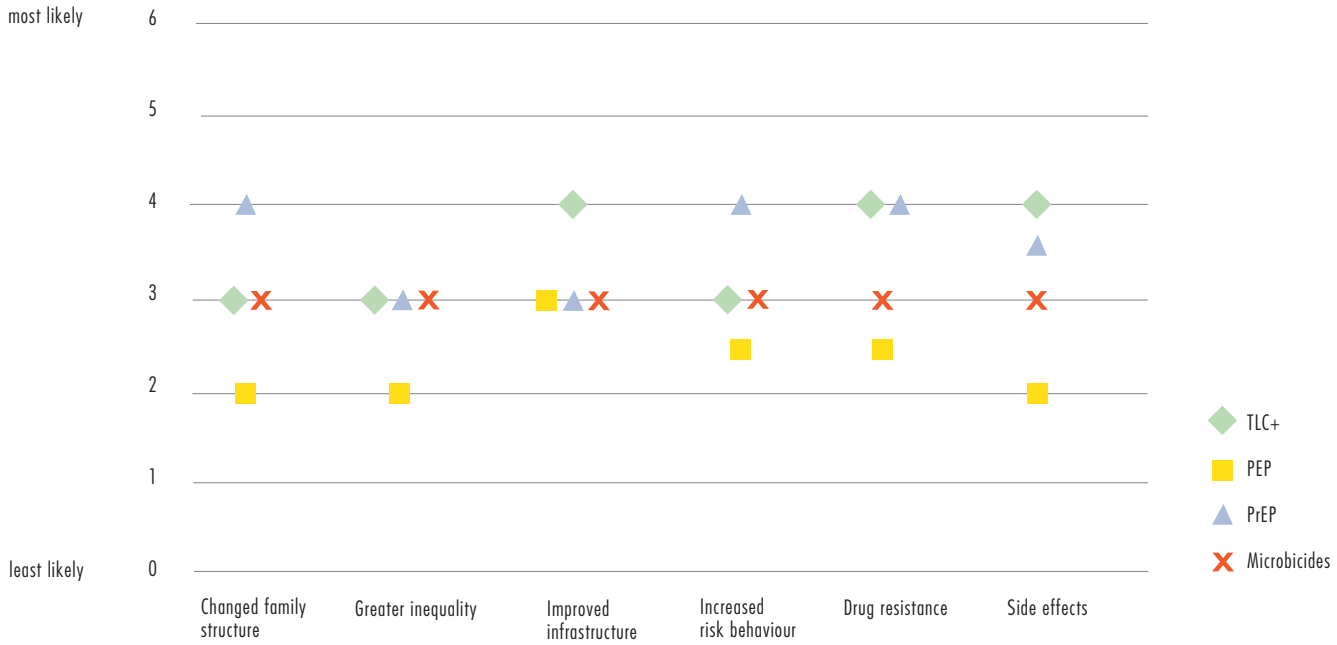
Overall, the levels of agreement did not change significantly after the discussions the experts had, although there was slightly more agreement that the presence of skilled medical and clinical staff was not important when delivering PrEP and microbicides – perhaps suggesting that other types of staff such as counsellors, healthcare workers and front-line staff could be important.

The likelihood of there being indirect outcomes from implementation of prevention strategies

The indirect outcomes examined were:

- changed family and community structures and dynamics (eg intimacy, conception practice, community cohesion)
- greater health inequality and disparity in access to health resources
- improved infrastructure and healthcare system benefits
- increase in population-level HIV risk behaviours

Figure 5-6
The relative likelihood of indirect outcomes for all strategies (median scores)



- increased likelihood of drug resistance emerging at a population level
- rise in unintended side effects across the population (eg damage to liver as a result of long-term ARV use).

We asked participants to rank the likelihood of any of these outcomes occurring for each of the prevention strategies (Figure 5-6). Participants suggested that generally TLC+ and PrEP were the strategies most likely to have the most indirect outcomes. In other words, there were more indirect than direct outcomes rated as highly likely for each of these strategies. Respondents felt that the most likely indirect outcomes would be drug resistance and side effects emerging, again in particular for PrEP and TLC+. Increase in risk behaviour was deemed most likely for PrEP users, as well as the rising possibility of greater inequality in healthcare as a result of the implementation of the strategy. TLC+ was rated most likely to lead to improved infrastructure, and microbicides were seen as most likely to lead to changed family structure.

However, underlying these median scores of likelihood is a very wide range of views, with high levels of disagreement. In the discussion, someone raised the possibility of another indirect outcome of ARV-based prevention: it could either divert resources from treatment or could attract more resources towards HIV/AIDS in general. Some experts were concerned by the share of funding that ARV-based prevention is starting to command and thought this was an indirect outcome which should be considered. They felt that ARV-based prevention strategies have already 'diverted attention away from treatment' (South African respondent) and that the 'NIH has budgeted $120 million in the US to study PrEP, which will ultimately benefit Gilead' (South African respondent).[40]

There was also a view that PrEP was akin to putting all eggs in one basket, a basket which has little

[40] We do not know where this figure comes from and are simply giving the direct quote from one of the participants here.

indirect benefits if its aims are not achieved, and alternatives are squeezed out. Some experts thought the likely lack of indirect benefits from PrEP was an extremely important issue, particularly for microbicides and PrEP, as they would have no positive indirect outcomes, and therefore are not worth investing in:

> *Microbicides and PrEP don't have any benefit beyond prevention, and if the prevention efforts are unsuccessful (due to infrastructure, marketing, stigma, biology, etc), then we reap no benefit at all. (US respondent)*

> *Official approval [of off-label Truvada] would allow it to be promoted as an alternative to condoms. (South African respondent)*

Others thought differently, remarking that ARV-based prevention, and in particular TLC+, may increase the size of the pie for all, and serve to increase attention and resources towards treatment as well:

> *By highlighting the value of ARVs as a prevention tool, momentum towards ARV access may be re-ignited. (US respondent)*

> *Treating HIV+ people reaps a prevention benefit. It's just another reason to end the waiting lists for AIDS drugs. (US respondent)*

> *Putting people with HIV on ARV is good for their health, thus the benefits of such a program are widely spread, increasing the cost-utility. (US respondent)*

> *What ART and other interventions have shown is that you can strengthen [healthcare and other] systems by implementing. (South African respondent)*

The relative levels of agreement and disagreement about the different types of indirect outcomes which might emerge from any of the strategies were not altered by the discussion. There was slightly more agreement that neither PEP nor PrEP would increase healthcare equality, nor improve infrastructure and healthcare systems, respectively. Again there was a wide divergence in views about the possibility of microbicides, in particular, leading to an increase in risk disinhibition, as there was high disagreement on this issue throughout.

