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HIV Preventives Technology and Market Landscape

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List of Acronyms

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CE Mark	Conformité Européenne
CCP	Comprehensive condom programming
CDC	Centers for Disease Control and Prevention (United States)
DFID	Department for International Development (United Kingdom)
DNA	Deoxyribonucleic acid
FACTS	Follow-on African Consortium for Tenofovir Studies
FDA	Food and Drug Administration
FHC	Female Health Company
FTC	Emtricitabine
GMP	Good Manufacturing Practices
HIV	Human immunodeficiency virus
HPTN	HIV Prevention Trials Network
HSV-2	Herpes simplex virus type 2
IPM	International Partnership for Microbicides
IUD	Intrauterine contraceptive devices
LMICs	Low and middle income countries
MC	Male condom
MOVE	Models for Optimizing the Volume and Efficiency
MPP	Medicines Patent Pool
MRC	Medical Research Council
MTN	Microbicides Trials Network
NIH	National Institutes of Health (United States)
NRTI	Nucleoside reverse transcriptase inhibitor
PATH	Program for appropriate technology in health
PrEP	Pre-exposure prophylaxis
PEP	Post-exposure prophylaxis
PEPFAR	President's Emergency Plan for AIDS Relief
PMTCT	Prevention of mother-to-child transmission
PSI	Population Service International
SCMS	Supply Chain Management System
R&D	Research and development
TDF	Tenofovir disoproxil fumarate
TIA	Technology Innovation Agency
UN	United Nations
UNAIDS	Joint United Nations Program on HIV/AIDS
UNFPA	United Nations Populations Fund
USAID	United States Agency for International Development
VMMC	Voluntary medical male circumcision
VOICE	Vaginal and Oral Interventions to Control the Epidemic
WHO	World Health Organization

1. Executive Summary

Introduction, methodology and acknowledgments

This landscape report is part of an ongoing initiative within UNITAID to describe and monitor the landscape for HIV commodities. It provides a broad overview of key HIV prevention tools, describing market dynamics around such prevention technologies and the primary factors that affect commodity access in HIV-endemic countries. Specifically, the report describes and analyses the market and technology landscapes for (i) male circumcision devices, (ii) barrier methods, (iii) microbicides, (iv) antiretroviral-based methods and (v) commodities needed for harm reduction. The report also explores market-based interventions that could alleviate current market shortcomings to improve access, focusing on key emerging products and product areas that are rapidly evolving. It should be noted that this report focuses exclusively on *commodities* for HIV prevention and not the behavioural and structural issues that must also be considered when developing comprehensive approaches to HIV prevention.

Information in this report was collected through a variety of methods, including desk research, literature reviews and expert interviews. An earlier version of this report was reviewed by experts from across the field of HIV prevention whose comments were taken into account in preparing this final version. The material presented in this report is current through 31 July 2013.

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Public health problem

The HIV epidemic remains one of the world's most serious health challenges. Although substantial progress has been achieved, the number of new infections per year is still estimated at 2.5 million. AIDS remains the sixth leading cause of death globally and the number one cause of death in Eastern and Southern Africa. In recent years, prevention of new infections among children has accounted for virtually all of the global reductions in new HIV infections, suggesting that progress has stalled in efforts to prevent new infections among adults and adolescents. New HIV infections are on the rise in certain regions, including Eastern Europe, Central Asia, the Middle East and North Africa. Unless the number of new infections is sharply lowered, long-term costs associated with the provision of lifelong antiretroviral therapy in low- and middle-income countries (LMICs) could soon become prohibitive, potentially threatening advances achieved to date in the global AIDS response.

Global context

Research on biomedical prevention interventions began in earnest in the early 2000's. In recent years, biomedical research breakthroughs have revolutionized the approach to HIV prevention and dramatically expanded the array of available options. These breakthroughs—which include voluntary medical male circumcision, a broad range of antiretroviral-based prevention methods and progress in developing promising vaginal microbicides—have generated considerable optimism that it is now possible to sharply alter the epidemic's long-term trajectory.

However, this optimism is tempered with caution, as the global community has been slow to bring new biomedical tools for HIV prevention to scale. As observed with efforts to scale up other biomedical tools, impediments to scale-up include costs associated with new biomedical tools, failure to invest in demand generation strategies, weaknesses in commodity procurement and supply management, human resource shortages, and inadequate support from international donors and national governments.

The leading purchasers of biomedical HIV prevention tools are the US Government (via the President's Emergency Plan for AIDS Relief [PEPFAR] initiative), United Nations Population Fund (UNFPA), the UK Department for International Development (DFID), and the Global Fund to Fight AIDS, Tuberculosis and Malaria. Although LMICs have ramped up domestic investment in HIV-related activities, national investments are heavily weighted towards care and treatment, with limited support for HIV prevention programmes. In large measure, current purchasers of HIV prevention technologies are focusing more on scale-up than on concerted action to affect markets, though some market-shaping activities are underway, for example, to support rollout of male circumcision devices in target countries. As pricing, manufacturing capacity and grassroots demand determine the pace and sustainability of scale-up of HIV prevention tools, there appear to be unique and important opportunities for organizations like UNITAID to affect market conditions in order to expand access and accelerate scale-up.

Male Circumcision Devices

Background

Clinical trials have found that medical male circumcision reduces the likelihood of female-to-male sexual HIV transmission by about 60%. WHO and the Joint United Nations Program on HIV/AIDS (UNAIDS) recommend scale-up of voluntary medical male circumcision (VMMC) as an additional strategy for the prevention of heterosexually acquired HIV in men in countries with high HIV prevalence and low prevalence of male circumcision. Thirteen countries in sub-Saharan Africa were identified as priority countries for VMMC scale-up.

Commodity access

HIV programs are facing challenges in implementing VMMC at large scale through traditional surgical methods due to limitations in resources, including insufficient numbers of trained staff to perform the interventions. These challenges have slowed progress in scale-up, with coverage just over 10% of the UNAIDS target number of procedures in 2012 for VMMC, although there are signs that the pace of service uptake is quickening.

Uptake of non-surgical VMMC devices for adults to date has largely been limited to clinical and field trials. Rwanda is something of an exception, as in 2012 WHO advised phased roll-out of the PrePex device in Rwanda, where extensive study of PrePex had occurred.

Little, if any, progress has been made towards implementing routine offer of circumcision for newborns, primarily because current donors are prioritizing the successful start of the adult VMMC program before allocating resources towards newborn programs. This is due to the relative immediacy of reducing HIV incidence as a result of circumcising those currently at risk of sexual HIV acquisition (adult men compared to newborn males), in line with WHO recommendations, and, consequently, the lack of clear guidance on infant circumcision in public health programmes.

Technology overview

WHO currently recommends one of three forms of surgery for VMMC, which has been the cornerstone of VMMC programs up to date. Medical devices that remove the foreskin without requiring sutures or extensive physician time have the potential to expedite VMMC scale-up. Although a number of medical devices for adult male circumcision currently exist, two (PrePex and Shang Ring) have piqued the interest of global health experts. PrePex is a relatively simple elastic collar compression device consisting of two plastic rings and one elastic ring, which has been developed for the African market. Shang Ring is a clamp-and-latch device that consists of two concentric plastic rings and has been used extensively in China. Each of these devices significantly reduces the time required to perform VMMC. Due to the lack of injected anesthesia and cutting of living tissue with the PrePex device, it is likely that nurse-based service delivery models in all countries would be feasible. The Shang Ring prevents bleeding and averts the need for sutures.

Several devices are available for circumcision of infant males and have been used for decades. One innovative disposable device, Accu-Circ, soon could be available in response to the documented shortcomings of available products.

Market landscape

While the target number of men circumcised in priority countries is 20 million by 2015, the potential market size is much larger. As neither PrePex nor Shang Ring has yet been marketed for public health uses in sub-Saharan Africa, much remains unknown about the market dynamics of male circumcision devices. PEPFAR currently funds the overwhelming majority of VMMC procedures in sub-Saharan Africa, reaching up to 2 million voluntary surgical procedures as of September 2012, and targeting up to a cumulative total of 4.7 million procedures by the end of 2013. Prequalification of the devices by WHO is a prerequisite for procurement. Likewise, the Global Fund has indicated an interest in increasing funding for VMMC scale-up. With the exception of South Africa, national investments in VMMC programming have been minimal.

PrePex is manufactured in Israel for Circ MedTech, the only product of this developer company, while Shang Ring is manufactured in China by WuHu SNNDA Medical Treatment Appliance Technology, which appears to have identified a distributor for the African region. PrePex was prequalified by WHO in May 2013. Prequalification of Shang Ring is expected soon. The innovative infant device, Accu-Circ, may be poised for prequalification over the next few years.

Market shortcomings and their reasons

Affordability: PrePex's current price is reported as high at US$ 20 per unit. At current pricing of new devices, several modelling studies have examined cost of devices versus surgery and failed to document cost savings with use of devices. Ideally, VMMC devices would be cheaper than surgery, based on potential manufacturing and raw materials cost, although training will be needed to equip health care workers with the skills needed to place, remove and monitor the devices, which may also make introduction of devices more costly initially. ***Reasons:*** A monopolistic market is expected in the short term with only one product prequalified (PrePex), until a second one (Shang Ring) is prequalified also. There is little prospect of other potential competitors in plastics manufacturing with global health expertise to rapidly enter and compete in the market. In addition, the devices are not necessarily interchangeable. Recovery of research and development costs seems critical for the manufacturer of PrePex, a new company with a single major product line. Demand is one of the primary drivers of unit cost in current surgical VMMC programs and likely to be a determining factor when devices are used. To date, demand for VMMC has not resulted in adequate utilization of existing capacity.

Quality: A lack of clarity exists regarding national regulatory approval requirements and requirements for prequalification of new analogous products. No single product is yet prequalified for use in adolescents. ***Reasons:*** National regulatory pathways for such devices in target countries are unclear or non-existent.

Delivery: Capacity of suppliers for the devices could be compromised with increased and unforeseen demand. Integration of devices in national programmes may encounter challenges. Shortages of lidocaine and other local anaesthetic products, required for device use, have been reported. ***Reasons:*** Unknown reliability on manufacturing capacity to deliver at sufficient scale. Needs forecasts remain uncertain. An absence of formal WHO guidance on introduction of the devices might slow their integration. There are a limited number of manufacturers of local anaesthetic products.

Potential market interventions

Potential market interventions to improve access to adult and adolescent VMMC commodities are presented in Table 1, together with the shortcomings that such interventions would address. This list is illustrative and not comprehensive.

Table 1. Summary of Potential Interventions for Adult and Adolescents Male Circumcision Devices

Shortcoming	Adult and Adolescent Male Circumcision Devices	Potential market interventions
Affordability	Reported initial prices of PrePex up to US$ 20 per unit, while production and raw materials costs are presumed to be low.	• Promote competition for male circumcision devices through incentives for additional manufacturers to enter market in each product category, e.g. support for research into novel device development and their market entry. • Support demand creation and price negotiation for prequalified devices, leveraging volumes to accelerate VMMC scale-up.
Quality	Only one product eligible for procurement.	• Support for clear regulatory pathways for competitor products for VMMC devices, including adolescents; clarify data required for approval of 'fast followers'.
Delivery	Limited uptake; slow scale-up.	• Support best practices for optimal demand creation including forecasting of needs.

Infant circumcision

Market-based intervention for infant circumcision devices may be premature. However, monitoring this field for developments is warranted.

Table 2. Summary of Potential Interventions for Infant Circumcision Devices

Shortcoming	Infant Male Circumcision devices	Potential market interventions
Quality	Lack of data compiled according to current WHO protocol.	Consider support for late-stage studies and prequalification of the Accu-Circ device, as needed.
Delivery	Slow scale-up.	Closely monitor progress in development of infant circumcision programmes.

Barrier Methods

Male condoms

Commodity access

Male condoms remain a cornerstone of HIV prevention efforts, but the effectiveness of condom programming is undermined by a global gap in the number of condoms available in LMICs. International donors account for the overwhelming majority of male condoms purchased for use in resource-limited settings, but the number of donor-provided condoms represents less than one-third of what is deemed necessary for HIV prevention. Access to lubricants, recommended during anal intercourse, is limited to one in five of men who have sex with men according to an international survey.

Market overview

There is little indication that market shortcomings are the source of the current access gap; the global condom market is highly competitive, with a notable number of manufacturers located in middle-income countries with lower production costs.

Potential market interventions

It is unlikely that a market intervention will lower cost or lead to increased uptake. Consideration should be given to potential market strategies to increase access to sexual lubricants, especially for men who have sex with men, as lubricants are especially required to facilitate condom use during anal intercourse.

Female condoms

The female condom is comparable to the male condom with respect to the level of protection it affords against transmission of HIV and other sexually transmitted infections. Studies indicate that the addition of the female condom to condom distribution programmes increases the proportion of sex acts that are protected.

Commodity access

Far fewer female condoms are available in LMICs than male condoms (43.3 million female condoms vs. 3.36 billion male condoms in 2011), although distribution of female condoms rose 136% in 2011, continuing a trend towards increased availability of the product.

Technology landscape

FC1, developed in the 1980s, was the first female condom approved by the US Food and Drug Administration (FDA) and prequalified by WHO. Altogether, there are now three primary products of clear public health significance—FC2 (the successor of FC1), Cupid, and a third product that is at an advanced stage of development and clinical evaluation (the Woman's Condom).

Market landscape

UNFPA and the US Government together are responsible for nearly all international purchases of female condoms, with UNFPA alone accounting for two-thirds of all female condoms purchased in 2011. UNFPA supplies condoms to national governments, other UN agencies, and non-governmental organizations, while the US Government purchases condoms for use in US-funded health programs. National governments typically look to international donors to supply condoms for disease prevention and contraception, and there is little evidence of a private market for the female condom in low-income countries.

FC2, manufactured by the Female Health Company is the most widely used female condom. FC2 is prequalified by WHO and approved for marketing by the US FDA. Nearly all female condom purchases for LMICs have been for this nitrile product. In 2012, WHO prequalified a second female condom—Cupid, a natural latex condom manufactured in India—potentially opening the door to purchases of this product for use in HIV prevention programmes, although Cupid is not eligible for procurement by US Government-supported programs as it is not FDA approved. A third female condom—the Woman's Condom, developed by the Program for Appropriate Technology in Health (PATH) and manufactured in China—is in the latter stages of clinical evaluation, with prequalification and FDA approval expected within a year. The Woman's Condom is made of soft polyurethane and is inserted through a capsule that dissolves in the vagina.

Manufacturing capacity for FC2 is currently being expanded (to permit production of 100 million pieces annually). Production capacity for Cupid is unknown, while evidence suggests that enhanced capacity will be required for the Woman's Condom.

Market shortcomings and their reasons

Availability: No ideal product exists that meets all target characteristics. The ideal female condom would be highly protective, stable, secure, easy to use, extremely inexpensive (ideally less than US$ 0.10 per unit), and disposable without harm to the environment. ***Reasons:*** Uncertainties about potential market might be discouraging further research in this niche. Difficulties exist in developing a product that is competitive in price with male condoms and meets target characteristics.

Acceptability: Uptake is extremely limited. ***Reasons:*** While acceptability studies have indicated a strong desire among many women for access to the female condom, actual real-world use for such a product is difficult to gauge, and there is considerable uncertainty regarding acceptability of the device. Studies have reported that women express a range of concerns about the products, such as difficulties with insertion and what some wom-

en perceive as the product's strange appearance. In addition, some have cited unfavourable attitudes among international donors as critical factor in limiting uptake.

Affordability: The price of the female condom is 20 times more than the male condom (unit price up to US$ 0.57 versus US$ 0.03); cost appears to be a primary barrier to accelerated scale-up. Cost-effectiveness is also a concern, as is potential for displacement of the less expensive male condom. ***Reasons:*** The female condom is larger than the male condom and more complicated to manufacture. There is limited demand for the female condom, and most of the donor market has been dominated by a single product (FC2).

Quality: Only a limited number of products are eligible for procurement by US-funded programs. ***Reasons***: The second product prequalified by WHO is not submitted for approval to US FDA and hence not eligible for procurement through US-funded programs.