The big picture: ranking the strategies across all issues and against each other

When asked how they would rank the relative importance of each set of conditions, as a whole, for each strategy, on average participants felt that clinical delivery conditions were least important for microbicides and TLC+, though the finding is strong in the case of TLC+ when we look at disagreement among the experts alongside the medial score (Figure 5-7). Individual characteristics and conditions were thought to be relatively important for microbicides, with fairly good agreement among experts on this point, and social and economic conditions appear to have the greatest importance for TLC+, and to a certain extent PrEP, but there was strong disagreement on this point.

Table 5-3 presents a summary of the average ratings and rankings, with a description of how much agreement there was for each of those.[41]

After asking questions about the ways in which specific conditions might affect each prevention strategy, we asked ExpertLens participants to assess the four strategies at a more macroscopic level:

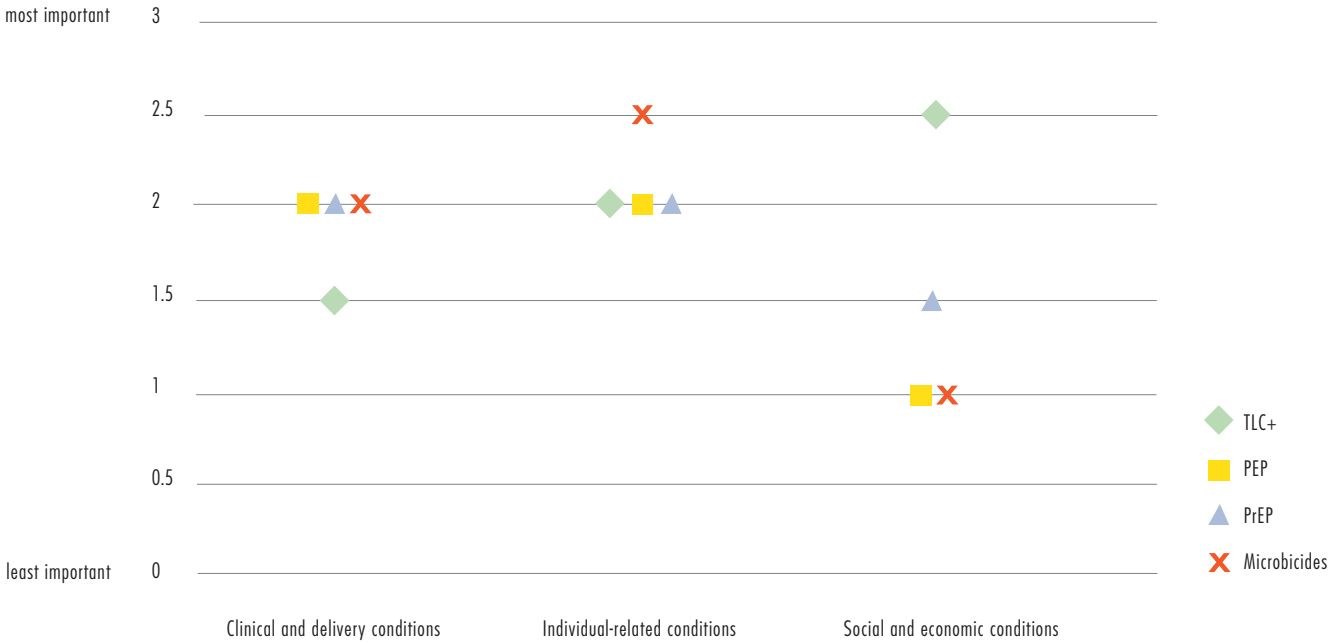
- the strength of the science underpinning the strategy
- the cost feasibility
- the readiness for implementation (as defined by cost feasibility and scientific strength)
- how funds should be allocated in their communities.

Figure 5-8 shows the answers to these questions for each strategy.

On average, TLC+ was rated as having the strongest science base and there was widespread agreement among the experts on this point. Moreover, this view did not change between the rounds. In discussion, experts cautioned that policy should move forward slowly and carefully because the science base is evolving rapidly and is yet to settle down, and it does not extend far enough, echoing views stated through-

[41] The table does not describe how these views were discussed in Round 2, nor the Round 3 responses.

Figure 5-7
The relative rankings of the importance of each set of conditions for each strategy (median scores)



out the Mapping Pathways project: 'one RCT is an insufficient basis for policy' (US respondent).

Microbicides were rated as most cost feasible on average, though it had the same median score as TLC+ and PEP. There was some disagreement on this score, however most experts ranked it as having a relatively high feasibility (either 4, 5 or 6). In discussion, several experts noted that a licensed product does not yet exist for microbicides and more investment and scientific evidence is required in order to have a discussion on this that is comparable to the other strategies. In particular, it was felt that 'microbicides show major promise but need additional investment' (Indian respondent) and that the CAPRISA trial was felt to show 'that microbicides can work, now they just have to optimize dosing timing etc and assess further in a larger pragmatic trial' (US respondent), although one person pointed out that 'the large confidence intervals (especially in CAPRISA 004), etc are all cause for concern' (South African respondent).

Experts felt that the clinical data for PrEP was unconvincing, as it had been for microbicides, and needed further investment:

> *The other approaches only have limited RCT data (with failed interventions also for microbicides and PrEP) without any proof of success with scale-up. (US respondent)*

In particular, iPrEx is a frequently cited trial that seems to illustrate a proof of concept, but needed further studies to apply results to real-world situations:

> *iPrEx is also very convincing but there are major concerns about its real-world applicability. (Indian respondent)*

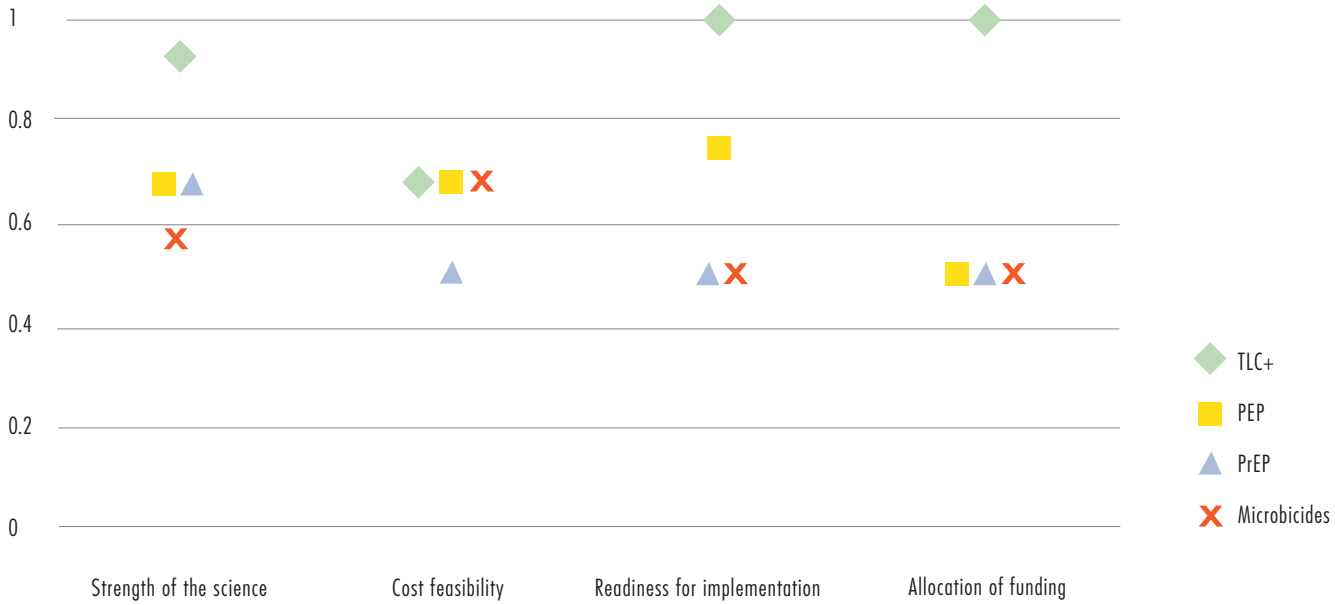
> *iPrEx was important as a proof of concept, but also raises many questions: benefit by sub-group varied widely (sexual practice and country) and the intensity of clinical monitoring required at present (q3m [every three months] HIV testing, etc) for a non-medical intervention makes it, at present, impractical in many resource-limited settings. (US respondent)*

Others suggested that the trial focused too much on gay men and other MSM populations and this complicated generalisability. Experts also noted that

Table 5-3
Summary of ExpertLens findings across conditions and strategies

Conditions	TLC+	PrEP	Microbicides	PEP	Conclusions
Patient-related conditions	Compliance and adherence, clinical and biological reliability all rated as important; disagreement on the importance of avoiding high-risk behaviours.	Compliance and adherence, clinical and biological reliability all rated as important; disagreement on the importance of avoiding high-risk behaviours.	Compliance and adherence, clinical and biological reliability all rated as important; disagreement on the importance of avoiding high-risk behaviours.	Compliance and adherence, clinical and biological reliability all rated as important; disagreement on the importance of avoiding high-risk behaviours.	Findings were the same across all strategies.
Individual groups	TLC+ was thought to be most useful for serodiscordant couples; expert opinion was divided on other groups.	Expert opinion was divided over the usefulness of PrEP for all groups.	Experts thought serodiscordant couples would find this useful; opinion was divided on other groups.	PEP was thought to be most useful for occupational health workers and victims of sexual assault; opinion was divided for other groups.	Disagreement about the usefulness of these strategies for different groups, with the exception of TLC+ and microbicides for serodiscordant couples, and PEP for health workers and assault victims.
Socio-economic conditions	A strong healthcare system was ranked most important; cultural acceptance was ranked least important.	Expert opinion was divided over what was most important, but there was agreement that cultural acceptance was least significant.	Expert opinion was divided over what was most important, but there was agreement that cultural acceptance was least significant.	A strong healthcare system ranked most important; cultural acceptance ranked least important.	Cultural acceptance of ARVs was least important for all strategies. For TLC+ and PEP, a strong healthcare system was most important.
Delivery conditions	Though ranked most important overall, the importance of skilled staff was contentious: half thought it was most important and the other half thought it least important.	Expert opinion was divided over what was most important, but there was some agreement that presence of skilled staff was least important.	Expert opinion was divided over what was most important, though many ranked suitable guidelines highly. Skilled staff was not seen as significant.	There was strong agreement that awareness and access was most important; presence of skilled staff was ranked least important.	Across the strategies, no clear consensus emerged except that the presence of skilled staff was less important than other conditions. This issue was the source of disagreement for TLC+.
Indirect outcomes	Experts rated most indirect outcomes as neither likely nor unlikely, but agreement was weak.	There was widespread disagreement, though limited agreement that there would be improvements to infrastructure and healthcare systems.	Unintended side effects across the population were rated by most as unlikely. There was disagreement about the likelihood of other possibilities.	All indirect outcomes were rated as unlikely.	It is not surprising that most indirect outcomes attracted high levels of disagreement given their uncertainty.
Conclusions and overarching conditions	There was weak agreement that socio-economic issues were most important and clinical delivery issues were least important.	There was weak agreement that clinical delivery conditions were more important than patient conditions, which in turn were considered more important than socio-economic conditions.	There was wide disagreement about the ranking of overarching conditions for microbicides.	Although there was disagreement over the importance of clinical delivery conditions and patient conditions relative to each other, there was strong agreement that socio-economic conditions were least important.	Overall, there seemed to be high levels of disagreement, though some issues of agreement emerging as listed above.

Figure 5-8
The relative ranking of each strategy against each key issue (median scores, normalised)



the latest decisions of the VOICE trial complicated matters:

> *The most recent update from VOICE makes one question whether oral chemoprophylaxis is going to be an effective HIV prevention strategy for younger women in high prevalence epidemics. (South African respondent)*

On average, TLC+ was ranked most ready for implementation, with a fairly high level of agreement. In discussion, participants emphasised the distinction between TLC+ and so-called 'test and treat' strategies:

> *TLC+ is an intervention with strong evidence to support (treatment of partners in serodiscordant relationships, increased ARVs in Vancouver, etc) and thus optimizing this approach makes lots of policy sense. Test & Treat is unproven and the multiple questions regarding this strategy leave it not yet ready for implementation. This is an approach in need of robust clinical trial data, not a Health Ministry policy document. (US respondent)*

In discussion, the large majority of experts felt that HPTN 052 results provided evidence which should result in treatment scale-up:

> *HPTN 052 seems to have the strongest evidence base because it confirms much of what we have observed anecdotally for years. (Indian respondent)*
>
> *052 provides an opportunity to make a case for treatment scale-up. (Indian respondent)*

However, there were still concerns about testing scale-up, real-world applicability of studies, and that HPTN 052 will not prevent infections transmitted in the acute phase of the disease. On average, TLC+ was ranked most ready for implementation, with a fairly high level of agreement. There was no discussion about funding allocations, though much may have been implicit through discussions on readiness for implementation.