Delivery: Common stock out episodes have been reported. Female condoms do not reach the end user in many cases. ***Reasons***: There is a lack of programmatic guidance. There are also uncertainties regarding demand and weak forecasting and supply management capacity at the country level.

Potential market interventions

The female condom is an important additional HIV prevention tool that affords protection of sexual acts that are otherwise unprotected. Smart programming should accompany distribution to minimize displacement of male condoms. It is not clear if additional products are needed in this market, as there are concerns that, given the relatively small size of the market, additional products could fracture the market and inhibit the capacity of manufacturers to offer volume-discounted pricing. Objectives for market-based interventions include decreasing the cost of existing female condom products and supporting demand creation with high-volume purchases, supported by smart programming of the product, that aim to achieve additional coverage of otherwise unprotected sexual acts.

The suggested market interventions for female condoms presented in Table 3 are linked and inter-dependent.

Table 3. Summary of Potential Interventions for Female Condoms

Shortcoming	Female condoms	Potential market interventions
Affordability	Price is up to 20 times higher than male condom.	• Determine price points for differing manufacturing volumes (e.g. it is suggested that price of FC2 could be halved if the number of units procured annually were to reach 3% of total male condom market). • Demand creation and price negotiation with increased volumes of product for distribution in LMICs, contingent on assurance that this additional volume will be maintained by public sector funders. • Analyse manufacturing processes for each of the prequalified products to assess potential for efficiency improvements.
Quality	Limited number of products eligible for procurement by all donors.	• Encourage submissions to FDA for approval of currently prequalified products. • Support alignment of procurement policies by main donors.
Delivery	Limited uptake.	• Provide assistance to support accurate demand forecasting in the context of programming.

Microbicides

Commodity access issues

Given the shortage of prevention methods that women can initiate and/or control, researchers have placed high priority on the search for a safe and effective vaginal microbicide to prevent sexually transmitted HIV infection. As no microbicide has been prequalified or received regulatory approval, no uptake of such products has occurred outside of clinical trials.

Technology landscape

First-generation microbicides used various substances in an effort to block HIV entry, but these proved to be ineffective. More recent candidate microbicides incorporate antiretroviral compounds, with a major clinical trial in South Africa in 2010 providing the first proof of concept for an antiretroviral-based microbicide.

Two leading microbicide products have emerged, although there is an active pipeline of many additional experimental approaches in earlier stages of clinical evaluation. The 1% tenofovir gel incorporates an approved antiretroviral drug manufactured by Gilead Sciences, which has provided a co-exclusive, royalty-free license to CONRAD (part of the Eastern Virginia Medical School in Norfolk, Va., USA) and the International Partnership for Microbicides (IPM) to develop 1% tenofovir gel for use in LMICs. Although the above-noted South Africa study results electrified the AIDS field, proof of efficacy has yet to be confirmed, with evidence strongly suggesting that adherence has a critical effect on the degree of protection. An arm of the VOICE study examining 1% tenofovir used daily rather than peri-coitally was stopped for futility when no effect from 1% tenofovir gel was seen. This lack of effect has been blamed at least in part to poor adherence. An additional study is ongoing to assess peri-coital dosing of 1% tenofovir gel.

The second product is a vaginal ring that contains dapivirine, an antiretroviral compound manufactured by Tibotec Pharmaceuticals, which has provided IPM with a royalty-free license to develop various dapivirine-based microbicide products. The dapivirine ring, which is being actively studied in clinical trials, requires removal and reinsertion of a new ring every 30 days.

Although 1% tenofovir gel and the dapivirine ring are the only products with a meaningful chance to be available for use in LMICs over the next several years, a robust microbicide pipeline could generate additional products in future years. Candidates currently being developed or studied include microbicides that incorporate more than one antiretroviral agent, products that provide dual protection against HIV and pregnancy (so-called multipurpose prevention options), microbicides suitable for use during anal intercourse, and products that use innovative delivery means (e.g. vaginal tablets, films).

Market landscape

As no microbicide has ever been marketed, the market dynamics that will affect their roll-out remain unclear. International donors are likely to be the major purchasers of a microbicide, including the US, UK, and other high-income countries that have provided major funding for microbicide research.

Market shortcomings

Availability: No microbicide is currently on the market and ready for rollout. Several questions remain unanswered about microbicides. These products, especially early ones, offer only partial protection that might potentially be offset as a result of increases in risk behaviour. Some concern exists about the potential for microbicides to facilitate the emergence of resistance in HIV strains among individuals who seroconvert while using a microbicide or who were already HIV-infected when they used a microbicide, although recent studies that shown that microbicides appear to act locally with little systemic exposure to the antiretroviral drugs in the products. ***Reasons:*** Research challenges of development of new classes of products. Limited focus until recently.

Acceptability: No ideal formulation developed yet. There are major concerns, reinforced by recent clinical trials, regarding whether women will rigorously adhere to microbicide regimens. Female acceptability and male perceptions of microbicide use are not fully understood, and how best to optimize user adherence remains unclear. ***Reasons:*** The VOICE trial results suggest that many healthy, uninfected women may find it challenging to take a daily prophylactic regimen. The monthly regimen for dapivirine may be less taxing than coital or daily dosing, although women will still need to replace the ring with a new one every month and avoid removing the ring or having it become dislodged during intercourse, urination or defecation.

Affordability: There is considerable uncertainty regarding likely market prices for 1% tenofovir gel. The current price of one-month dapivirine ring is potentially too high for public health purposes (presently up to US$ 8 per unit). ***Reasons:*** With no marketable product currently available and manufacturing and distribution partnerships yet to be fully established by product sponsors, precise pricing information for these products is not available. Currently productions costs, in the case of davipirine ring as it is manufactured in Sweden, for instance, are high. Current packaging accounts for an estimated 90% of manufacturing costs of tenofovir gel.

Delivery: Manufacturing capacity is a potentially important concern for future microbicides. IPM's investigation of options to date has underscored worries about manufacturing capacity. ***Reasons:*** Capacity challenges appear especially pronounced for the dapivirine ring, given the generally limited global capacity for large-scale manufacture of intravaginal rings with few existing manufacturers globally. Possibilities to expand capacity have not yet delivered.

Potential market interventions

In addition to ongoing interventions aiming to decrease the cost of candidate products (e.g. the Bill & Melinda Gates Foundation is funding IPM to explore strategies to minimize the unit cost of the dapivirine ring with the aim of ensuring a unit price of US$ 2-4; PATH is currently working to develop a paper applicator for tenofovir gel). Other opportunities for intervention might arise once products are proven effective and evidence is available for wide-scale implementation.

Table 4. Summary of Potential Interventions for Microbicides

Shortcoming	Microbicides	Potential market interventions
Affordability	Uncertainty about market price of tenofovir gel.	Analyze support needed to continue or accelerate development of paper applicator for administration of vaginal gels replacing more expensive plastic one.
Delivery	Uncertainty about manufacturers' capacity to scale up.	Make time-limited investments to assist microbicide developers in identifying capable manufacturers and building manufacturing capacity to facilitate timely manufacturing scale-up and expedited roll-out of selected products (once accepted for scale-up).

Other Antiretroviral-Based Prevention Methods

Commodity access

Research has validated a number of antiretroviral-based prevention methods, including: antiretroviral treatment for prevention, pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) in persons without HIV infection, and prevention of mother-to-child transmission (PMTCT).

- Access to PrEP is very low in the US (the only country in which it is approved for use); outside the US, PrEP is largely limited to demonstration projects underway in a number of African countries.
- In LMICs, current coverage of PEP for occupational exposure or survivors of sexual assault is generally unknown.
- In 2012, 66% of pregnant women living with HIV received ARV prophylaxis for PMTCT.

Technology landscape

The potential for strategic use of antiretrovirals for HIV prevention has not been fully characterized. With respect to antiretroviral treatment for prevention, for example, questions remain regarding when to initiate therapy and which regimens are optimal to maximize both prevention and treatment benefits. Questions also persist regarding PrEP, including how best to deliver the intervention in resource-limited settings, optimal populations to be targeted, the magnitude of the demand for the intervention among HIV-negative people, and whether recipients of the intervention will adhere to regimen. Adherence is a critical factor as target populations might face specific challenges in adhering to antiretroviral therapy, as these populations are otherwise healthy yet may experience adverse effects as a result of the products.

In addition to the tenofovir/emtricitabine combination, several early studies are underway on other PrEP options, including at least two Phase I or II trials investigating other single and combination antiretroviral agents, including maraviroc, S/GSK1265744, ibalizumab, and a long-acting injectable formulation of ripilvirine.

As per new WHO antiretroviral guidelines, released on 30th June 2013, countries are advised to provide the same, simplified one-pill once-a-day regimen for first-line treatment in antiretroviral programs, including, for example, antiretroviral treatment for prevention of transmission in serodiscordant couples, as well as PMTCT.

Market landscape

For the current combination under study for PrEP (tenofovir/emtricitabine), the market in most countries appears to be competitive, with at least five generic lower-priced formulations available in addition to the originator. In the case of ZDV/3TC, the dual combination traditionally used for PEP, the market is highly competitive, with at least 15 products prequalified by WHO and/or approved/tentatively approved by US FDA, including products manufactured in India, South Africa and Zimbabwe.

The specific market dynamics for antiretroviral medicines are extensively covered in forthcoming complementary HIV/AIDS medicines landscape, and only included here to provide a comprehensive view of biomedical products for prevention.

Market shortcomings

Affordability: The high cost of antiretroviral therapies is an impediment to their use as prevention, including expansion of treatment for prevention, and life-long treatment for mothers in PMTCT programs. Likewise, the high cost of the preferred combination for PrEP programmes remains an impediment to accelerating scale-up and comprises long-term sustainability. ***Reasons:*** The market is split across different formulations and regimens; there is limited demand for the newly recommended preferred full-regimen formulation for first-line treatment. There are a limited number of manufacturers eligible for procurement by primary donors. Where intellectual property barriers exist, countries cannot choose among multiple suppliers.

Delivery: The continuity of supply for antiretroviral formulations specific for prevention purposes could be at risk. ***Reasons***: A lack of clarity on demand for formulations specifically used for prevention (e.g. dual FDCs), and increased demand for the newly recommended preferred three-drug FDC for first-line treatment, could lead to supply risk for low-volume formulations.

Potential market interventions

UNITAID and stakeholders are actively implementing a number of market-based interventions to reduce prices and increase availability of antiretroviral products. In addition, as a potential specific intervention in the case of PrEP, investments could support initial product introduction to identify optimal populations for intervention, quantify demand, and determine whether recipients of the intervention will adhere to regimen.

Harm Reduction Commodities

Commodity access issues

Harm reduction involves a package of up to 12 interventions to mitigate the negative effects of drug use, including access to sterile injecting equipment, oral opioid substitution therapy and other drug treatment interventions, and a range of essential health services. Although an overwhelming body of evidence, including considerable on-the-ground experience in many countries, has demonstrated the effectiveness of harm reduction, intervention coverage remains inadequate, contributing to the continued rapid spread of HIV through drug use, especially in Eastern Europe and Central Asia. One harm reduction component that has yet to be brought to scale is opioid substitution therapy, with methadone or buprenorphine, the recognized therapeutic substitutions for individuals with opioid dependence.

Market shortcomings

Affordability: Monthly commodity costs for methadone are as low as US$ 7, but buprenorphine, an essential alternative to methadone which can be taken sublingually, often costs 10 times as much. ***Reasons:*** Due to the fragmented and low-level nature of global funding for harm reduction programmes, purchasers may currently lack the market power to obtain optimal prices for buprenorphine.

Potential market intervention

A possible market intervention to accelerate uptake of harm reduction commodities would involve aggregating demand for buprenorphine to increase volumes and drive down long-term prices for the drug.

Longer term pipeline for HIV prevention commodities

Other potential HIV prevention tools are under investigation, including a preventive vaccines and methods to mitigate the role of herpes simplex virus type 2 (HSV-2) in facilitating sexual HIV transmission. These advances are substantially downstream, with new technologies unlikely to emerge for a number of years.

As this landscape analysis reveals, the field of HIV prevention commodities is rapidly evolving. Numerous market interventions to facilitate expanded access to affordable commodities that are already available or will likely enter the market in the near future warrant careful consideration. As new commodities are likely to emerge over the next several years, stakeholders interested in market interventions should continually monitor developments in the field and anticipate how focused market interventions might enhance the long-term public health impact of prevention innovations.

2. Introduction

This landscape report is part of an ongoing initiative within UNITAID to describe and monitor the landscape for HIV commodities. It provides a broad overview of key HIV prevention tools, describing market dynamics around such prevention technologies and the primary factors that affect commodity access in HIV-endemic countries. Specifically, the report describes and analyses the market and technology landscapes for (i) male circumcision devices, (ii) barrier methods, (iii) microbicides, (iv) antiretroviral-based methods and (v) commodities needed for harm reduction. The report also explores market-based interventions that could alleviate current market shortcomings to improve access, focusing on key emerging products and product areas that are rapidly evolving.

This landscape report is intended to inform decision-making by the UNITAID Executive Board, its committees, and the UNITAID Proposal Review Committee. It is also intended to serve as a resource for other stakeholders, global health organizations and country-level HIV/AIDS programs that would benefit from this analysis of the HIV preventives landscape.

The focus of this landscape analysis is on emerging biomedical strategies; it does not cover other HIV prevention interventions. Optimally effective HIV prevention involves the strategic combination of biomedical, behavioural and structural interventions that respond to HIV-related needs in national and sub-national contexts. (1) One of the principal impediments to implementing strategic combinations of HIV prevention strategies is the historic unavailability of suitable biomedical tools. Currently, many biomedical prevention tools are emerging, and although challenges and questions around these new products have not yet been fully addressed, there is a need to capitalize on current opportunities to maximize the uptake and effectiveness of these emerging prevention tools. UNITAID's mission focuses on global health commodities; a focus on biomedical prevention strategies—where well defined, discrete commodities are available and needed—therefore aligns with UNITAID's mission.

This report is structured as follows:

- **Section 3** describes the methodology utilized for preparing the landscape and its review.
- **Section 4** describes the focus of this report and provides an overview of HIV prevention strategies and current gaps and deficiencies in prevention approaches;
- **Section 5** describes current global health architecture for HIV prevention;
- **Section 6** provides, for each category of preventive tools, and overview of:
  - ◊ the commodity access issues;
  - ◊ the technology landscape, including the range of available and emerging products ones, as well in the research and development (R&D) pipeline;
  - ◊ the market landscape;
  - ◊ the major market shortcomings and their reasons; and
  - ◊ a potential range of interventions that could address the market shortcomings and increase access to the needed tools.
- **Section 7** provides concluding remarks

3. Methodology

This landscape analysis was informed by an extensive desk review of published and grey literature, supplemented by interviews with key informants with knowledge of the market dynamics and state of the art for specific HIV prevention technologies.

The review of available literature involved several steps. First, published literature on HIV prevention generally, and for each of the key HIV prevention technologies, was reviewed and analysed. Priority was given to publications in peer-reviewed professional journals, although presentations at major scientific conferences were also incorporated in this literature review, especially for late-breaking developments that have yet to be captured in the peer-reviewed published literature.

Second, an extensive review was conducted of the market literature for each of the prevention technologies. Sources reviewed included analyses of specific markets (e.g. male circumcision devices, condoms), specific industries, financial regulatory filings (e.g. mandatory filings before the US Securities and Exchange Commission, company websites, market-related press reports, and procurement reports by key funders).

Third, regulatory filings before major regulatory agencies and submissions to the WHO pre-qualification program were reviewed.

The desk review was supplemented by interviews with key informants for VMMC, microbicides, male and female condoms, and harm reduction commodities. In addition, relevant staff at key procurement agencies (e.g. President's Emergency Plan for AIDS Relief [PEPFAR], Global Fund, United Nations Populations Fund [UNFPA]) were interviewed or contacted via email.

Finally, a peer review process was performed on an earlier version of this report, obtaining valuable comments from five technical experts in the fields covered in this report.

The material presented in this report is current through 31 July 2013.