Discussion of the ExpertLens survey

A few major issues stand out and complement the findings from other parts of the Mapping Pathways project. First, for all the ARV-based prevention strat-

egies, there was broad agreement on the high importance of each individual's adherence and the underlying biological reliability of ARVs but disagreement on how patients' risk behaviours may affect the success of ARV-based prevention strategies. As was apparent in the literature review and interviews, there is disagreement about the usefulness of ARV-based strategies for individual groups, and a call for more research. In discussing which populations would benefit from the prevention strategies, experts valued clinical trial evidence but noted difficulties in generalising to other populations. In addition, as with other perspectives within the Mapping Pathways project, there was at times a hesitancy to take the clinical trials at face value, and a concern that more needed to be done to establish a robust evidence base. This certainly came through in the final set of questions about the relative strength of the science.

Second, there was a striking lack of consensus and shared understanding about the types of conditions that would affect the strategies and in what ways. Socio-economic conditions were thought to be highly important for TLC+, and in particular there was agreement that the presence of a strong healthcare system was needed for this strategy to be successful and effective. However, no other agreement emerged for any of the other strategies on this issue and experts brought up many other issues they thought were important to consider, such as the importance of political and legal contexts, along with a need for better education, engagement and community participation to drive cultural change about HIV/AIDS stigma.

In addition, no clear consensus emerged across the strategies on the importance of delivery conditions to the success of prevention strategies. This is not necessarily surprising since we are in the early stages of implementation, and indeed when this ExpertLens was conducted there was very little, if any, implementation of the strategies apart from clinical trials. The levels of disagreement and divergence suggest that there is a strong need for further research into this area, as suggested in the literature review. It is interesting to note the somewhat surprising debate about what kind of clinical and medical staff would be required for the strategies as an example of the need to further define what kinds of conditions and skills are needed. In discussion respondents argued that while skilled clinical and medical staff may not be essential to prevention strategies, they thought the training of healthcare workers, front-line staff and counsellors is nevertheless very important. This emergent and iterative re-definition of the skilled staff category by respondents was followed by greater agreement between them on the lesser importance of clinical and medical staff in their Round 3 responses. This shows how continued discussions can help to change the way we think about and respond to these issues, and the value of bringing many diverse perspectives together to do so.

Third, a number of indirect outcomes were rated as being likely from the implementation of ARV-based prevention strategies, but once more there was very little agreement about what kinds of outcomes might result and how likely they would be. Once more this suggests that more focused research and attention is needed on these kinds of issues as they will inevitably have a bearing on which kinds of prevention strategies might be most beneficial in different contexts. Equally, they could help to avert potential problems in implementation, which could render the strategies much less effective for individuals than they could be.

Finally, despite the uncertainties and lack of consensus on the more nuanced issues, experts seemed to have clearer views when asked to make stark trade-offs between the strategies and compare them against each other. Again they differed over the perceived strengths and weaknesses of the strategies, with microbicides receiving the best average cost feasibility rating and TLC+ scoring the highest rating for strength of science and readiness for implementation. Though there were quite high levels of agreement, the ensuing discussions revealed considerable caution and reservations implicit in respondents' answers. Throughout all four perspectives and sets of snapshots from the Mapping Pathways project there has been concern about the pace of change in scientific understanding and the limited scope for generalising on the basis of one or two RCTs.

Before concluding, it is worth briefly reflecting on some of the limitations of our approach. First, we had very low levels of engagement from experts in India. Since this low level of engagement was also

observed in the grassroots survey, we believe there may be particular cultural challenges to engaging people through online forums such as those used here, which should be considered in any future study going forward. Similarly, across the whole of the ExpertLens survey we had a much higher response rate from US experts than from those in India and South Africa, even though similar numbers were recruited in the US and South Africa. Therefore, the findings should be interpreted with this caution in mind. Finally, we also had a fairly high drop-off rate between Round 1 and Round 3. This limits the extent to which we can draw conclusions about the way people's attitudes changed in response to the discussion round, and the reader will note we say very little about changes in views throughout the analysis presented above. As we highlight in the next chapter, all of these variables need to be considered in designing future studies because though they do not undermine the principle of gaining different perspectives on the evidence base, they do pose challenges for the methods used to do so.

Conclusion and looking ahead

This chapter has shown how the unique process of ExpertLens blends the advantages of surveys and face-to-face meetings or interviews to gain insight into the complexity of issues surrounding ARV-based prevention strategies. The ExpertLens survey identified a wide range of stakeholders for recruitment into the ExpertLens – clinicians, researchers, policymakers, advocacy groups and industry employees – and successfully engaged them in an iterative elicitation process with high participation rates.

By analysing average and median ratings and rankings alongside the distribution of responses we were able to determine which issues were most pertinent. We were also able to derive a sense of how much agreement there was between the experts, and how discussion might have altered their views so that the group as a whole may converge or diverge in their expert opinion.

This may be where some of the most compelling insights from the Mapping Pathways project originate from. Though it highlighted many areas where fault-lines exist, and where many are yet to be drawn because of a lack of information, ExpertLens has shown that even in the light of exciting RCT results across all strategies, there are still many areas where experts agree to disagree, and many that require further localised evidence to support policy formulation on the ground.


6
OUR INTEGRATED PERSPECTIVE: HOW TO MAP PATHWAYS TO GOOD DECISION MAKING

Where has the journey taken us?

HIV continues to proliferate in geographical regions around the world. It is argued that current HIV prevention options are not sufficient; a broader portfolio of approaches, or pathways, to prevention is needed. In many ways the Mapping Pathways study is a microcosm of a wider trend in our ever more complex societies. In ways we have not seen before, today's scientific advances, both biomedical and otherwise, are not only shared around the globe in record time, but each advance is accompanied by concerns over risk, uncertainty, institutional interests and cultural norms. The situation is compounded by the rapid pace of scientific and technological progress – innovation often outpaces policy decisions, and by the time decisions are made the social, economic, health and even scientific context itself, may have moved on.

This was certainly the case in the Mapping Pathways project as new trial data was being released regularly throughout the project, so each individual interview or piece of survey data was literally a unique snapshot in time, each drawing on new and continuously evolving understandings of the evidence base. Not only does this pose challenges for how the science responds to such rapid changes in understanding, but it presents even greater challenges for how policymakers, clinicians, advocates, community members and people living with HIV synthesise and integrate their understanding of the evidence base for different treatment and prevention options and decisions.

However, with such challenges come equally intriguing opportunities. Though estimates vary for how many infections could be averted through the successful uptake of ARV-based prevention strategies, such strategies could both save lives and contribute to annual cost savings amounting to billions of dollars. Clinical trials may have shown the efficacy of these strategies, but the broader empirical evidence base for approval and implementation is arguably still under development, so the contextual importance of decisionmaking is still a critical missing piece.

In this chapter we bring together the different elements of the Mapping Pathways project and explain our thinking about adaptive policy in the sphere of ARV-based prevention approaches and research that might inform that type of policymaking. We also think about how the approach might inform policy research more broadly. In a sense this chapter should be viewed as the beginning of a new journey in thinking about how the approach we have taken in this project might inform future research agendas and policy analysis more broadly. It will help us to go right back to the beginning and revisit some of our early thinking about the Mapping Pathways project and why we think the concept of adaptive, real-time policymaking is important, relevant and timely for this research.

Four integrated and intertwined perspectives on the evidence base

As we have discussed throughout these pages, new evidence suggests that, in addition to providing effective treatment for AIDS, ARVs may also be effective in preventing HIV transmission. The four ARV-based prevention strategies show promise. TLC+ provides earlier treatment for HIV-positive people and can thereby prevent transmission to HIV-negative individuals. PrEP provides HIV-negative people with ARVs to prevent HIV transmission, while vaginal and rectal ARV-based microbicides are topical applications, also for use by HIV-negative people to prevent transmission. Finally, PEP provides ARVs to HIV-negative people with a potential recent exposure to HIV.

Results from across the four elements of the Mapping Pathways project have yielded broad, divergent and incomplete evidence related to the viability of implementing ARV-based prevention strategies. Though each perspective highlights strengths and weaknesses associated with each strategy, our aim was not to make a definitive determination about which, if any, of the ARV-based strategies is stronger than any other. Rather, we have shown how the different perspectives and snapshots of the evidence for each strategy brings into focus features which still need to be explored.

The literature review pointed to the prominent role of clinical trials in shaping current policy and the need for further research into the contexts and

conditions that will shape the real-world 'trials' that now need to take place as communities consider how these strategies may or may not be implemented. The literature shows there is a strong focus on *efficacy*, but more limited evidence on *effectiveness.* This is crucial, as a theme emerging from all four strategies was that adherence will play a central role in the relative successes and potential failures of any ARV-based prevention strategy. It is intertwined with efficacy, alongside other parameters which determine effectiveness, such as behaviour, drug resistance, side effects and the wider socio-political context. This strongly inter-dependent nature of the different variables that determine efficacy and effectiveness needs to be a central aspect of future research agendas. Moreover, any understanding will be dependent on the wider health system and socio-political context in which the prevention strategies are to be implemented. The influence of these factors is not yet examined, however, and there is little to no data or evidence about wider spillover effects or externalities of ARV-based prevention strategies. These issues are crucial to supporting long-term decisionmaking about new prevention strategies, and the evidence base might be considered incomplete if they are not taken into account.

The grassroots perspective demonstrated that people need more information in order to better understand and make individually appropriate decisions for their communities. There was general support for using ARVs as a prevention strategy, in particular TLC+ and PrEP, but the types of concerns people expressed about what would happen if these strategies were implemented varied by country and call our attention to the very real worries the front-line communities have about the effects of these strategies on their communities. In particular, their apprehension about drug resistance and adherence, the need for improved education and awareness strategies, the gaps in evidence about how the healthcare systems would cope, and the open and very real questions about resource and cost trade-offs cannot be overlooked.

Mirroring this, but coming from the grasstops, the findings from the policy stakeholder interviews showed the divergent ways stakeholders in different countries viewed the scientific evidence base. It was striking that within each country the same sets of scientific data were interpreted, framed and perceived in different ways depending on the local context. Stakeholders who are in positions where decisions are made were seemingly highly reluctant to make significant decisions on the basis of one clinical trial or study. Differences in local circumstances, particularly socio-cultural differences in the make-up and nature of sexual relationships and liaisons, were often important mitigating factors for the more sceptical stakeholders. Context mattered to them, and replication studies conducted with the local population(s) of interest need to do more than prove the efficacy of the strategy; they must also explore how the strategy would be implemented in a local context and what social arrangements are needed to support it in order to make it not just efficacious, but also effective.

Finally, the ExpertLens survey on the evidence base showed us where the fault-lines in the evidence base exist. First, for all prevention strategies, there was broad agreement on the high importance of each individual's adherence and the underlying biological reliability of ARVs, but disagreement on how a patient's risk behaviours may affect the success of ARV-based prevention strategies. Second, there was a lack of consensus and shared understanding about the types of conditions that would affect the strategies and in what ways. The levels of disagreement and divergence suggest that there is a strong need for further research into this area; indeed this was also highlighted in the literature review. Third, a number of indirect outcomes were identified as likely, but again little consensus or agreement emerged, suggesting that more research is needed in this area. However, despite the uncertainties and lack of consensus on the more nuanced issues, experts seemed to have clearer views when asked to make stark trade-offs between the strategies and compare them against each other. When asked to allocate funding, the experts strongly agreed that the science and evidence showed we were ready to allocate more funding to TLC+ strategies, providing faster and earlier treatment for people living with HIV.

To a certain extent these perspectives and views are not unexpected. The science policy literature has for many years demonstrated how different groups

of stakeholders bring different framings and perspectives to scientific and policy questions. What it does do, though, is pose important questions for how we, as researchers and advocates, communicate and disseminate our own findings which can be of use to these different communities.

In particular, by integrating these perspectives and mapping them onto the evidence base, we highlight gaps in current research and show a clear need for further policy-relevant analysis. This includes the need to develop a series of validated variables and questions that will feed into future models and tools. This will enable decisionmakers and communities to make real-time, evidence-based and appropriate decisions about HIV/AIDS strategies. But how can this be done and what kind of questions should be asked?

This is where the role of our adaptive framework and analytical lens allows us to bring things into focus (as illustrated in Figure 1-3). Consider the following proposition: even though the 'physical technologies', the scientific innovations that allow us to use ARVs to prevent HIV, have been proven in principle, we still don't know how this proverbial turning of the first wheel will affect the turning of the second and third cogs in the innovation system. To put it another way, are there social and cultural elements, or institutional and organisational variables, which, if not arranged in such a way as to work in a complementary fashion with the physical technologies, will stop the cogs from turning? Will there be optimal configurations of our health systems, the delivery mechanisms for the strategies, the support mechanisms for those using a prevention strategy and so on that will lead to optimal success? We must understand what these interactions are and how we achieve them.

Moreover, as the ARV-based prevention strategies will inevitably interact with the demographic and epidemiological landscape of the countries in which they are applied, good understanding of individual choices and risk behaviours are also important to understand within their local context. The series of Mapping Pathways perspectives and snapshots from a highly dynamic and emerging evidence base may not be able to provide the answers, but they do highlight the importance of locally contingent factors in understanding how and why different strategies may or may not be effective in different communities.