4. Public Health problem and Commodity access

Although the last decade has seen the first sustained progress in the response to HIV since the epidemic's appearance more than three decades ago, HIV remains one of the world's most pressing health challenges. HIV is the leading cause of death in sub-Saharan Africa, the leading cause of death among women of reproductive age, the third leading cause of death in low-income countries, and the sixth leading cause of death worldwide. (2) (3)

Since 2001, the annual number of new HIV infections worldwide has declined by 21% (4), but most of this decline occurred several years ago, with more modest progress recently. There is little doubt that the world has witnessed important progress in reducing the spread of HIV; however, the latest epidemiological data suggest much greater progress in reducing the rate of new infections among children than among adults and adolescents, as the number of new adult infections has remained stable in recent years. (4) Indeed, the annual number of new HIV infections among adults and adolescents has not fallen since 2008, with prevention of mother-to-child transmission (PMTCT) accounting for all reductions in new infections over the last five years. (5)

This failure to reduce the number of new infections among adults and adolescents has occurred at a time when opportunities in HIV prevention have become increasingly promising. Antiretroviral treatment, which significantly reduces the potential for sexual HIV transmission, (6) is rapidly being brought to scale, with the number of people receiving HIV treatment increasing by 63% from 2009 to 2011. (5) In addition, the toolkit of validated HIV prevention methods has never been more expansive, as powerful new tools have emerged over the last decade, including VMMC and antiretroviral-based prevention methods, as well as new non-technological approaches such as conditional cash transfer programs for vulnerable young people. (7) The fact that progress in reducing new infections has stalled at the very moment that HIV prevention seems most promising suggests an urgent need to enhance the effective use of available tools.

Sharply greater progress in reducing the number of new infections will be required to ensure the viability and sustainability of HIV treatment programs. Although 9.7 million are currently receiving antiretroviral therapy (8), all of the more than 34 million currently living with HIV will require lifelong HIV treatment at some point. There is growing evidence for the value of earlier initiation of therapy (9), and new WHO guidelines recommend earlier treatment, i.e. with initiation at higher CD4 counts (10). With the queue for HIV treatment rapidly expanding, challenges will inevitably arise in mobilizing the resources required to support lifelong therapy for tens of millions of people worldwide. These resource demands will intensify as people currently receiving first-line regimens need more costly second- and third-line regimens in future years. Unless the number of individuals entering the queue for HIV treatment is sharply lowered, the global push to ensure universal treatment access may never achieve sustainability.

A lack of critical prevention tools has undoubtedly hindered progress towards reducing the number of new infections, with the most notable gaps including an effective vaccine, one or more women-initiated prevention methods, and clearly defined and well-validated structural interventions (i.e., policy interventions such as cash transfer programmes or legal changes). Yet even when new tools have emerged, their implementation has often been delayed. More than a decade elapsed between documentation of the prevention benefits of antiretroviral drugs for newborns before antiretroviral prophylaxis reached a majority of HIV-infected pregnant women. Simi-

larly, nearly eight years after the first major clinical trial documented the prevention benefits of adult medical male circumcision, this intervention has reached only slightly more than 10% of the target number of uncircumcised adult men in priority countries.

Deficiencies in the planning, implementation and oversight of HIV prevention programmes may also have contributed to suboptimal gains in reducing new HIV infections. According to a consortium of international experts, HIV prevention programmes are often insufficiently strategic, poorly planned, inadequately managed, and insufficiently monitored. (11) A recent analysis of HIV-related spending patterns in low- and middle-income countries (LMICs) found that prevention allocations are poorly matched with epidemiological patterns and fail to allocate sufficient resources for strategies that are most cost-effective and likely to have the greatest public health impact. (12) In addition, there is often political resistance to implementing proven HIV prevention strategies. This is especially true for programmes focused on heavily affected marginalized populations, such as sex workers, people who inject drugs, men who have sex with men, and transgender people. (4)

Better use of evidence-based tools and a more strategic allocation of resources could achieve considerably superior results. According to modelling commissioned by UNAIDS, focusing resources on the most cost-effective interventions, combined with additional investments to enable basic programmatic activities to be optimally effective, would avert 12.2 million new infections and 7.4 million deaths during the current decade. (13) While treatment, care and support accounted for 89% of HIV-related spending in 100 LMICs in 2011, an investment approach would shrink the proportion of HIV-related spending devoted to treatment to 64%, with commensurate increases in spending on VMMC, condom promotion, PMTCT, and programmes for key populations at higher risk. (4)

5. Global architecture in HIV Prevention Landscape

Investments in Research and Development

This section describes the leading investors in HIV prevention research, and explains the prevention approaches of key international stakeholders.

In 2011, approximately US$ 1.2 billion was invested in R&D focused on HIV prevention technologies. This included US$ 824 million in spending on HIV vaccine research, US$ 186 million on microbicide R&D, and US$ 203 million on other prevention technologies (including male circumcision, antiretroviral treatment as prevention, breastfeeding interventions, female condoms, and oral PrEP). Amounts spent in 2011 were roughly equivalent to R&D expenditure in 2010 (US$ 14 million lower), but HIV research spending in 2011 was less than in 2007, prior to the global financial and economic crisis.

Although most high-income countries have invested in HIV-related research, the US has long been the global leader in HIV-related research investments. The US National Institutes of Health (NIH) played a central role in sponsoring studies that helped generate an array of HIV-related technologies, including antiretroviral therapy, PMTCT, early antiretroviral treatment as prevention, and adult male circumcision. In 2011, NIH accounted for 67% of all HIV vaccine R&D spending, outstripping contributions by the second leading funder more than seven-fold. NIH also accounted for more than half of all microbicide R&D spending in 2011 and for more than 75% of research expenditure related to PMTCT. Other US Government institutions also play prominent roles in financing HIV prevention research. With respect to HIV vaccine R&D, the US Department of Defense and US Agency for International Development (USAID) represented the third and fourth most important funders in 2011. USAID was the second leading funder of microbicide research in 2011.

Other high-income countries also make notable investments in HIV prevention research. Arms of the UK Government were the 5th (DFID, US$ 11.8 million) and 11th (Medical Research Council [MRC], US$ 6.2 million) leading funders of HIV vaccine research in 2011, as well as the 5th (DFID, US$ 3.2 million) and 10th (MRC, US$ 1.3 million) leading funders of microbicide research. The French Government provided US$ 7.3 million for HIV vaccine research in 2011, sponsoring a major trial on antiretroviral treatment as prevention, and continuing to provide leadership on research relating to VMMC and oral PrEP. Other high-income countries such as Denmark, Ireland and the Netherlands also contribute to HIV prevention research.

Emerging economies are increasingly investing in HIV prevention research. China was the 9th leading investor in HIV vaccine research (US$ 6.9 million) in 2011, and South Africa was the third leading investor in microbicide R&D (US$ 10.0 million). While providing limited direct financial support for HIV-related research, low-income countries with generalized epidemics provide substantial institutional support, providing regulatory approval and oversight for clinical trials.

The Bill & Melinda Gates Foundation is another leading funder of HIV prevention research. In 2011, the Foundation was the second leading funder of HIV vaccine R&D (US$ 78.5 million) and the fourth leading funder (US$ 7.0 million) of microbicide research. The Bill & Melinda Gates Foundation is currently providing financial support for field trials of male circumcision devices and focusing substantial funding on research to enhance the efficiency and effectiveness of HIV prevention programmes.

Stakeholder Analysis

This section offers a brief overview of key players in the HIV prevention field. It explores how HIV prevention is financed, how prevention policy is developed, how stakeholders' approach to HIV prevention may be evolving, and how various stakeholders have engaged on issues pertaining to new prevention technologies.

PEPFAR: The US is the leading funder of HIV programmes in LMICs. In 2011, the US provided more than half (59%) of all HIV-related disbursements by donor governments. Although PEPFAR, when created, focused primarily on antiretroviral treatment, it has over the years increased its investments in HIV prevention programming. In particular, PEPFAR is a major funder of PMTCT programmes, the primary global funder of VMMC, and a leading provider of male and female condoms. In Fiscal Year 2011 (the last year for which such information is available), PEPFAR allocated 46% of its resources towards care and treatment, 29% for prevention, and 26% for other programs and activities.

In 2011, PEPFAR launched a new strategy to bring about what it calls an "AIDS-Free Generation". Under this new approach, PEPFAR will prioritize funding for evidence-based interventions including antiretroviral treatment (together with HIV testing and other related services), PMTCT and VMMC. To implement this evidence-based approach, PEPFAR released a detailed programmatic blueprint in 2012. In individual countries, PEPFAR efforts are guided by a Country Operational Plan, which is negotiated with national governments. To implement its new, more strategic approach that prioritizes efforts to drive down the number of new infections, PEPFAR country teams have worked with national partners to undertake a comprehensive assessment of the HIV prevention portfolio. In a number of cases, marked changes in funding priorities have been implemented. In particular, PEPFAR has instructed country teams to de-prioritize behavioural interventions (such as abstinence programs) in order to enhance funding for priority interventions.

PEPFAR has shown flexibility in responding to research advances and the emergence of new HIV prevention tools and strategies. Within a few weeks of the release of early results from HIV Prevention Trials Network (HPTN) 052 trial, for instance, PEPFAR convened its scientific advisory committee and agreed on programme adaptations to capture the prevention potential of antiretroviral therapy. PEPFAR has also led global efforts to respond to clinical trials demonstrating the prevention benefits of adult medical male circumcision.

The Global Fund: The Global Fund plays a pivotal role in financing HIV programmes in LMICs. The Global Fund supports nearly half of all people receiving antiretroviral therapy, and the organization has also supported uptake of PMTCT, HIV testing and counselling, and other HIV interventions. Altogether, the Global Fund is responsible for 21% of all HIV-related financing. As of 2011 (the latest year for which such information is available), 30.4% (US$ 1.9 billion) of its HIV portfolio was for prevention activities, 28.0% for treatment and care, 14.0% for health systems strengthening, and 27.7% for other activities.

Non-US Bilateral Donors: European governments accounted for 34% of HIV assistance by donor governments in 2011. By total expenditure, leading non-US donors in 2011 were the UK (12.8% of all HIV assistance), France (5.4%), the Netherlands (4.2%), Germany (4.0%), and Denmark (2.5%). The balance between prevention and treatment in non-US bilateral HIV support is unclear, as is the distribution of financing among different HIV prevention approaches.

National Governments: An important trend is the increasing trend among many LMICs to self-finance a larger share of their national AIDS response. In 2011, for the first time, countries themselves accounted for a majority (51%) of total HIV-related expenditures (US$ 16.8 billion).

Increasingly, global experts are focusing on LMICs as potentially vital sources of funding for HIV programmes. According UNAIDS analysis taking into account current and projected economic growth, African governments could generate annual additional funding of US$ 4.7 billion by bringing national HIV allocations into line with the epidemic's actual health burden and with commitments made by African countries to allocate 15% of their national budgets to health. However, major shifts in national policy will be needed, along with robust economic growth, in order to make this scenario feasible. Among 33 sub-Saharan African countries with available expenditure data, 26 relied on international sources in 2011 for more than half of their HIV-related resources, with 19 looking to external sources for at least 75% of all HIV-related spending.

In addition to allocating a larger share of domestic public sector spending towards HIV, countries will also need to strengthen their focus on HIV prevention. While domestic sources account for the majority of global spend-

ing on antiretroviral treatment, international sources account for the vast majority of spending on HIV prevention. National resistance to evidence-based HIV prevention is especially acute with respect to programmes for marginalized populations. In 2011, international donors accounted for 92% of all HIV-related funding for people who inject drugs, 91% of funding of prevention activities among sex workers, and 92% of all spending for men who have sex with men.

United Nations: The UN agencies play a prominent role in the global AIDS response through the collection and dissemination of strategic information, issuance of normative guidance, and the delivery of technical support, in addition to limited implementation roles by certain UN agencies (e.g. UNFPA, UNICEF). In the case of new technologies, donors and national governments look to UN agencies to develop programmatic guidance on their use of new tools, including the prequalification of products (medicines, condoms, vaccines and devices). UN-led technical support facilities exist in numerous regions to respond to national requests, including, but not limited to, assistance for the roll-out and management of health technologies.

6. Review of HIV Prevention Commodities

The following section analyses current access, research pipeline and market conditions for the different categories of HIV prevention commodities. It aims to provide UNITAID and other stakeholders with the information needed to evaluate the feasibility of market interventions to increase and accelerate commodity uptake.

6.1. Male Circumcision Devices

Considerable international interest has focused on two devices to facilitate the scale-up of VMMC: PrePex and the Shang Ring. By avoiding the use of sutures and potentially shortening the time required for a procedure, it is hoped that the devices will help accelerate scale-up by limiting the reliance on surgeons or other advanced medical personnel in the delivery of VMMC. In addition, some have suggested that the devices might help increase demand for circumcision by potentially alleviating fears and anxieties associated surgical techniques.

Before examining each of these devices in detail (and addressing other VMMC devices in somewhat less detail), this section provides background information on the HIV prevention benefits associated with circumcision. The subsequent discussion also explores important limitations and challenges associated with surgical circumcision, and explains why the devices have attracted such international interest.

Background

Globally, male circumcision is one of the oldest and most common of all surgical procedures, with an estimated 30% of males over age 15 having been circumcised. (14) However, prevalence of circumcision varies widely within and among countries, with Muslims accounting for 70% of all circumcised males worldwide. National prevalence of circumcision among males 15 and older in 2007 was 14% in Uganda and 35% in South Africa. (14)

In the 1980s, epidemiological studies detected notably lower HIV prevalence in settings where male circumcision was common. (15) Numerous other studies subsequently confirmed the association between circumcision status and HIV risk, with circumcised men consistently less likely to be HIV-infected than their uncircumcised counterparts. (16) (17)

As this powerful evidence emerged, investigation focused on physiological characteristics of the foreskin that might explain the link found in epidemiological studies. After extensive study, a scientific consensus emerged that the concentration of Langerhans' cells along the inner surface of the foreskin served as an effective entry point for HIV. (18) In addition, it was theorized that the foreskin might experience tears or abrasions during sexual intercourse that could facilitate entry of the virus. Moreover, extensive evidence links lack of circumcision with a heightened risk of numerous sexually transmitted infections (STIs) (16), which enhance the odds of HIV transmission and acquisition. (19)

Notwithstanding the considerable evidence associating circumcision status with HIV risk, many experts were initially sceptical that the documented correlation necessarily meant that circumcision status itself was responsible for the differential risk observed. Some questioned whether background HIV prevalence or social and cultural patterns might explain the higher HIV risk observed in settings where the prevalence of circumcision was low.

During the previous decade, three large prospective randomized clinical trials were mounted to evaluate whether circumcising adult males reduced their risk of becoming infected. Conducted in Kenya, South Africa, and

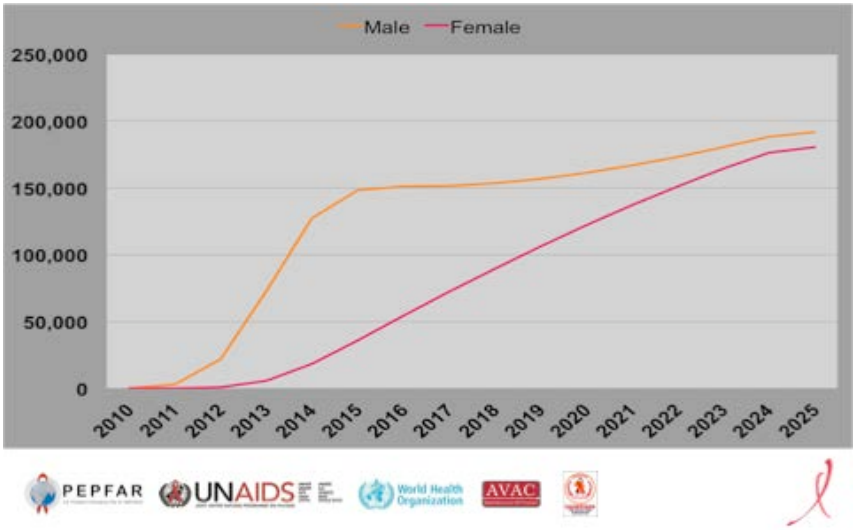
Uganda, these three trials reached remarkably similar results, finding that VMMC reduced the risk of female-to-male HIV transmission by roughly 60%. (20) (21) (17) Follow-up on trial participants has documented the durability of the protective effect more than five years after the circumcision procedure, with some indication that the degree of protection may increase over time. (22) (23)

Based on these compelling findings from clinical trials, in 2007 WHO and UNAIDS formally recommended the scale-up of VMMC in settings with high prevalence of sexually transmitted HIV and low prevalence of male circumcision. (24) Initially, WHO recommended that VMMC be scaled up in settings in sub-Saharan Africa with high prevalence of HIV and low prevalence of male circumcision. Thirteen countries (Botswana, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, the United Republic of Tanzania, Zambia and Zimbabwe) have added this intervention to national HIV prevention programmes. Subsequently, WHO and the Joint United Nations Program on HIV/AIDS (UNAIDS) have begun encouraging and monitoring the roll-out of VMMC in parts of Ethiopia and are considering expanding their recommendations to parts of additional African countries.