Three countries, but multiple points of view

One of the most important findings from our study is that the results of any evidence base for ARV-based prevention are not necessarily generalisable. Looking at the exact same data and reports, stakeholders in India, South Africa and the US often came to very different conclusions about their implications and relevance for HIV prevention and treatment policies in their countries. This raises important questions about what these different views are, and how we approach them to aid in the mapping of pathways to decisions about ARV-based prevention strategies.

In India, stakeholders from the grasstops and the grassroots seemed to offer the most scepticism throughout and the most hesitancy about 'buying into' the idea that efficacy in a clinical trial means effectiveness on the ground. We had a strong sense that Indians, more than other stakeholders we spoke to, wanted to ground everything in their own setting and were less willing to accept outside views at face value. As they think about what kinds of new questions the existing evidence base will need to answer, stakeholders in India will need to understand the evidence for their own epidemic and contextualise it in their own way. This insight has been made by others in the field and could be an area of further exploration to better understand the extent to which these findings holds true for other public health challenges (see for example, Bisht, Pitchforth and Murray, 2012) Indian stakeholders were particularly interested in understanding the spillover benefits of ARV-based prevention strategies, and cited the potential positive indirect outcomes of TLC+ as a key reason for their support of it.

In South Africa, stakeholders were consistently apprehensive about trade-offs and resource decisions that would need to be made. They were concerned that existing prevention strategies and approaches to treatment might be side-lined in favour of this new science, and about the ability of the South African healthcare system to handle the burden of any large scale, ARV-based prevention initiative. The inter-

views were going on during a time when a national debate was occurring about the future of healthcare in South Africa, and this could perhaps have influenced some of these considerations. On the whole, South African stakeholders were not as enthusiastic and positive about the new types of ARV-based prevention strategies and were slightly more sceptical about the strength of the science behind them. This was particularly the case for microbicides, which is interesting given one of the most promising microbicide trials, CAPRISA 004, was conducted in South Africa. Nevertheless, South African stakeholders were more positive than the Indian stakeholders about many of the strategies, but not as enthusiastic as US stakeholders.

Stakeholders from the US seemed most willing of all the stakeholders to accept scientific data at face value. They were consistently the most positive about each of the ARV-based prevention strategies and least worried about the nature of the science, although they had doubts, notably over resource constraints. This demonstrates that no matter the economic standing of a country, resources and costs will always be at the forefront of people's minds. These concerns were usually qualified with the idea that additional research could help answer those questions. This enthusiasm for the science did not come out as strongly in the grassroots surveys, where the overwhelming message was a plea for more education, awareness raising and empowering of individuals to make informed choices for themselves.

Looking across all three countries it is worth reflecting that these divergences in views were not necessarily driven by unique concerns. The stakeholders in all countries cared about issues such as costs, resources, efficacy, effectiveness, adherence and resistance, but differed in the weight or priority given to any one of them. Arguments that might be persuasive in one country, such as the views of different experts on the relative importance of one strategy over another, might have little impact in another where the concern is more about how to strengthen the healthcare system in such a way that basic HIV services can be provided, alongside any new prevention ones. Thus efforts to find 'pathways' for increasing the adoption of evidence-based practices in a given country have to take into account not only the strength of the scientific evidence, but also how that evidence is perceived as being applicable to a given set of circumstances. Innovation in drug treatment regimes is complex, and advances in the physical technologies will only mean that the other cogs in the wheel have to experience related and iterative advances and attention as well, in order to keep the system operating in a way that is effective and meaningful for all.

How adaptive policy research leads to the mapping of pathways

The Mapping Pathways approach

From the outset of our research our hope has been that Mapping Pathways would contribute to adaptive policy design and implementation. Our approach is rooted in three basic observations about policy related to ARV-based prevention strategies:

- The contexts in which ARV-based prevention policies and strategies may be introduced vary significantly. Incidence and prevalence rates differ in each country from those in the others covered in this study. The socio-political, historical context, governance challenges and roots of civil society engagement are just a few of the many variables that determine how successful any prevention strategy will be. The Mapping Pathways team explicitly intended to explore the various perspectives and opinions of the stakeholders in the different environments in which ARV-based prevention might be introduced, and the significance of that variation. The ExpertLens and survey work were particularly designed to capture these findings.
- Policymakers need to address the various concerns of stakeholders from different standpoints. Because opinion and analysis differ in and across contexts, effective policy and implementation strategies need to be devised with the opinions and views of a range of stakeholders in mind. The project's adoption of grassroots and grasstops data relates to this desire to understand a broad range of relevant experience and perspective.
- A high degree of uncertainty and a large number of scientific, social and economic variables influ-

> ence the impact that policy might have, and this complexity rules out clear predictions of how policy might need to evolve. Rather than try and develop rigorous and formal models of the future, the Mapping Pathways approach was keen to identify the range of variables in different contexts that might be important in determining outcomes.

These observations and subsequent choices about methodology encouraged us to reflect on the limitations of many conventional approaches to policy and think more broadly about the evidence base needed for effective policymaking.

An analogy to adaptive clinical trials and an alternative to RCTs in policy research

In recent years 'adaptive clinical trials' have become an increasingly popular evolution in classical randomised clinical trials (RCTs) for new drugs. The more adaptive clinical trial approach is gaining attention for its ability to employ frequent statistical paradigms, which enable a dynamic rather than static response to real-time clinical data. Lowe (2006) suggests that adaptive clinical trials of a Bayesian design can

> *provide for a transition from merely sequential to continuous monitoring of trial data, [and] they can also allow for a wide range of other parameters to be changed. Designs can be developed that can, on the fly, vary the number of patients needed, eligibility for joining the trial, how patients are to be divided between arms of the study, and what doses of the investigational drug they'll receive.*

In some respects we see the type of policy-related evidence being generated in the Mapping Pathways study as analogous to the evolution demonstrated in adaptive clinical trials. Both enable a real-time response to improving decisionmaking about whether to either approve a new drug, or implement a new policy. Let us first look at why the other approaches are lacking in this respect.

Currently, RCTs designed to test the efficacy of new chemical and biological entities are often required by regulatory agencies to trial the new treatment with a stable cohort of patients and compare the outcomes against a group of people who do not receive the new formulation. The trial design, protocol, dosage and so on remain constant over the life time of the trial. RCTs have been at the core of pharmaceutical regulatory systems in the US and Western Europe for many years and are increasingly used in other areas of the world as they become integrated into the global pharmaceutical industry. They are widely viewed as the key standard for evidence on safety and efficacy and have proved enormously powerful in generating a body of evidence that can be used to make decisions about which drugs should be released on the market and for what purposes. Therefore they have been fundamental to decision-making by regulators and purchasers.

However, RCTs have significant limitations in the laboratory-based world of biomedical clinical trials, and their relevance is also questioned in a real-world context. First, they can be time consuming and expensive. In drug development, they represent the bulk of the costs involved in getting drugs to market (Rawlins, 2004) and in social policy some authors argue that their cost relative to their benefit makes them prohibitive (Cartwright, 2007).

Second and relatedly, because the rigour that they offer comes at the cost of scope of findings, the evidence provided by RCTs is often very narrow. As Cartwright has argued (2010), assumptions made about the relation between the trial and applicability to a broader target population can often be called into question.

Third, and perhaps most importantly in the context of Mapping Pathways, these issues will only intensify and become more relevant when we think about how to construct robust evidence for prevention strategies. The very nature of how we think about the role of clinical trials in testing new or existing drug treatment paradigms shifts. To date clinical trials for TLC+, PrEP and microbicides have had to factor in the need for a mix of prevention strategies, including condom provision, testing for sexually transmitted diseases (and treatment) and behavioural counselling, to name a few. It is therefore very difficult to determine whether a new prevention product or intervention works or not, and to disentangle this from the complex contextual factors any individual experiences when they make individual choices about the kinds of sexual or other

encounters they engage in which may expose them to HIV. The message is that the nature of prevention science is significantly different from that of other drug treatments and the window of opportunity to have true placebos is closing. RCTs must and should adapt in response and it is our role in the wider research and advocacy communities to ensure they do so.

Despite these shortcomings for trials, following the work of Dufflo and Banerjee (2009) and others, RCTs are now increasingly being used to test policy in the realm of social, economic and policy research. The benefits of using RCTs in this way are spelt out in a recent UK Cabinet Office report called *Test, Learn, Adapt: Developing Public Policy with Randomised Controlled Trials* (Haynes et al., 2012). The report argues that RCTs can produce a much more substantial evidence base in certain situations on which to base policy than more ad-hoc or politically motivated approaches to evaluating the impact of policy. We argue that we must take the positive aspects of strengthening the evidence for policy this trend is leading to, but not get bogged down in the static nature of certain models of RCTs.

As efficacy testing is evolving with the use of adaptive clinical trials, the methodology we have used in Mapping Pathways offers a parallel adaptive and dynamic approach to compiling evidence about effectiveness of new drugs and particularly the new use of drugs and what policy decisions are required. One reason that the Mapping Pathways approach may be particularly appropriate in cases where existing therapies are proposed as preventative treatments is that communities and other stakeholders already have considerable experience of the medication, so their views and experience are crucial as part of the evidence base. Thus, while adaptive clinical trials broadens the base of biomedical evidence that can be used in trials and the set of statistical techniques that can be deployed, methodologies such as those adopted in the Mapping Pathways project broaden the type of evidence used to assess the viability, design and impact of policy.

Adaptive policy design

Adaptive policy is not an entirely new concept. RAND colleagues and others have previously and explicitly explored it. The work of Dufflo and Banerjee (2009) and recent writings from policy analysts such as Haynes et al. (2012) writing for the UK Cabinet Office all relate to modes of policymaking based on iteration between policy and evidence. Previous work at RAND also relates to the need to build in a capacity for policy adaptation on the basis of research, and a number of research projects have explored different quantitative and qualitative approaches for doing this (RAND, 1997; Lempert and Groves, 2010). Equally, policy research is also seeking to understand the way people behave in response to policy. A wide range of discrete choice experiments, game theory, future scenarios techniques such as robust decision making, and innovative modelling approaches such as agent-based modelling are now used to try and understand the ways in which policy can be designed to maximise intended impacts.

The basic contention of all of this work is that policy needs to evolve on the basis of evidence that captures the importance of contextual difference and the impact of a range of social, economic and behavioural factors that impact on outcomes. There is widespread agreement that this is particularly important in areas of policy where there are high degrees of uncertainty.

One thing that follows from the underlying premise that policy needs to change on the basis of real-world evidence is the importance of interdisciplinarity: the introduction of policy in real-world contexts is not something that can be understood using narrow disciplinary tools. A wide range of political, economic, social and cultural factors can influence the way in which policy is received and the impact it has. Methodology needs to draw on an appropriate blend and mix of disciplines; and what is itself deemed 'appropriate' needs to be determined on a case by case basis and by careful reflection on the particular policy issue or problem. Just as adaptive statistical methods are challenging the traditional notions of clinical trial design, so too will this challenge methods of policymaking.

Thus, in thinking about how to investigate the potential of ARVs in preventing HIV/AIDS we considered a range of methodologies including some of those mentioned above. While a number may be rel-

evant and useful, particularly in future, we felt that many of these more quantitative techniques would require excellent qualitative inputs and ground work and would ideally build on the type of research that we eventually decided to carry out in the Mapping Pathways project. We believe that the methodologies we have used and combined in this project can be employed to monitor the way in which expert and user community views and experiences change as policy evolves. In this respect, the logic of a Mapping Pathways approach differs fundamentally from that of many research designs, which are often aimed at providing more definitive, ex-ante conclusions about the likely impact of policy before it is rolled out, and not as mechanisms to give more real-time evidence to feed adaptation over time and in relation to the role out of policy in different contexts.[42] Real-time assessment is particularly important where prevention is the aim, because the clinical, social and economic impacts of prevention can take many years to become apparent. While we are not naïve to the challenges this may pose to policymaking, and indeed the evidence and research which needs to underpin it, we do believe that the different methodologies of real-time assessment should, and can, be more robustly explored. The approach taken in this study – of developing four different perspectives on the evidence base and considering them in an integrated manner – is just one which could be used. The more fundamental point is that whatever approach is taken, and whichever methodologies are used, the research is carried out in real time and with a keen understanding of the adaptive nature of the insights and evidence which are produced.

Is the policy environment right for more real-time and adaptive approaches?