Modelling has determined that rapidly scaling up VMMC over a five-year period to reach 80% of uncircumcised males between ages 15-49 in the 13 original priority countries would reduce projected HIV incidence by more than 20% through 2025. (25) Although the direct prevention benefit from VMMC is to men, women will benefit as well from VMMC scale-up, through a reduction in the number of males infected with HIV and other STIs. According to modelling, the long-term prevention benefit to women as a result of VMMC will roughly equal the benefit to men by 2025. (25)

As an intervention that offers only partial protection, it is important to situate VMMC within the broader context of programmes that combine multiple HIV prevention interventions, including behaviour change communication, promotion of male and female condoms, treatment scale-up, prevention programmes for key populations, and education of newly circumcised men and their partners about partial protection.

Total New HIV Infections Averted



The number of VMMC procedures needed to achieve 80% coverage varies considerably among priority countries, with more than 4 million circumcisions required in South Africa and Uganda each. The potential prevention benefit also varies among countries. While reaching the VMMC target coverage of 80% would prevent 9.2% of new infections projected to occur in Tanzania through 2025, scale-up would avert an estimated 41.7% of new infections in Zimbabwe during this time period. (25) Because the prevalence and incidence of HIV in the 13 countries varies, the number of VMMC procedures needed to prevent a single case of HIV infection also differs, ranging from four procedures in Zimbabwe and five in Lesotho, South Africa and Swaziland, to 44 in Rwanda and 26 in Namibia. (25)

As an HIV prevention intervention, VMMC has particular advantages. Unlike many HIV prevention interventions—such as condoms or antiretroviral-based prevention technologies, which require ongoing adherence by the user—VMMC is a one-time procedure that offers lifelong protection. Analyses have found VMMC to be the most cost-effective of all HIV prevention interventions. (26) (27) (28) (29) Rapid VMMC scale-up—i.e., reaching 80% of uncircumcised adult males by 2015 in the 13 original priority countries—is projected to save an estimated US$ 16.6 billion in averted health care costs between 2011 and 2025. (25) A recent model based on experience in South Africa concluded that VMMC is substantially more cost-effective than providing antiretroviral therapy to all persons with HIV infection, regardless of CD4 count, with VMMC having a cost per infection averted roughly one-sixth that of early treatment as prevention. Moreover, this modelling exercise concluded that high treatment coverage (at CD4 count < 350) combined with high VMMC coverage provides approximately the same HIV incidence reduction as early treatment alone, for US$ 5 billion less from 2009–2020. (30)

Commodity access issues

Surgical methods

Although six years have elapsed since WHO and UNAIDS recommended roll-out of VMMC in priority countries, scale-up to date, based mainly on surgical methods, has been slow. There are signs that the pace of scale-up is quickening, although uptake will need to accelerate dramatically in order to achieve the 80% coverage target for 2015.

Up-to-date VMMC coverage figures are not available (as there is typically at least a six to twelve month delay in reported coverage), but it is reported that, through September 2012, PEPFAR had supported VMMC for 2 million men in sub-Saharan Africa. (31) With PEPFAR financing roughly 80% of VMMC procedures in the region, it appears that the 13 priority countries collectively are more than 10% toward the goal of circumcising 20 million men by 2015.

Evidence indicates that efforts to bring VMMC to scale are experiencing increasing momentum. More VMMC procedures were performed in 2011 than in the previous three years combined.

Progress varies among the priority countries. The greatest gains have been achieved in Kenya, where nearly 500,000 men have been circumcised since 2008, mostly in Nyanza Province, where circumcision prevalence is much lower than the national average. (32) Through VMMC promotion efforts, Kenya has circumcised a majority (52.2%) of previously uncircumcised men in Nyanza Province. (33) Elsewhere, progress has been much slower, with Ethiopia and Swaziland the only countries along with Kenya that had reached at least 20% of their national VMMC targets as of December 2011. The numbers required to reach the 20% coverage threshold are much lower in these countries—15 438 and 38 912 in Ethiopia and Swaziland, respectively—than in countries such as Uganda and South Africa. (4)

Number of Male Circumcisions Performed in the 14 Prioriy Countries: 2008–2012

Country	Number of MCs carried out per year						% achieved of estimated number of MCs needed to reach 80% prevalence by end of 2011
	2008	2009	2010	2011	2012 (end August)	Total by end of 2011	
Botswana	0	5,424	5,773	14,661	26,423	25,858	7.5
Ethiopia	0	769	2,689	7,542	9,600	11,000	27.5
Kenya	11,663	80,719	139,905	159,196	118,517	391,483	45.5
Lesotho**	No data	No data	No data	No data	5,953	No data	N/A
Malawi	589	1,234	1,296	11,881	No data	15,000	0.7
Mozambique	0	100	7,633	29,592	69,249	37,325	3.5
Namibia	0	224	1,763	6,123	3,607 (July)	8,110	2.5
Rwanda	0	0	1,694	25,000	33,100	26,694	1.5
South Africa	5,190	9,168	131,117	296,726	No data	442,201	10.2
Swaziland	1,110	4,336	18,869	13,791	8,728	38,106	20.8
Tanzania	0	1,033	18,026	120,261	116,673 (July)	139,320	10.1
Uganda	0	0	21,072	77,756	104,721(March)	98,828	2.3
Zambia	2,758	17,180	61,911	85,151	No data	167,000	8.6
Zimbabwe	0	2,801	11,176	36,603	25,700	50,580	2.6
Total	21,310	122,988	422,924	884,283	(522,271)	1,451,505	7.0

Source: Ministries of Health
No data available for Lesotho

Demand has frequently been robust when services are first offered, although reports indicate that demand sometimes declines over time, especially among men over age 25. In one relatively mature VMMC programme in the Iringa region of Tanzania, 77% of circumcisions are conducted on men under the age of 20 years. (34) In Kenya, where VMMC scale-up has been most pronounced, the median age of VMMC clients is 17 years. (33) Although reaching teenage males with VMMC confers a prevention benefit, the impact on population-level incidence is delayed, as most adolescent males have yet to initiate sex or to become involved in regular sexual relationships. Reasons why older men have been less likely than teenagers to seek VMMC may include reluctance to miss work (and potentially forfeit associated income), resistance to the recommended period of abstinence following the procedure, and perceived low risk because of being in stable relationships. Programme implementers have developed tailored approaches to reach older men, including holding after-hours and weekend clinics and separating men over 25 years from young adolescents. It has become clear that demand generation efforts need to be tailored to different populations and age groups. In an effort to build evidence for best practices for demand creation, the International Initiative for Impact Evaluation recently issued a call for research topics in this area (35) and plans to award research grants for innovative demand creation strategies in 2013.

Although numerous studies have found VMMC to be broadly acceptable in sub-Saharan Africa (36) (37) (38) (39), actual demand for VMMC in the real world has been variable. (40) Even in the generally favourable scientific literature on VMMC acceptability, more than one-third of uncircumcised men say they are not willing to be circumcised. (37) If extended to the real world, this degree of refusal would prevent programme implementers from reaching country targets of 80% coverage. While robust demand for VMMC has been reported in some settings (41) (42) (43), demand in other settings has been less apparent. With numerous countries reporting increased success in rolling out VMMC, there are signs that demand challenges can be overcome. Ultimately, health officials aim to establish new social norms favouring routine offer of male circumcision in priority countries, building in part on favourable "word of mouth" from the increasing number of men who have been circumcised.

Kenyan VMMC Campaign—2009

There has been considerable effort devoted to social marketing of VMMC. Kenya has embarked on rapid response initiative campaigns, involving intensive community awareness efforts and deployment of multiple VMMC teams to deliver services. Celebrities (such as the rap star Winky D in Zimbabwe) have been mobilized to encourage men to be circumcised. Many social marketing efforts use humor, such as a posters in men's restrooms in Uganda depicting a woman who expresses shock upon learning that her partner is uncircumcised. Marketing campaigns also target women, and national militaries have partnered with PEPFAR to offer VMMC to incoming military recruits. There is some evidence that these mass marketing initiatives are having an effect, with awareness of VMMC and its benefits increasing in South Africa between 2009 and 2012. (44)

Several factors have contributed to the slow pace of VMMC scale-up, including, first and foremost, weaknesses in health care infrastructure. As a surgical procedure, VMMC currently requires trained medical personnel and the dedication of sufficient clinical space for VMMC procedures to be performed. According to studies in Kenya and Zambia, standard surgical circumcisions require about 20 minutes for trained medical staff to perform. (45) Recognizing the role of limited health care resources in slowing scale-up, WHO has recommended adoption of Models for Optimizing the Volume and Efficiency (MOVE) of male circumcision services. (46) A critical element of the MOVE model is task-shifting, which looks to nurses to perform components of VMMC delivery that have traditionally been undertaken by surgeons. MOVE also involves the strategic design of surgical settings to streamline patient flow, use of optimally efficient surgical techniques, and use of approaches that swiftly stop post-operative bleeding, such as diathermy cautery. It is estimated that full implementation of the MOVE model could increase by four-fold the number of VMMC procedures that could be performed with the same number of staff. (40) In countries that have implemented the MOVE model, task-shifting and other efficiency-promoting practices have contributed to swifter scale-up. (33) In several countries, weaknesses in the underlying health care infrastructure are compounded by limited capacity within Ministries of Health to develop and manage a VMMC programme.

Adult and Adolescents Male Circumcision Devices

Uptake of the VMMC devices to date has largely been limited to clinical and field trials. Rwanda is something of an exception, as in 2012 WHO advised phased roll-out of PrePex in Rwanda, where extensive study of PrePex had occurred. The Government of Rwanda envisages PrePex as central to the country's aim to circumcise 2 million adult men in the next 24 months and projects that using PrePex as the centrepiece of its VMMC programme will enable the country to reduce HIV incidence by 50%, although these estimates have not been validated by real-world experience. As of mid-2012, 4,200 men in Rwanda had received VMMC with PrePex.

The implications that the emergence of PrePex and Shang ring will have on HIV prevention are unclear. It is believed that they could help accelerate scale-up by reducing the need to involve surgeons and by reducing the time required for standard surgical circumcision by about two-thirds.

The degree to which national health authorities will endorse the use of nurses to deliver VMMC through these devices also remains uncertain. In addition, the MOVE model has already been demonstrated to reduce time required for performance of surgical VMMC, making the actual time saved from the devices somewhat unclear. Programmes would need to determine how to best strategically configure themselves in order to capitalize on the potential time-savings offered by the devices.

Many experts believe that introduction of one or more of the devices will facilitate scale-up, if only by offering uncircumcised men another option in addition to surgery. VMMC advocates hope that the client's ability to avoid sutures will be a powerful selling point for many currently uncircumcised men and that the avoidance of injected anesthesia in the case of PrePex will be a further incentive to men. Others wonder if the need for two visits (one for placement and one for removal) could affect their appeal.

Infant circumcision

Little, if any, progress has been made in rolling out infant circumcision in priority countries, partly because conversations with appropriate stakeholders have not occurred to any significant extent and sources of reliable funding to support this sustained activity have not been identified. This is viewed by some as a lost opportunity. Unlike the catch-up phase for adolescent and adult VMMC that is envisaged as a time-limited vertical programme, circumcision of infants or young boys will need to be sustained and likely integrated into existing services, such and maternal and child health programmes, vaccination programs or perinatal care. Parental consent is mandatory. Policies on techniques to be used and on the cadres of health providers who will deliver services have yet to be developed.

Delivery of male circumcision in infants is simpler than adolescents and adults, in that it can be integrated into pre-existing neonatal care. Neonatal male circumcision is safer than adult and adolescent VMMC and will likely be less expensive. An analysis in Rwanda suggests that the potential to achieve very high coverage of male circumcision is much greater with infant circumcision than with adolescents and adults. (47)

Although data demonstrate that infant circumcision is easier, faster, safer and less expensive than VMMC in adults and adolescents, the impact of infant circumcision on HIV incidence will not be seen for approximately 15 or more years, when circumcised infants reach adolescence or adulthood and become sexually active. However, some countries, such as Botswana and Zimbabwe, have expressed interest in implementing infant male circumcision as part of their overall programme.

Technology landscape

Surgical methods

In contrast to infant male circumcision, the techniques recommended to date for adult male circumcision were only surgical, requiring suturing for haemostasis and wound closure, and hence technically more difficult and longer to perform. With the exception of field trials of new non-surgical devices, the vast majority of VMMC procedures in sub-Saharan Africa are performed surgically. WHO recommends three surgical methods for VMMC, each of which is performed with local anaesthesia (48):

- ***Forceps-Guided:*** After marking the intended line of incision on the foreskin, the surgeon uses forceps to grasp the foreskin. The surgeon extends the foreskin until the incision line is beyond the end of the glans. Using his or her hands to feel for the glans, the surgeon applies the forceps across the foreskin beyond

the glans. A scalpel is used to cut away the foreskin along the edge of the forceps such that the forceps is between the cut edge of the foreskin and the glans, protecting it from the scalpel. Appropriate measures are taken to stem the bleeding, and sutures are used to close the wound.

- ***Dorsal Slit:*** The dorsal slit procedure requires somewhat greater surgical skill than the forceps-guided method, but a potential advantage of the approach is that the surgeon is able to see the glans when cutting away the foreskin, thus decreasing risk of injury to the glans during the procedure. After marking the line of incision, the surgeon uses forceps to extend the foreskin, and surgical scissors to make a single slit (dorsal slit) from the end of the foreskin to the point of intended incision. Surgical scissors are used to remove the foreskin. Appropriate measures are taken to stem the bleeding, and sutures are used to close the wound.
- ***Sleeve Resection:*** The sleeve resection method requires the greatest surgical skill, and WHO recommends its use in hospital rather than clinic settings. With this method, the surgeon makes two circumferential incisions around the penis and removes the foreskin tissue between the two cuts, taking care not to cut through to the underlying tissue, after which haemostasis is achieved and the wound is closed with sutures. While cosmetic results are superior with the sleeve resection method, it is the most human resource-intensive of all surgical methods and surgical error and damage to the penis from cutting too deep with the incisions or dissection of tissue is possible if the procedure is not correctly performed.

Men who receive circumcision must abstain from sex for four to six weeks to allow the wound to heal, as the presence of an open wound on the penis could actually increase the risk of HIV acquisition or transmission to sexual partners, in the case that the man has HIV infection. (48) According to a recent study, roughly one in four men who receive VMMC have sex during the healing period. (49) At a population level, there remains a clear prevention benefit for men even in the face of such high rates of premature resumption of sexual activity, although HIV-related risks for the female partners of recently circumcised men are highly sensitive to the prevalence of sex during the healing period. (49)

Traditionally, many African men have been circumcised during adolescence in the context of ethnic rituals. Some traditional ethnic rituals in the region result in only partial removal of the foreskin and other complications, such as bleeding, infection and even death. Men who obtain only partial circumcision through traditional rituals have comparable HIV risk as uncircumcised men and are significantly more likely to acquire HIV than men who have been medically circumcised (i.e., full removal of the foreskin). (50)

Adult and Adolescent Male Circumcision Devices

As VMMC scale-up emerged as a major global health priority, devices emerged as an option to decrease the skills and time required for the procedure and potentially to reduce costs associated with the intervention. Several male circumcision devices are available in sizes for adults and adolescents, although until recently little data were available on the safety and acceptability of their use, especially in African countries.

Based on the mechanism of action, WHO has developed a classification scheme for VMMC devices consisting of four categories:

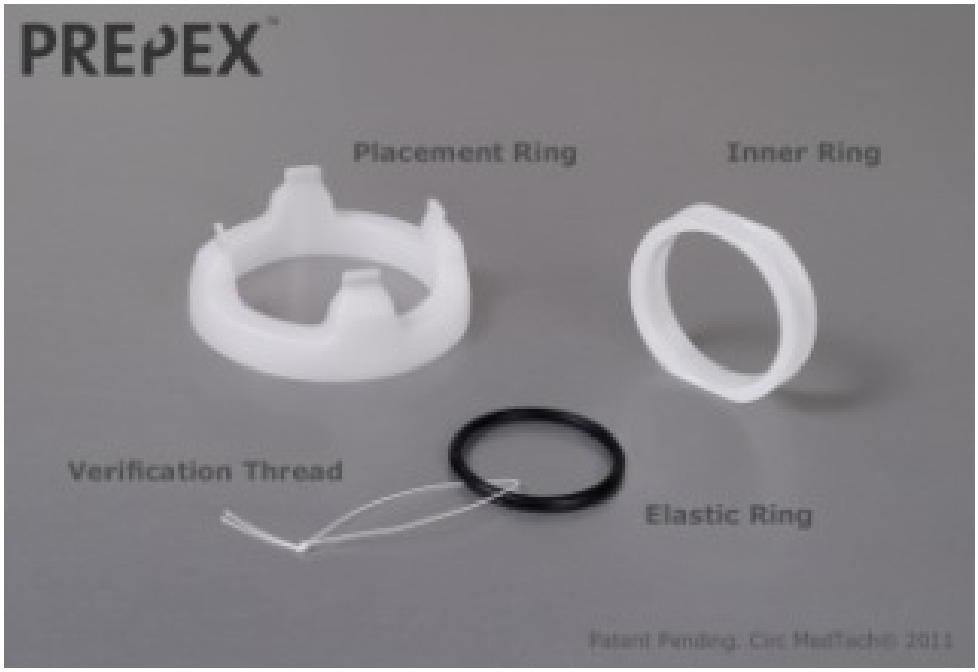
- *Surgical Assist Male Circumcision Devices*: Reusable metal devices employed during surgery and not worn by the client after the procedure.
- *Clamp and Latch Male Circumcision Devices*: Disposable devices that are worn about seven days, utilize a clamping mechanism to hold the device in place on the foreskin, and achieve haemostasis after the foreskin is cut at the time of placement.
- *Male Circumcision Devices with Ligature Compression*: Worn for seven days, these devices use a ligature around the device to hold it in place. This ligature achieves and maintains haemostasis after the foreskin is cut at the time of placement.
- *Male Circumcision Devices with Elastic Collar Compression*: With these devices, compression with an elastic band leads to necrosis of the intact foreskin. The device and necrotic foreskin are removed at the same time, about seven days after placement.

Of the devices available in sizes for adolescents and adults (51), two—the PrePex and Shang Ring—have particularly piqued the interest of global health experts and health officials in priority countries.

PrePex

PrePex is a relatively simple *elastic collar compression device* consisting of two plastic rings and one elastic ring. Rings are available in different sizes, allowing the health worker to choose the appropriately sized device by reference to a sizing gauge included in the PrePex kit. During the procedure, the elastic ring is loaded on the placement ring and placed over the penis shaft. The foreskin is then stretched to permit insertion of an inner ring between the inner aspect of the foreskin and the glans, with the elastic ring placed over the inner ring at a pre-marked circumcision point, trapping the foreskin between the elastic and inner rings. The placement ring is then removed. (51)

PrePex Device



The individual leaves the clinic with the inner ring and elastic ring attached to the penis. Over the following week, the foreskin desiccates, as the device restricts the flow of blood. Seven days after placement of the PrePex device, the client returns to the clinic, where a health worker removes the necrotic foreskin. The elastic ring is cut and removed along with the inner ring. To finish the procedure, the health worker dresses the wound. (52)

PrePex appears to have several advantages over many other circumcision methods. Intended for use in non-sterile settings, administration of PrePex requires no sutures or injected local anesthesia (although a topical anaesthetic or oral pain relief medicine may be administered prior to placement of the device). (52) Placement of PrePex by physicians has been documented to be safe in a small study in Rwanda. (53) A recent study of use of PrePex in 590 men, also in Rwanda, indicates that trained nurses are also capable of safely and effectively delivering VMMC with the PrePex device. The study found that PrePex delivery by nursing teams that received formal PrePex training was associated with complete circumcision and that there were no severe adverse events. (52)

PrePex requires considerably less time from health care workers than standardized surgical circumcision. For the last 125 patients who received VMMC with PrePex in the above-noted, the average time for PrePex placement and removal (including time required for preparation) was 4 minutes, 39 seconds. (52) Additional studies on Prepex have been conducted in Zimbabwe and Uganda, although results have not yet been published. Healing after use of PrePex is longer than that seen with surgical circumcision and displacements and self-removals have been observed (54).

Shang Ring

Another simple device, the Shang Ring, is *a clamp-and-latch device* that consists of two concentric plastic rings and is available in 22 sizes from infant to adult. Before placing the device, a health care worker measures the client's penis to determine the appropriate size for the device. After injection of a local anaesthetic, the inner ring is placed on the outside of the foreskin at the circumcision point, the foreskin is everted over the inner ring, and an outer ring is placed, sandwiching the foreskin in place. The health worker then cuts the foreskin away. (45) (51) One week later, the client returns to the clinic for removal of the device. The outer ring is opened and removed, the inner ring is removed, and the health worker dresses the wound. (45)

Shang Ring Device

Studies have found Shang Ring to be safe and effective. (55) Shang Ring has a rate of adverse events that it is comparable to experience with conventional surgical circumcision. (45) According to a recent study in Kenya and Zambia, the rate of client satisfaction with the appearance of the penis following VMMC was significantly greater for recipients of Shang Ring than for men who had been surgically circumcised. (45) Clients who received Shang Ring reported levels of pain that were comparable to their surgically circumcised counterparts. (45)

Like PrePex, VMMC with Shang Ring requires considerably less time to perform than standard surgical circumcision. Total time required for placement and removal of Shang Ring is seven minutes—roughly one-third of the time required for surgical circumcision. (45)

Shang Ring involves little, if any, blood loss, and no sutures are required. A sterile setting is required, and local anaesthesia is administered prior to placement of the device. (51) Field research in Kenya and Zambia suggests that the post-procedure healing period is somewhat longer for Shang Ring (44.1 days) than for conventional surgery (38.9 days). (45)

Other Adult and Adolescent Male Circumcision Devices

Although PrePex and Shang Ring are the devices that have captured the attention of the global health field, there are other circumcision devices. Most of these tend to be somewhat bulkier than PrePex or Shang Ring:

- *Ali's Klamp:* Manufactured in Turkey, this clamp-and-latch device was originally designed for neonatal circumcision, although experimental devices have been developed for adults and tested in a small study in Kenya. Like Shang Ring, Ali's Klamp restricts blood flow to the foreskin once cut so that sutures are not required. A removable plastic tube protects the glans from injury while the foreskin is cut. (51) The average duration of VMMC with Ali's Klamp ranges from 3 minutes (56) to 4.5 minutes. (51) A 58-person study in Kenya found VMMC with Ali's Klamp to be safe and well-tolerated. (56) Its supply is restricted to medical providers who have been trained in its use. In 2012, Ali's Klamp was being marketed in about 20 countries. There are indications that Ali's Klamp may be vulnerable to removal by the patient and by displacement as a result of an erection. (51)
- *Smartklamp:* Manufactured in Asia, Smartklamp is another clamp-and-latch device that operates much like Ali's Klamp. Smartklamp largely disappeared after the liquidation of the Dutch company Circumvent BV (51), but it has re-emerged in Malaysia. Initially produced only in children's sizes, Smartklamp is now available in experimental adult sizes. (51) Issuing a finding of "substantial equivalence" to other approved devices, the US FDA has approved marketing of Smartklamp for circumcision of "newborns and older males." (57)
- *Tara KLamp:* The Tara KLamp was the first single-use, clamp-and-latch device to be marketed. (51) It functions much like Ali's Klamp and the Smartklamp, although the latch on the device is especially secure, reducing the risk of removal by the client. (51) Tens of thousands of men in KwaZulu-Natal Province of South Africa have been circumcised with the Tara KLamp, which is a mainstay of provincial efforts to bring VMMC to scale, although outcomes with use of the device have not been published, and its use in KwaZulu-Natal has generated considerable controversy. An earlier clinical trial found a high rate of adverse events associated with use of the Tara KLamp and the trial was halted early. (58) In 2012, the Treatment Action Group has asked public prosecutors to investigate purchase of the Tara KLamp in South Africa. (59)

Infant male circumcision devices

There are at least 12 devices for infant circumcision, including several that are also available for adults and adolescents. Only Gomco Clamp, Mogen Clamp and Plastibell are listed by WHO for use in infant circumcision in the WHO/UNAIDS/Jhpiego "Manual for Early Infant Male Circumcision under Local Anaesthesia" (60). The manual recommends one surgical method (the dorsal slit) and the three devices for infant male circumcision. If clinical studies outlined by WHO are completed and other infant devices are prequalified, it is likely that WHO will expand its recommendations to cover other infant circumcision devices.

Some devices to assist with infant male circumcision have been in use for over 50 years (Gomco clamp has been used in the US since the 1930's; Mogen clamp and the disposable Plastibell since the 1950's), and several have been well studied, including in randomized clinical trials. These devices also have been in use for some time in African countries and considerable clinical data are available on their use. A comprehensive review of 52 studies from 21 countries of circumcision in infants and children, including those performed by surgery and devices, found few severe complications following circumcision including in low- and middle-income settings. Mild or moderate complications are seen, especially when circumcision is undertaken at older ages and when it is performed by inexperienced providers or in non-sterile conditions. Complications are substantially more common with freehand circumcisions (27%) than with using Plastibell (8%).

Gomco and Mogen Clamps are metal reusable devices that require cleaning and sterilization between uses. Gomco, consisting of four separate parts, has an excellent safety record when used as directed, although serious complications may develop if parts from differently sized devices or from different manufacturers are used. A complication of Mogen Clamp is the potential for injury to or even severing of the glans. Plastibell has been associated with penile injury and necrosis from proximal migration of the ring component on the penis, especially if the wrong sized device is used. (61)

In an effort to avoid such safety concerns, a new device, Accu-Circ, was designed in a manner to shield the glans and use an internal blade to cut the foreskin; studies examining this device are ongoing in Botswana and Zimbabwe.

Market overview

Demand

As national programmes move to embrace combination prevention, integrating VMMC referral into programs such as home-based testing may increase demand for services.

Achievement of the current target for VMMC in the 13 original priority countries of sub-Saharan Africa (80% VMMC coverage by 2015 in men 15-49 years old) would require delivery of VMMC services to about 20 million men. (25) This figure increases to nearly 30 million with the addition of boys who will age into this cohort. In reality, the VMMC market is considerably larger, as it is based on the assumption that the 80% target will be met by 2015 and that infant circumcision will immediately be brought to scale. However, the 80% target is unlikely to be achieved given the current pace of scale-up, and infant circumcision programmes have yet to be introduced. As a result, adult and adolescent VMMC will need to continue longer than originally anticipated, enlarging the potential market for these new devices.

Main buyers: International donors account for the overwhelming bulk of financing for VMMC scale-up. Currently, PEPFAR is only major funder of VMMC services, supporting an estimated 80% of VMMC procedures in sub-Saharan Africa. PEPFAR has established and aggressively pursued a programme target of reaching at least 4.7 million men with VMMC in 2012 and 2013.

National political and financial support for VMMC scale-up has varied, sometimes slowing the pace of scale-up, (62) with at least six priority countries devoting less than 2% of their overall budget for HIV prevention to VMMC activities in 2011. (4) In 2012, national governments appeared to increase their engagement in VMMC scale-up, working more closely in partnership with international donors to increase VMMC uptake. (63) However, only two countries—South Africa and Zambia—currently allocate domestic resources for VMMC activities. In the case of South Africa the investment has been sizable. While the Government of Rwanda has been extremely enthusiastic about rolling out PrePex in its VMMC programmes, the degree of interest among other priority countries is less clear.

Factors that may diminish political support for VMMC include competing priorities, a desire to avoid championing a potentially controversial cause, cultural practices around circumcision and misconceptions regarding the effectiveness of VMMC in preventing new HIV infections.

With respect to the **purchase of non-surgical circumcision devices**, there appear to be two main players—the US Government's PEPFAR programme, and the Global Fund, both of which are prepared to purchase devices to promote uptake in VMMC programmes in priority countries as they become prequalified by WHO.

To date, the Global Fund has approved approximately US$ 29 million for VMMC activities in five countries, with the bulk of this funding (US$ 20 million) earmarked for scale-up with PrePex in Rwanda. The Global Fund has expressed interest in increasing its investments in VMMC.

PEPFAR and the Bill & Melinda Gates Foundation have made funding available for pilot introductory studies aimed at examining device use in a programmatic context as they are prequalified. Such studies are planned for several countries; Kenya has launched its pilot study, and similar studies are anticipated to begin soon in Botswana, Mozambique and Zimbabwe. As part of these studies, countries need to define the in-country regulatory pathway needed for device use. The interest expressed by a number of countries in hosting such pilot implementation studies for PrePex suggests that they may be keen to incorporate this device.

The private market for non-surgical circumcision devices for adults is expected to be minimal in sub-Saharan Africa in the near term, although this could evolve overt time as national health insurance programmes become more widespread.

Quality and safety requirements: In response to the growing interest in possible use of devices in scale-up of adult and adolescent VMMC, WHO held consultations with stakeholders, established a Technical Advisory Group on Innovations in Male Circumcision, and published the "Framework for Clinical Evaluation of Devices

for Adult Male Circumcision", (64) which outlines recommended clinical evaluation of devices for use in VMMC scale-up in adults and adolescents. The WHO framework provides for a series of studies to establish safety and acceptability for each discrete class of male circumcision devices, rather than individual devices. In addition, WHO has established a formal programme for prequalification for adult VMMC devices. The programme aims to provide technical information to other UN agencies and WHO Member States on each male circumcision device; promote and facilitate access to safe, appropriate and affordable devices of assured quality; and facilitate rigorous regulatory oversight in settings where regulatory processes are weak or non-existent. The prequalification process includes review of the application form; review of the product technical dossier, including clinical evidence; and inspection of the manufacturing site(s). As data for each of these devices solely addresses use of the device in men who are 18 years or older, prequalification of these devices will be limited to use in this population. WHO has outlined the additional studies that will be needed to assess device safety in other populations, such as adolescents under the age of 18.

PEPFAR will support purchase of devices for adolescents and adults only after prequalification; requirements for infant devices have not been stated. The Global Fund requires that, for purchase, products are selected from an applicable list of prequalified products, once such list is on place, and are in compliance with the quality standards applicable in the country where such products will be used.

Supply

PrePex is manufactured in Israel and was developed by Circ MedTech, which is incorporated in the British Virgin Islands. The company has donated devices for some of the trials and provided PrePex for other trials, reportedly at a cost of approximately US$ 15-20 per device.

PrePex has generated considerable interest in global health circles. Circ MedTech received a Business Action on Health Award from GBCHealth, which seeks to increase business engagement on global health issues. The Acumen Fund, a non-profit global venture fund that focuses on poverty reduction in South Asia and East Africa, announced in 2011 that it had invested in Circ MedTech to build the company's capacity for wide-scale roll-out of PrePex in sub-Saharan Africa. (65) Commercial sources exist for elastic rings, although this has not been validated by Circ MedTech. Circ MedTech has claimed to have the capacity to produce 500,000 devices per month.