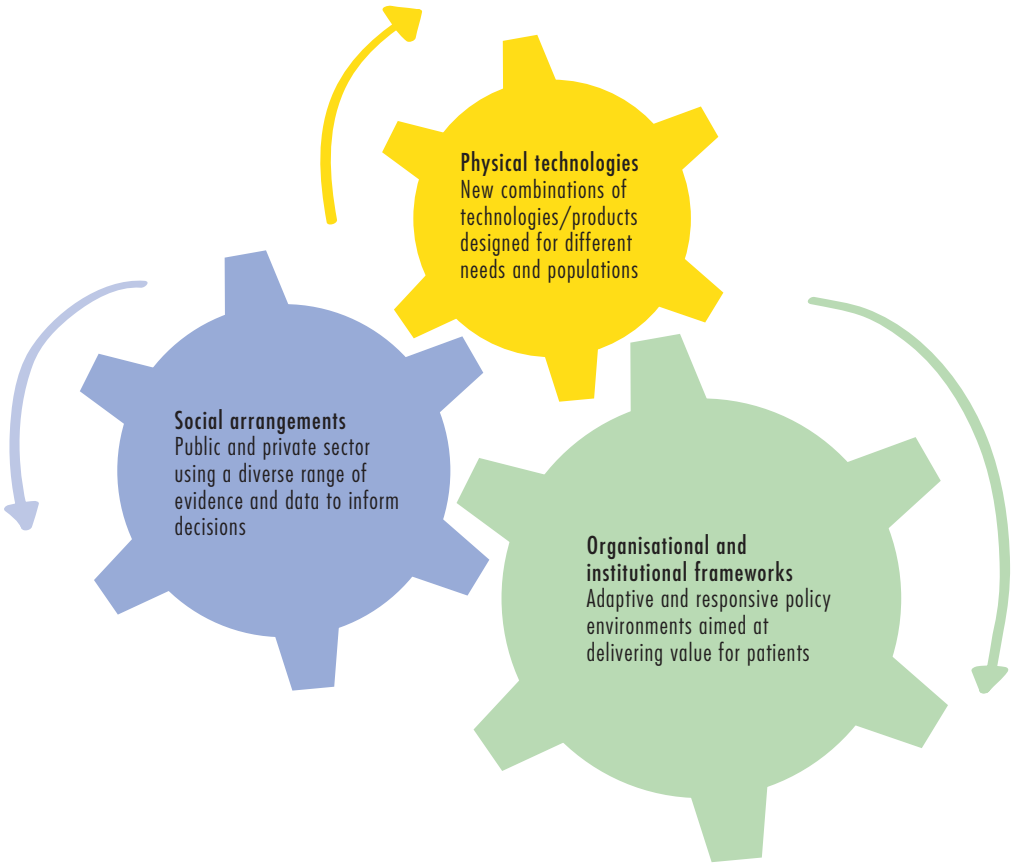
In considering the reasoning that led us to the methodology used in the Mapping Pathway project, we argue that the approach may have broader relevance to health innovation policy and policy research more broadly. In particular we think that the real-time dimension to the research approach we have devised has clear relevance to a wider set of current issues in health innovation. As funders of new drugs, treatments and prevention solutions struggle with decisions about what to fund and at what price, they have increasingly begun to insist that reward for new innovative products be determined on the basis of effectiveness in clinic and in practice rather than simply efficacy in clinical trials. This move is widely known as value-based pricing (Deloitte Center for Health Solutions, 2012). If drugs are to be assessed and rewarded on the basis of value they deliver to patients, research to inform assessments will need to draw on practitioner and patient choice and experience, so this type of evidence will take on a new significance in health innovation. We therefore view approaches such as Mapping Pathways as having potentially a broad relevance to creating a new evidence base for health innovation decisions beyond the immediate issue of ARVs in HIV/AIDS prevention strategies.

This may particularly be the case if the logic of value-based pricing begins to change the way in which drugs are developed. If efficacy is the measure of performance and reward for drug development, the incentive is to create a drug with a narrow but absolutely definable impact. However, if value to the patient is the measure of reward we may see the pattern of drug development responding to a more complex set of incentives. We may see more emphasis being placed on delivery mechanisms that make it easier for patients to use and enhance compliance, or we may see ARVs being developed and packaged differently for those who are using the drugs in a preventative way as opposed to those who are being treated with ARVs. We may also see combinations of drugs and healthcare regimes being proposed and marketed. Again, these developments seem to necessitate a new evidence base, which captures diversity of opinion and experience and is based on observed use of drugs and treatments by practitioners, experts and patients in clinic.

Although the examples given here relate to HIV/AIDS the issue is also clearly a broader one. ARVs are not the only drug that has been adapted from a therapeutic to use in prevention. Consider the following examples: aspirin as a preventative medicine for heart attacks and a range of other diseases;

[42] For more detailed discussion of real-time evaluation see Marjanovic et al., 2012.

Figure 6-1
Our future approach to adaptive policymaking



statins for the prevention of coronary disease; and chemotherapy being used to prevent development of certain cancers. The use of medicines to prevent disease presents a range of challenges to those interested in assessing the effectiveness, impact and value of drugs. Prevention, then, is not a one-off occurrence. Clinical, social and economic impact can take years to become apparent and the thus the value of a preventative approach can be even more challenging to assess. This will necessitate a range of more adaptive approaches as evidence is accumulated over time. The benefits of integrating individual, behavioural evidence with better scientific data and analysis of system level factors are apparent in those seeking to understand how medicines can best be deployed in preventative as well as therapeutic modes.

Let us return once again to the metaphor of cogs turning together to create different patterns of innovation. We might imagine that different interdisciplinary research approaches, combining natural science, social science, community-based observation and including real-time components, might follow from and indeed reinforce a different and more adaptive institutional macro policy environment, and may lead to different products. Our cogs diagram could look something like that in Figure 6-1, and this should be used to guide future decision-making, the questions raised, and the ways in which evidence is gathered and considered.

The long road ahead

Our journey is not over and we hope this report and the insights, questions, concerns and issues raised within it are a continuing resource for those who are part of the broader community working to stop the spread of HIV. Before this leg of the journey ends, we would like to leave you with a few final thoughts.

Science is the key to unlocking the future end to HIV. It will lead us to new ways of fighting the spread of the virus, helping to make people's lives better who are living with HIV, and providing us with new tools to prevent it. However, it is also interpreted differently by different communities; understood in different ways for different reasons; and utilised for different means and ends. We cannot take it for granted that everyone will view scientific findings in the same way, nor should we rest on our laurels.

In order to shift the paradigm we all have to work together to raise new questions, break down existing barriers and modes of working such as those of RCTs, and work in real-time, dynamic fashions to capture those snapshots that matter most and can help to inform decisionmaking in the future. The social arrangements, organisational frameworks and requisite shifts in institutional structures will be key to unlocking some of these challenges. Innovation is only successful if applied appropriately, and new ways of thinking will be required as things shift at multiple levels. We cannot forget that there is a social side to science, as well as a scientific side to social issues. Structured, engaged and adaptive research can help us move forward, map pathways and work together to prevent the spread of HIV.

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