PrePex has been approved by the FDA and approved for use in the European Union. WHO prequalification was granted as of 31 May 2013 for use in those 18 years and older (with use recommended in settings where there is access to surgery in 6-12 hours in the case of presentation of complications that need to be managed with surgical circumcision). (66)

With manufacturing costs believed to be quite low for PrePex, it is expected that amortization of R&D investments will likely constitute the bulk of the initial price of the device. Manufacturing costs are believed to represent a small fraction of the company's anticipated asking price for this simple device as the manufacturing process for PrePex is believed to utilize injection moulding, a simple and inexpensive process for production of the placement and inner rings. Circ MedTech will undoubtedly seek to recoup its R&D costs as soon as possible, especially as PrePex is the company's primary focus and single major product line. It is estimated that the company needs to recover amounts in the range of US$ 4 million in R&D costs. (67)

Shang Ring is manufactured in China by WuHu SNNDA Medical Treatment Appliance Technology Co. Ltd. As no manufacturing site visit has yet occurred for purposes of the company's prequalification application, details on the manufacturing process for Shang Ring are not available. No meaningful information is readily available with respect to pricing or supply outside China.

While manufacturing processes have not been verified, inexpensive injection moulding techniques could likely be used to produce the device's components. Informants report that the company has the capacity to produce 200,000-300,000 Shang Ring devices per month. This, however, will need to be verified. To date, about 200,000 Shang Ring devices have been sold in China.

Shang Ring has been approved by FDA for marketing in the US and has also been approved for use in China by the Shanghai FDA. The series of clinical studies recommended by WHO have been conducted for the device, and a prequalification decision for Shang Ring was pending at WHO at the time this report was released.

Manufacturing cost for Shang Ring is believed to be similar to that of PrePex. Concerns regarding recoup of R&D investments may be less pronounced for WuHu SNNDA, which has an existing market for the Shang Ring, albeit modest, in China. In China, the device sells for US$ 80-85. The price at which the company would be willing to offer Shang Ring for use in VMMC programmes in sub-Saharan Africa is unknown, as thinking about potential purchases far less advanced for this device than for PrePex, but may be in the range of US$ 7-9 for the device alone.

There have been discussions between the Shang Ring manufacturer and Tiger Medical, a China-based medical supply company with an established distribution network throughout Africa. These discussions have focused on packaging the Shang Ring with a kit of surgical supplies. Apart from the local anaesthetic that has a shorter shelf life than other supplies, the kit will contain the disposable instruments and other supplies needed for male circumcision with Shang Ring and may be priced around US$ 10.

Other adult and adolescents devices: None of the other devices has been extensively tested in clinical or field trials consistent with the WHO Framework for Clinical Evaluation of Devices for Adult Male Circumcision. Manufacturers of Ali's Klamp and Tara KLamp have submitted initial applications for WHO prequalification, but full technical dossiers have not yet been received.

Infant Devices: Gomco and Mogen Clamps are widely available from surgical suppliers, and there are multiple manufacturers of Plastibell. Accu-Circ is supplied through Clinical Innovations, a small US-based company. Six infant devices are US FDA-approved (Gomco clamp, Mogen clamp, Plastibell, Smartklamp, Shang Ring, Accu-Circ), and one has a CE Mark (Ali's Klamp). Trials of Accu-Circ are underway in Africa using the WHO clinical evaluation framework recommendations for study design. It may be poised for prequalification in the next couple of years.

Market shortcomings and their reasons

Affordability: PrePex's current price is reported as high at US$ 20 per unit. At such a price, modelling studies have failed to document cost savings with use of devices versus surgery (the difference in cost-effectiveness is found to be just 2% when compared with current surgical method) (68). ***Reasons:*** The cost of surgery has recently declined by about one-third, as reported by PEPFAR, to roughly US$ 13 since VMMC programming in priority countries began. For devices, no competition yet exists, with only one product eligible for purchase by main donors following the WHO prequalification of PrePex. There is little prospect that other potential competitors, except for Shang Ring, might rapidly enter the market and compete. In addition, the devices are not necessarily interchangeable, as they have different modes of operation and different protocols for placement and removal. Demand has also been limited, while there is abundant evidence that demand is likely to be a critical driver for cost, regardless of the method used, surgery or devices. To maximize cost-effectiveness, VMMC sites will need to function at or close to capacity.

Quality: A lack of clarity exists regarding national regulatory approval requirements and requirements for prequalification of new analogous products. No single product is yet prequalified for use in adolescents. ***Reasons:*** Regulatory requirements for the licensure of new medical devices vary from country to country and, in many African countries, medical devices are effectively unregulated. Clinical data for devices submitted to WHO prequalification solely address use of the device in men who are 18 years or older, and subsequently prequalification of these devices is limited to use in this population. WHO has outlined the additional studies that will be needed to assess device safety in other populations, such as adolescents. Once a device category is endorsed by WHO and an initial device is prequalified, similar 'fast-follower' devices could emerge. WHO has not indicated if all clinical studies it has recommended for a first-in-category device will be needed for other devices in the same category, with this question to be addressed in planned future consultations.

Acceptability: Devices are promising tools, as they avoid sutures and, in the case of PrePex, injected anesthesia. However, while pilot studies have yielded favourable feedback from clients and providers on PrePex and Shang Ring, the acceptability for devices as a method for VMMC remains to be seen.

Delivery:

- It is unknown whether manufacturers of PrePex or Shang Ring will be able to ensure adequate supplies with increased and unforeseen demand. ***Reasons:*** Although information exists about their manufacturing

capacity and plans for investment, it is difficult to project how reliable these entities would be in ensuring a continuous, reliable supply of quality-assured devices, as neither Circ MedTech nor the manufacturer of Shang Ring has experience marketing and distributing medical devices in sub-Saharan Africa.

- Ensuring reliable and uninterrupted supplies at the country level may be a challenge. ***Reasons:*** Countries will need to have effective forecasting, procurement and supply chain management systems in place to ensure ready access to new devices and to avoid potential stockouts. An expenditure tracking study of experience with surgical VMMC found that expenses associated with supply chain and waste management amounted to roughly US$ 60 per circumcision, nearly doubling the total per-procedure programme costs. (69) Because these costs may not be apparent at the level of service delivery, they may not always be incorporated into cost estimates. Supply Chain Management System (SCMS), the supply chain contractor for PEPFAR, indicates that many priority countries lack the technical capacity to forecast commodity needs, frequently submitting budgets for requested assistance that completely ignore supply chain management costs. SCMS has urgently recommended that focused technical support be made available to priority countries to increase their capacity to ensure a reliable, uninterrupted supply of male circumcision devices and other essential commodities. Proper waste management is also a priority, especially as programmes are brought to scale.
- Ensuring integration in national programmes and access at country level for the needed devices may be a potential challenge. ***Reasons:*** Countries will need to embrace the new devices and routinely offer them in VMMC or infant circumcision programmes. No formal WHO guidance has yet been issued for introduction of either PrePex or Shang Ring. Consistent with current practices, it is possible, even with available international financing, that some countries will hesitate to promote a new circumcision device in the absence of formal WHO guidance on the introduction of devices in national programmes. The development of official WHO recommendations can often be a time-consuming process, and it is presently unclear how much time might be required from actual prequalification until issuance of formal guidance on device introduction. In addition, the pathways for in-country regulatory approval are not clear for all of the priority countries. For those countries that endorse new devices, national policies will need to be developed regarding which cadres of health worker are permitted to perform the procedure and where such procedures may be performed. For the cadres of health care workers authorized to perform VMMC with one or more devices, appropriate training and capacity building and ongoing supervision will be needed. In Rwanda, nurses receive a three-day training course in performance of VMMC with PrePex. (52)
- A global shortage of lidocaine and other related anaesthetic products is beginning to have effects at the clinical level in sub-Saharan Africa, with VMMC clinics reporting interruptions in their ability to perform surgical VMMC due to an inability to provide adequate pain control. ***Reasons:*** Causes for the supply problem include a limited number of manufacturers, discontinuation of the production of various local anaesthetic products by at least one manufacturer, and a growth in demand that has outstripped current manufacturing capacity and led to reports of delivery delays reported for main producer of lidocaine. (70) Lidocaine administration is a component of the protocol for VMMC with the Shang Ring, while placement of PrePex involves use of a topical anaesthetic that may also be affected by this shortage.

Potential market interventions

Market interventions for male circumcision devices should aim to ensure accessibility and achieve the lowest possible price, with the ultimate aim of maximizing the responsible use of public sector funds. Efficient use of resources is dependent not only a reasonable price for all supplies for VMMC, including devices, but also on maintaining sufficient demand at the service delivery points to maximize provider efficiency. Accurate forecasting is also essential to facilitate effective coordination of supplies, demand and providers. As manufacturing costs are already believed to be quite low for these simple non-surgical devices, it is unlikely that technological innovations in product manufacturing would have a substantial impact on future pricing.

- **Increase competition:** Prequalification of both PrePex and Shang Ring would theoretically offer purchasers an option of more than one non-surgical device (assuming WuHu SSNDA affirmatively seeks to market Shang Ring for use in VMMC programmes in sub-Saharan Africa).
- **Negotiate prices:** PEPFAR has expressed interest in purchasing PrePex when it becomes prequalified by WHO to accelerate scale-up and help the programme achieve its targets for VMMC. For PEPFAR, its supply management vendor, SCMS, would handle negotiations and ultimate purchase of any non-surgical device.

Assuming that PEPFAR and the Global Fund work together in price negotiations with Circ MedTech, uncertainty remains around the volume of any initial purchase and the pricing that would be acceptable for the public health purpose for which PrePex is intended.

- **Clarify national regulatory pathways:** In an effort to better delineate the regulatory requirements needed on a national basis, PEPFAR has asked countries planning on performing pilot implementation studies of male circumcision devices to define the in-country requirements for registration and approval.
- **Increase volumes:** No meaningful market has yet developed for PrePex outside Rwanda, given that WHO prequalified it only very recently. At the 2011 International Conference on AIDS and STIs in Africa, a senior official from Circ MedTech said the company would be willing to consider a sales price of US$ 15-17 per device, assuming sufficient volume. This estimate does not include the cost of reusable equipment required for removal of the device.
- **Market aggregation:** Competition is clearly linked with exerting downward pressure on prices. In the case of non-surgical VMMC devices, however, there is some concern that the entry of multiple products might fragment the market to such a degree that companies would have difficulty amortizing R&D costs or make a sufficient profit to remain economically viable. Potential purchasers may be interested in focusing on the most attractive device and aim to drive the cost lower through higher-volume purchasers and agreement with the manufacturer on volume-driven thresholds at which specific price cuts would take effect.

Table 5. Potential Interventions for Adult and Adolescents Male Circumcision Devices

Shortcoming	Adult and adolescent Male Circumcision devices	Potential market interventions
Affordability	Reported initial prices of PrePex up to US$ 20 per unit, while production and raw materials costs are presumed to be low.	• Promote competition for male circumcision devices through incentives for additional manufacturers to enter market in each product category, e.g. support for research into novel device development and their market entry. • Support demand creation and price negotiation for prequalified devices, leveraging volumes to accelerate VMMC scale-up.
Quality	Only one product eligible for procurement.	• Support for clear regulatory pathways for competitor products for VMMC devices, including adolescents; clarify data required for approval of 'fast followers'.
Delivery	Limited uptake.	• Support best practices for optimal demand creation. Assure that providers are trained in the safe use of devices and that sufficient supplies are maintained through: ◊ Support for training a set number of providers and/or trainers to prevent staff shortages from delaying scale-up of device-assisted VMMC; ◊ Provision of technical assistance for forecasting device needs; ◊ Financial, logistical and technical support to ensure a functional distribution network for supply of devices.

At this point, consideration of specific market interventions for infant circumcision devices may be premature. Infant devices may be an important addition to programmes once they are established and funded. Guidance from WHO and funders regarding requirements needed for recommendation and purchase will be important in determining next steps. While clinical data on Gomo Clamp, Mogen Clamp and Plastibell are sufficient, clinical studies of Accu-Circ are needed to evaluate the acceptability, feasibility and safety of the device in priority country settings.

Table 6. Potential Interventions for Infant Circumcision Devices

Shortcoming	Infant Male Circumcision devices	Potential market interventions
Quality	Lack of data compiled according to current WHO protocol.	• Consider support for late-stage studies and prequalification of the Accu-Circ device, as needed.
Delivery	Slow scale-up.	• Closely monitor progress in development of infant circumcision programmes.

6.2. Barrier methods

6.2.1. Male condoms

The effectiveness of male condoms in reducing the odds of sexual HIV transmission has been repeatedly demonstrated. Laboratory tests have determined that HIV and pathogens that cause several other sexually transmitted diseases cannot penetrate male latex condoms. (71) A meta-analysis of available studies determined that consistent condom use reduces HIV incidence by 80%. (72) As instances of condom slippage or breakage associated with improper use were considered as condom failures in this meta-analysis, it is likely that the effectiveness rate for correct and consistent condom use is higher than 80%.

Commodity access issues

Although condom promotion has served as a centrepiece of HIV prevention programming since the 1980s, only modest progress has been made towards encouraging correct and consistent condom use by sexually active adults and adolescents. In 14 countries with generalized epidemics, more than 70% of men and women who reported high-risk sex over the past year said they did not use a condom the last time they had sex. (73) In recent years, trends in condom use have been mixed, with condom use on the rise in some high-prevalence countries but declining in others. (4)

Condom use remains disappointingly low, partly due to lack of acceptance and poor promotion programmes. Notwithstanding extensive marketing efforts, many men resist using condoms due to the real or perceived effect of condoms on sexual pleasure. Many women lack the ability to negotiate condom use with their male partners due to fear of violence, economic dependence on men, or other factors associated with inequitable gender norms. Many couples also refrain from using condoms due to the desire to conceive or as a result of the belief that condoms diminish the intimacy of sexual intercourse.

While rates of condom use in the general population are low in many high-prevalence countries, condom programming has had important successes when it has been carefully focused on discrete populations. According to 2011 surveys in the capital cities of 85 countries, 85% of sex workers reported having used a condom at last sex. (4)

There are signs in some settings of increased emphasis on condom promotion at national level. In 17 high-prevalence countries in which HIV expenditure data were available for 2008-2010, spending on behaviour change and condom promotion rose by 28% during the three-year period. (4)

Too often, however, there simply are not enough condoms for those who need or want them. In 2012, an estimated 3.4 billion condoms were purchased for use for HIV and STD prevention in LMICs—far short of the 13 billion target for 2015. (74) According to UNFPA, only nine donor-supported male condoms were available for every male (15-49 years) in sub-Saharan Africa in 2011. (4) As international sources account for the overwhelming majority of condom purchases, the gap between the number of donor-purchased condoms and the target figure is believed to roughly represent the actual global gap in the number of condoms available for distribution in LMICs. PEPFAR has termed the global condom gap "quite disturbing," noting that persistent condom stockouts occurred in 9 out of 10 high-prevalence countries surveyed in sub-Saharan Africa in 2008-2010. (75)

Sexual lubricants have emerged as an important factor in determining the actual success of condom programming in preventing new HIV infections. While lubricants are recommended for use during anal intercourse (in part to reduce the risk of condom breakage), an international survey of nearly 5,800 men who have sex with men found that, while nearly 40% reported having meaningful access to condoms, only one in five had access to sexual lubricants.

Technology landscape

Male condoms can be made of a range of materials—including polyurethane and lambskin—but the vast majority of condoms used in LMICs are made of natural rubber latex, a simple, readily available and inexpensive raw material. Through a simple dipping process, the male condom is straightforward to manufacture. It is exceedingly inexpensive in comparison to other HIV prevention commodities, costing less than US$ 0.03 per unit in 2012, according to the UNFPA 2012 procurement catalogue. Indeed, its simplicity and affordability are among the attributes that have long led global health experts to regard condom promotion and distribution as among the most cost-effective health interventions.

Use of lubricants along with condoms is recommended during anal intercourse. The access gap for sexual lubricants has given rise to various proposals, such as including packets of lubricants with condoms distributed during prevention programs. The evidence base on the use of sexual lubricants is evolving. While lubricants continue to be recommended for use during anal intercourse, various studies have suggested that some standard sexual lubricants appear to damage rectal tissue and may be associated with an increased risk of acquiring an STI. (76) Advocates have recently approached the US National Institutes for Health (NIH) and asked the agency to develop and implement a comprehensive research agenda to assess the safety of sexual lubricants.

Market landscape

Demand

In general, donor purchases of male condoms have not seen a significant variation in recent years. (77) In 2010, donors spent US$ 72.6 million on purchases of male condoms (for a volume of 2.8 billion units), representing a 5% increase compared with to 2009. (74) In 2010, UNFPA and USAID were the largest suppliers of male condoms (30% and 26.5%, respectively), followed by other donors including the UK (16%), and by Population Service International (PSI) (16%). In general, European donors devote a larger share of their HIV prevention assistance to male condom programming than the US. (78) The Global Fund represents an additional important source of funding for male condom procurement; in 2011, the Global Fund funded the purchase of more than 278 million male condoms (almost 10% of all donor-procured units), for a total cost of nearly US$ 11.3 million. (74)

Market analysts project substantial growth in the global condom market, with the number of condoms rising to 27 billion by 2015, up from 20 billion in 2012. (79) Whether this trend will continue is uncertain, as there are reports that, for instance, PEPFAR, a major provider of condoms, is de-emphasizing behaviour change communication and condom promotion in favour of increased funding for evidence-based biomedical prevention interventions.

Supply

The global condom market appears to be robustly competitive. A global directory of condom manufacturers and exporters identifies 49 companies producing male condoms worldwide. (80) As of June 2013, UNFPA, managing the Male Latex Condom and Intrauterine Contraceptive Devices (IUD) Prequalification Schemes for the UN system, had prequalified 26 different manufacturing sites for male condoms. (81)

While a small number of manufacturers (e.g. Durex, Trojan) dominate the condom market in North America and Europe, the top five condom-producing countries worldwide are in Asia, where all but two of 26 prequalified manufacturing sites are located. Analysts suggest that Asia's prominence in condom manufacturing is likely related to its proximity to the rubber plantations that supply the critical raw ingredient. Lower manufacturing costs in India, China, and other countries where major producers of condoms are based are also likely a factor in the geographic distribution of condom manufacturing.

Potential market interventions

There is little reason to believe that market shortcomings are responsible for shortfalls in access to condoms, though limited donor support for condom programming is a concern. A healthy, competitive market for condom manufacture is already in place and rapidly growing, with production centred in a region where the raw material is produced, manufacturing costs tend to be lower, and existing market dynamics reflect a class of products that is readily available and inexpensive. In summary, there is little evidence that a traditional market-based intervention would enhance condom access or uptake.

In addition, there is no reason to believe that short-term investments in altering field conditions—such as training providers—would meaningfully improve rates of condom use. Rather, increased commitment of resources from national programmes and donors to increase supply, given stagnating funding for condom procurement, combined with smarter programming, appears more likely than market-based interventions to be effective in improving condom use rates.

Consideration could be given to potential market strategies to increase access to sexual lubricants, especially for men who have sex with men, to facilitate condom use during anal intercourse.

6.2.2. Female Condoms

The female condom is the only female-initiated method currently available for the prevention of sexual HIV transmission. Female condoms offer protection against pregnancy that is comparable to the male condom. (82) (83) Numerous randomized trials have found that integration of female condoms in HIV prevention programmes offers protection against STI transmission that is at least as great as that seen in programmes that distribute male condoms alone. (84) (85) (86) (87) According to several studies, adding the female condom to condom distribution programmes results in an overall increase in the proportion of protected versus unprotected sex acts. (86) (88) (89) (90) (91) (92)

Implications for HIV Prevention

The degree to which current usage levels of the female condom have affected HIV incidence is unknown, although studies finding that female condoms increase the proportion of protected sex acts suggest that the product is providing a prevention benefit for those who use it consistently. The female condom expands options for HIV prevention and contraception for both men and women. A meta-analysis of HIV prevention interventions focused on sex workers and their clients found a reduction in HIV incidence at three months following initiation of female and male condom promotion. (93) One modelling exercise found that correct, consistent use of the female condom would reduce by 90% the odds of HIV acquisition by a woman who has intercourse two times a week with a man who is living with HIV (94)—a degree of protection comparable to that provided by the male condom. A cost-effectiveness analysis found that expanding distribution of FC2 (one female condom product, described below) to 10% of current male condom distribution in South Africa would prevent more than 9,500 new infections, at a savings of US$ 985 per infection averted. (95)

An economic modelling study determined that cost savings would accrue if women with casual sex partners used the female condom in 12% of their sexual encounters. (96) A recent cost-utility analysis of a programme to promote female condoms in Washington D.C. found, based on the number of estimated infections averted, that the initiative resulted in substantial cost savings. (97) Altogether, available evidence indicates that female condoms are an important addition to interventions for HIV prevention.

An important motivation for developing and promoting the female condom is to provide women with a prevention method they can initiate on their own, obviating or minimizing the need to rely on men to use a condom during sexual intercourse. However, more than 80% of rural women surveyed in Zimbabwe said they would have to seek permission from their male partners before using the female condom. (98) Indeed, by its design, covert use of the product is quite difficult, underscoring the fact that in most situations male knowledge and consent will likely be needed for a female condom to be used. Some women, though, report use of the female condoms in situations where they lack the means to negotiate use of a male condom. (99) A recent study involving sex workers along the Mexico-US border found that having had a client become angry at the suggestion of condom use was independently correlated with sex workers' use of the female condom. (100)

There has been some concern that the female condom might reduce the cost-effectiveness of HIV prevention efforts by supplanting use of the considerably less expensive male condom. Optimal programming would provide coverage of unprotected acts with female condoms, with minimal migration from the male condom. Although available information indicates that integration of the female condom in condom distribution programmes increases the proportion of sex acts that are protected by some form of condom, some studies have detected varying degrees of product displacement. In one Kenya study that confirmed an overall increase in protected sex acts following introduction of the female condom, the female condom replaced the male condom in 30% of sex acts reported by participants. (101)

The scientific literature on female condoms includes vigorous debates regarding the optimal programmatic approaches to accelerate uptake of the product. In some cases, condom promotion programmes may have been poorly planned, badly executed, insufficiently monitored, and inadequately adaptable to feedback from the field. To promote effective condom programming, UNFPA and its UN partners recommend a 10-part approach based on social marketing, outreach and partnership cultivation through the Comprehensive Condom Programming (CCP) Framework approach. UNFPA recommends that countries have national coordinating mechanisms in place to ensure commodity security, as well as multi-stakeholder teams to support effective condom programming. Countries are advised to develop a national strategy on condom programming, develop multi-year operational plans, take steps to increase condom demand, and integrate condom programming in national monitoring and evaluation mechanisms.

Given some health providers' discomfort with the female condom (102) (103), it has been suggested that roll-out strategies include training for both providers and end users. (104) It has been asserted that current condom promotion efforts often use hierarchical approaches that give the male condom priority over the female condom because of the difference in cost between the two products. To encourage faster uptake of female condoms, some experts have recommended that programmes place the male and female products on an equal footing and promote them as equally effective in preventing sexual transmission. (104) According to studies, knowledge of the female condom is strongly correlated with actual use of the product (105) (106) (107), as are discussions about female condom use within social networks. (108)

Social marketing approaches have been used to increase acceptance and uptake of the female condom. (109) (110) (111) After initiation of a social marketing campaign aimed at sex workers in Brazil, the number of women who reported ever using the female condom significantly increased, with users citing as an advantage of the female condom the ability to have sex in any position without the device breaking or slipping. (112) To promote uptake of FC2, the Female Health Company (FHC) has trained barbers, hairdressers and other community stakeholders on how to educate community members about the female condom and also forged public-private partnerships for promotion and distribution of the product. (113)

Coupling condom distribution with focused behavioural interventions also appears to increase uptake, although increases in utilization of the female condom following the intervention have sometimes been rather modest. (87) (114) In a notable study conducted at STI clinics in the US state of Alabama, female condom use rose without male condom use declining following implementation of a multi-component intervention that included practice sessions with a nurse on insertion of the female condom and a promotional video for male partners. (115)

In an extensive critique of current female condom programming, Marseille and Kahn argue against calls to normalize or mainstream the female condom in LMICs. Instead, they recommend more focused programming that work to reduce commodity costs and pro-actively prevent displacement of the male condom. (116) Critics of efforts to mainstream the female condom suggest that promotion of the product should focus on serodiscordant couples—an approach, it is argued, that would increase the cost-effectiveness of female condom programming. Reasons for prioritizing serodiscordant couples include the diminished likelihood of displacing male condoms, which are not frequently used by many stable couples.

Commodity access

Uptake of the female condom has been slow, although scale-up has accelerated in recent years. Female condoms account for only 1.6% of worldwide condom distribution. In 2011, nine male condoms were available for every man in sub-Saharan Africa between ages 15 and 49, compared to only 0.1 female condoms for every female ages 15-49. (110) In 2010, in only one country in sub-Saharan Africa (Zimbabwe) was at least one female condom available for every adult woman. (117)

Although uptake of the female condom remains limited, total distribution of the female condom has steadily increased since 2000. Whereas 5.0 million female condoms were distributed in 2000, this number had increased more than five-fold by 2007, reaching 25.4 million (116). From 2005 to 2009, global distribution of female condoms more than tripled. This upward trajectory in female condom distribution has continued, with annual global distribution rising from 26 million female condoms in 2009 to 47 million in 2012. It is the opinion of many experts that there is room for growth in the distribution of this product. (118) Substantial advocacy is focused on further accelerating female condom uptake.

Technology landscape

No product currently on the market meets all ideal characteristics for a female condom, although products currently on the market or in development offer various attributes that move towards the ideal product envisaged by global health practitioners.

FC1, developed in the 1980s, was the first female condom approved by the US FDA and prequalified by WHO. It remained the mainstay of female condom distribution programmes worldwide until 2006, when its less expensive but effectively equivalent successor, FC2 (marketed under various names, including Reality, Femidom, Femy and Care in different parts of the world), was prequalified by WHO.

A plethora of female condoms have been since developed, although FC2 accounts for the bulk of those purchased for female condom programming for HIV prevention in LMICs. Two female condoms have obtained WHO prequalification (FC2 in 2006 and Cupid in 2012), a prerequisite to widespread scale-up in disease prevention and family planning programmes. Described below are the three primary products of clear public health significance—FC2 and Cupid (both of which are currently on the market), along with a third product (the Woman's Condom), which is at an advanced stage of development and clinical evaluation. There are also a number of additional niche products in various stages of development. Current female condom products offer dual protection against HIV and other STIs as well as pregnancy.

FC2

Prequalified by WHO in 2006 and approved by the US FDA in 2009, FC2 is a nitrile product that has a similar design and appearance to FC1. About 30% less expensive than FC1, which was made from more costly polyurethane, FC2 is the most widely used female condom. (The manufacturer of FC2, the Female Health Company, ceased manufacturing FC1 in 2009). (119)

FC2 – Female Condom

FC2 has a soft sheath, with an external ring of rolled nitrile and an internal ring of polyurethane. (120) The sheath lines the vagina, preventing direct skin-to-skin contact. The internal ring aids with insertion, while the external ring, partially covering the external genitalia, permits removal of the product following intercourse. (120) (Insertion without the internal ring is possible if the condom is placed on the erect penis prior to intercourse.)

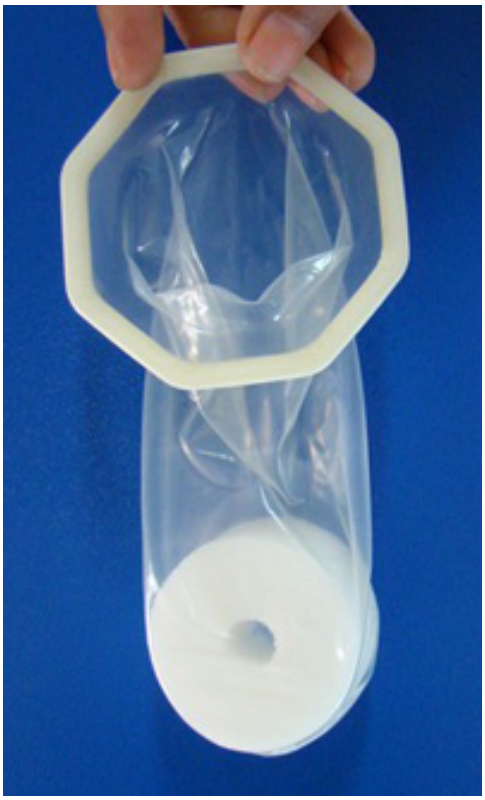
According to the Female Health Company, the synthetic latex nitrile polymer with which FC2 is made is stronger than the natural rubber latex found in most male condoms. Another claimed benefit of the FC2's primary raw material is that it transfers heat, potentially contributing to a more natural and enjoyable sexual experience. Unlike natural latex, no allergies have been reported for nitrile polymer. FC2 comes lubricated, and it is recommended for a single sex act. (120)

Some users of FC1 reportedly complained about the crinkling sound that the product emitted during sexual intercourse. (83) Made with a softer nitrile material, FC2 is believed to have improved this aspect of product usage.

Cupid

A natural latex condom manufactured in India, Cupid was prequalified by WHO in 2012, may be marketed in the European Union, and has been approved by the India Drug Control Authority. It is pre-lubricated, has an octagonal outer frame, and includes a sponge to anchor the condom inside the vagina. The product is currently distributed in India, with less extensive availability in some other countries, such as Brazil and Indonesia. (121)

Cupid – Female Condom



Some users report that Cupid is easier to use than other female condoms on the market. However, its reliance on latex may make the product somewhat less appealing for the segment of users who have reactions to latex. (An estimated 1-2% of people are allergic to latex.) (122) Because it has recently been prequalified, it has not been included in public sector purchases of female condoms to date, but may be included in future purchases. Because of cost implications for required studies, it does not appear that the manufacturer of Cupid will seek approval of the US FDA.

Woman's Condom

Manufactured in Shanghai and promoted by the Program for Appropriate Technology in Health (PATH), the Woman's Condom has yet to be WHO prequalified, although it has been approved for marketing in China by the Shanghai Food and Drug Administration and has received approval for marketing in the European Union. (121) (123) Clinical evaluation of the product is continuing, including studies on contraceptive efficacy, with WHO prequalification and approval by the US FDA expected in 2013. The emergence of a potential alternative to existing female condoms—and one backed by the global reach of PATH—has attracted interest in global health circles.

Woman's Condom – Female Condom

PATH developed the product in an effort to enhance ease of use, increase comfort for both partners, address concerns about acceptability and increase stability. (124) Short-term studies have found the product to be acceptable to potential users. (125) One small study indicated that women preferred the Woman's Condom to FC1, the predecessor to the market-leading FC2, due to its ease of use, lessened likelihood of irritation, and lower failure rate. (126)

The product is made of soft polyurethane, with the pouch enclosed in a gelatine capsule that aids insertion and quickly dissolves once it is in the vagina. After the capsule dissolves, the condom unfolds and four small foam pieces attached to the inner sheath cling to the vagina to hold the condom in place. The Woman's Condom is packaged without lubrication, although the package includes a small packet of water-based lubricant. At present, the Woman's Condom is available only in China, where it has achieved limited distribution through the private sector. (121)

Other Products

Several other female condoms have been developed, although most have yet to figure prominently in HIV prevention and family planning programming in LMICs. Some of the leading alternative female condoms include:

- **V-Amour/Protectiv:** A natural latex condom made in India by MedTech, this product is no longer being produced, as its manufacturer has suspended operations. When it was available, it was generally less expensive than FC2, with a unit price of US$ 0.23, suggesting relative cheaper price of a latex product compared to nitrile. (110) (127) Also known as the "Reddy" female condom, it was pre-lubricated, had a triangular frame, and used a sponge to secure the condom in the vagina. (121) The Reddy condom has been registered in Brazil, and received regulatory approval in India. (127)
- **Phoernurse:** The Phoernurse female condom is a polyurethane, pre-lubricated product that has limited distribution in China, although the company is reportedly seeking to enter the Brazilian and South African markets. (127) In 2011, a South African court blocked the national Government from purchasing 11 million Phoenurse condoms on the grounds that they were too small for South Africans and had not been prequalified by WHO. (128)
- **Panty Condom:** There are several brands of panty condoms, in which the condom itself is attached to underwear. These products are available in Europe and South America. (129) Panty condoms consist of a cotton or nylon thong-like panty that includes an interior membrane containing a self-adhesive condom for use during sexual intercourse or a reusable panty with replaceable female condoms. According to one panty condom manufacturer, the product is made of a polyethylene resin that is purportedly thinner and stronger than latex, as well as transparent and odourless. (130)

Pipeline

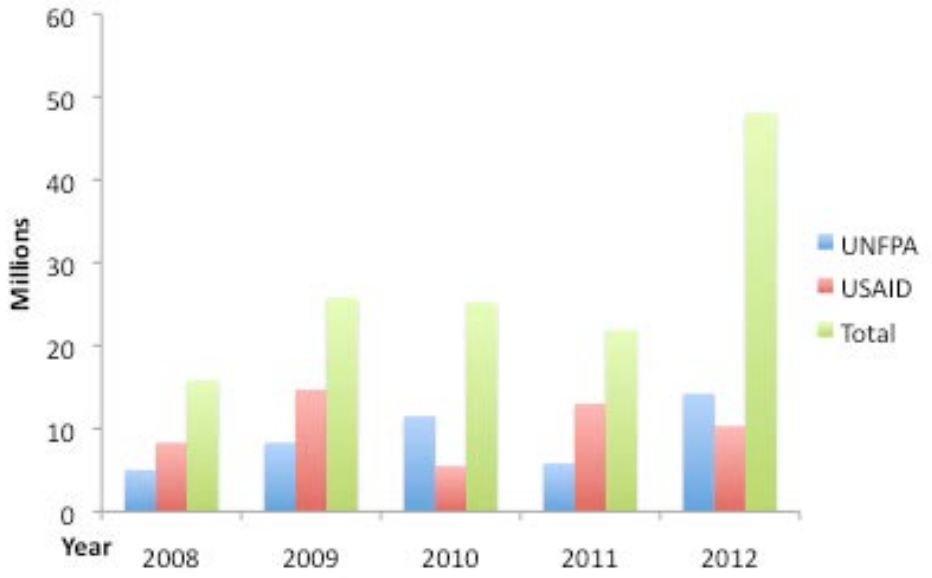
The female condom has been specifically designed for insertion into the vagina to protect against unwanted pregnancy or disease transmission during penile-vaginal intercourse. Although no existing female condom has been designed for use during anal intercourse—and no evidence exists that it is safe and effective for such use—men who have sex with men have experimented with off-label use of the female condom during anal intercourse. (131) It is anticipated that future research might focus on the suitability of the female condom for anal intercourse and that product manufacturers may work to create a product specifically designed for this use.

Market landscape

Demand

Public sector buyers account for the overwhelming majority of purchases of female condoms. Surveys in Zimbabwe (98), India (132) and elsewhere indicate that the price of the female condom is too high to support a robust private market. Indeed, a 2012 review by the United Nations determined that a private market for condoms is "almost non-existent in sub-Saharan Africa." (129)

Female Condom Prcurement 2008–2012



Source http://rhi.rhsupplies.org/rhi/index.do?locale=en_US

National programmes play a relatively modest role in the condom market. The overwhelming majority of LMICs have no budget line for male or female condom acquisition, looking instead to donors for access to essential commodities. (129) A number of middle-income countries—including Botswana, Brazil, India and South Africa—use domestic funds to purchase female condoms. (129)

Although donor purchases of female condoms have steadily increased in recent years, procurement of female condoms represented just 0.38% of total HIV-related donor expenditures in 2009. (133) In 2011, donor outlays for female condom procurement were less than one-quarter amounts spent on the purchase of male condoms. (134)

Donor support for female condom procurement began rising in 2007, doubling in 2009 from US$ 14 million to US$ 29 million, but then decreased sharply to $18.5 million in 2010. (129) Procurement patterns in 2012 differ somewhat from earlier years (where UNFPA and USAID predominated), primarily due to a purchase by the Pan American Health Organization for 20 million female condoms for use in Brazil.

UNFPA is the largest purchaser of female condoms. The number of female condoms purchased by UNFPA increased from 3.5 million in 2008 to 16.7 million in 2011, with the percentage of UNFPA's contraceptive budget

devoted to female condom programming rising during this period from 4.1% to 19.0%. (135) In 2011, UNFPA accounted for two out of every three female condoms purchased by international donors. (134)

USAID, the leading bilateral purchaser of female condoms, has dramatically increased its investments in female condom purchases. The number of female condoms purchased by the US Government rose from under 2 million in 2006 to more than 14 million in 2009, representing an annual increase of 84%. (136) In 2011, the US accounted for 30% of donor purchases of female condoms. (134) USAID uses subcontractors to oversee purchase and distribution of the female condom, with the aim of matching purchases with the distribution needs of each country. (133) The PEPFAR blueprint, released in November 2012, calls for promotion of female condoms as "an essential part of an overall condom strategy." (137)

USAID and UNFPA now jointly purchase female condoms, leading to modest declines in the price of FC2. Countries are able to avail themselves of the lower price by using the USAID/UNFPA joint purchasing mechanism.

In addition, in 2011, the Global Fund spent US$ 212,430 for the procurement of 285,580 female condoms. (134) To support procurement and distribution of female condoms, the Global Fund depends in large measure on countries' inclusion of female condom programming in their funding proposals.

Quality and Procurement requirements: In 2012, WHO and UNFPA issued "Female Condom Generic Specification, Prequalification and Guidelines for Procurement". This document provides guidance to manufacturers and purchasers of condoms regarding such issues as product specifications, manufacturing quality, product design, and performance standards, as well as the required steps of the prequalification process. Global Fund recipients are only authorized to use grant funds to procure female condoms if the products are compliant with specifications indicated in WHO/UNFPA guidelines.

PEPFAR purchases of female condoms focus on FC2, approved by the US FDA; although the Cupid female condom has been prequalified by WHO, the US Government may not purchase the product unless it receives approval by the US FDA. An additional contraceptive efficacy clinical trial will be needed before the FDA will consider approval of Cupid, and there do not appear to be plans for the company to support such a study. (110)

Other demand drivers: Women's willingness, ability and desire to use the female condom will have a critical effect on the size of the market for the product. Studies of short-term acceptability have found that the vast majority of women surveyed reported either a willingness to use the product or satisfaction with the product after having used it. Advantages of the female condom cited in acceptability studies include the woman's ability to initiate use, enhanced sexual pleasure for men, and the ability of users to avoid having to interrupt sexual intercourse to apply a condom. In a small, 160-woman study in South Africa, women preferred the Women's Condom and FC2 over V-Amour, citing such issues as ease of use, feel, appearance and overall fit. Although disease prevention is a primary aim of global health proponents of condom programming, evidence indicates that pregnancy prevention is the main motivating force for women to use condoms.

But information from acceptability studies also suggests that certain characteristics of female condoms may deter some from using it. Some study participants simply felt female condoms looked strange, while others experienced challenges when trying to insert the condom into the vagina. Field studies indicate that initial aversion to the female condom and difficulties using it often diminish over time, especially when counselling is provided to potential users. In acceptability studies, the response of male sexual partners to the female condom ranged from enthusiastic to negative.

Supply

Given the requirements of the primary international purchasers of female condoms, FC1 and FC2 have accounted for virtually all public sector purchases to date.

FC2: FC2 is manufactured by FHC at its facilities in Selangor, Malaysia, and Kochi, India. In Malaysia, FHC produces 75-80 million units a year, although the company is expanding the annual production capacity at the 16,000-square-foot site to 100 million units. FHC's production site in India is much smaller, with an annual capacity to generate 7.5 million units. (120). Since FC2's predecessor (FC1) was approved by the US FDA in 1993, FHC has manufactured and sold roughly 332 million female condom products. (120) FHC has sole and exclusive rights to the nitrile polymer formulation that serves as FC2's central ingredient. (120)

For the nine months ending in June 2011, FHC reported net revenues of US$ 25,122,196 and net income of US$ 7,114,116. FHC revenues were higher in the third quarter of 2012 than in any previous reporting period. (120) As the global demand for female condoms has grown, FHC has begun returning a profit, and 2012 paid dividends to its shareholders for the first time.

With the public sector serving as the primary market for FC2, FHC reportedly incurs minimal sales and marketing expenses, suggesting that increased public sector demand for FC2 will translate into increased profit for the company. FHC markets FC2 directly to consumers in 16 countries, including Brazil and India.

FHC has said use of a less costly material that allowed for automated manufacturing played an important role in FC2's lower price in relation to FC1. (138) FC2 is made by a dipping process that allows for large volume production and utilizes equipment similar to that used for production of medical gloves. Unit price for FC2 in 2012 was US$ 0.57.

Cupid: The Cupid female condom is manufactured by Cupid, Ltd., which is based in Mumbai. The company reports annual turnover of US$ 6 million, as well as manufacturing facilities that have been certified as adherent to Good Manufacturing Practice (GMP). (139) Production capacity of Cupid is unknown. The product is made through a standardized latex dipping process similar to the manufacture of male condoms, although manual assembly is required to produce the final product. (140) Expansion of the dipping process to achieve greater volumes is relatively straightforward, although the assembly step of production may need to be improved for larger capacities. The stated price per unit for Cupid was US$ 0.56 in 2012.

Woman's Condom: The Woman's Condom is manufactured by the Dahua Medical Apparatus Company in Shanghai. The first professional manufacturer of disposable medical supplies in China, Dahua has a factory that occupies 35,000 square meters that complies with GMP. The manufacturing process for the Woman's condom is more complex than that for FC2 or Cupid and involves welding the polyurethane sheath. (141) The number of Woman's Condoms that Dahua has the capacity to produce is unknown. At present, Dahua has limited capacity to manufacture the Woman's Condom, although a key step in the manufacturing process is currently being automated, which may expand capacity somewhat. Even with this anticipated expanded capacity, production limitations remain a concern for the Woman's Condom.

As the Woman's Condom has not been widely marketed for use in LMICs, its initial price is unclear. As it is made from more expensive polyurethane, it is expected to be more expensive than FC2, although some of this difference in price might be overcome by lower manufacturing costs in China. In China, where the product has received limited distribution, it is available at US$ 0.87 wholesale, with volume discounts offered. (128)

Market shortcomings

Availability: No ideal product exists that meet all target characteristics for the female condom (142). The ideal female condom would be highly protective, stable, secure, easy to use and extremely inexpensive (ideally less than US$ 0.10 per unit), and disposable without harm to the environment. ***Reasons:*** Uncertainties about potential market might be discouraging further research. Difficulties exist in developing a product that is competitive in price with male condoms and meets target characteristics.

Acceptability: Uptake to date has been extremely limited, and important questions persist regarding acceptability of the female condom. ***Reasons:*** While acceptability studies have indicated a strong desire among many women for access to the female condom, actual real-world use for such a product is difficult to gauge and studies have reported a range of concerns of women on using these products, such as difficulties with insertion and what some women perceive as the product's strange appearance. Acceptance by donors might also be low, and some critics have alleged that the primary impediment to scale-up of the female condom is the perceived disfavour in which the product is held in international policy circles.

Affordability: There is compelling evidence that the price of the female condom is an impediment to uptake. Cost-effectiveness is also a concern, as is potential for displacement of the less expensive male condom. Whereas male condoms cost roughly US$ 0.03 per unit on average, unit costs for female condoms exceed US$ 0.50, suggesting that female condoms are currently nearly 20 times more expensive than male condoms. (143) (144). ***Reasons:*** Because it is a larger, more complicated device than the male condom, prices for female condoms will always be costlier than male condoms. There is also limited demand and limited competition, especially

in the donor market, which is dominated by a single producer. In addition, compared to male condoms, female condom programming involves training and education costs that are estimated to be at least 4-5 times higher. (144) This is especially true in the early stages of product introduction. Nonetheless, in Zimbabwe, where female condoms have achieved the greatest uptake, programme costs have declined over time, as awareness of the product has grown. (144)

Quality: The number of products eligible for procurement by US-funded programs is limited. ***Reasons:*** PEPFAR procurement requirements limit purchases of female condoms to FC2, the only product approved by the US FDA; although the Cupid female condom has been prequalified by WHO, the US Government may not purchase the product unless it receives approval by the US FDA. An additional contraceptive efficacy clinical trial will be needed before the US FDA will consider approval of Cupid, and there do not appear to be plans for the company to support such a study.

Delivery: According to civil society analyses, stock-outs of female condoms are common. (145) In Mozambique, for example, UNFPA estimates that only one in four female condoms procured by USAID and UNFPA actually reached end users in 2008. (144) ***Reasons:*** Weaknesses in forecasting and supply chain management at the country level.

Potential Market Interventions

The female condom is an important additional HIV prevention tool that affords protection of sexual acts that are otherwise unprotected. Smart programming should accompany distribution to minimize displacement of male condoms. It is not clear if additional products are needed in this market, as there are concerns that, given the relatively small size of the market, additional products could fracture the market and inhibit the capacity of manufacturers to offer volume-discounted pricing. Objectives for market-based interventions include decreasing the cost of existing female condom products and supporting demand creation with high-volume purchases, supported by smart programming of the product, that aim to achieve additional coverage of otherwise unprotected sexual acts.

- **Increase volumes:** Increasing demand may be the most important factor in reducing prices for the female condom. The Female Health Company, for example, has suggested that the price for FC2 could be cut by more than half—to US$ 0.22—were the number of purchased female condoms to reach 3% of male condoms purchased. (146) Similarly, Cupid's marketer indicates that a price of US$ 0.35 is available for a volume purchase of 1 million. (127) Manufacturers of female condoms, including the FC2 producer, have expanded production capacity as demand for their respective products has increased. These steps suggest that manufacturers of female condoms believe a potentially profitable market exists, but that profitability will be dependent on actual demand for the product.
- **Increase competition and market aggregation:** USAID has suggested that the lack of competition in the market for female condoms is an important reason why product prices remain so high. (110) However, others question the wisdom of promoting multiple market entrants that might fragment the market and make economies of scale more difficult to achieve. Given the limited demand to date for female condoms, a more efficacious approach, some suggest, would be focus on increasing uptake of perhaps two (or three) products. It is believed by some that this approach would generate purchase volumes sufficient to lower the price of the product.
- **Decrease production cost:** Little is currently known about manufacturing innovations in the female condom market, as product manufacturers have concentrated on obtaining WHO prequalification and gaining a foothold in the public sector market. As noted, the emergence of FC2 was based in part on FHC's ability to move towards automated manufacturing. In addition, to reduce effective programme costs associated with the female condom, some experts have suggested that women might safely reuse female condoms, which are currently indicated for a single use. One study found that 295 of 300 re-used female condoms were structurally sound after up to seven uses. While stopping short of actually encouraging this approach, WHO issued a protocol for the safe reuse of a single female condoms up to five times. The protocol calls for soaking a female condom as soon as possible after use in diluted bleach, with the cleaned product then dried and re-lubricated for future use. The feasibility, acceptability and frequency of re-use of the female condom are unknown.

Table 7. Potential Interventions for Female Condoms

Shortcoming	Female condoms	Potential market interventions
Affordability	Price is up to 20 times higher than male condom.	• Determine price points for differing manufacturing volumes (the manufacturer of FC2 suggested that the product's cost could be halved if the number of units procured annually were to reach 3% of the total male condom market). • Establishing price points for differing manufacturing volumes to reach production levels that will translate more favourable pricing. • Demand creation and price negotiation with increased volumes of product for distribution in LMICs, contingent on assurance that this additional volume will be maintained by public sector funders. • Analyze manufacturing processes for each of the prequalified products to determine if improvements can lead to increased efficiency on production with decreased cost; support manufacturing innovations or improved equipment to decrease production costs.
Quality	Limited number of products eligible for procurement by all donors.	• Encourage submissions to FDA for approval of currently prequalified product not yet FDA-approved. • Support alignment of procurement policies by main donors.
Delivery	Limited uptake.	• Provide financial and technical assistance to support accurate demand forecasting in the context of programming.

6.3. Microbicides

Increasingly, second-generation microbicides are regarded as a form of antiretroviral pre-exposure prophylaxis (PrEP), along with oral agents. Due to the distinct development strategies that have been undertaken for vaginal microbicides, as well as the likelihood that such products will require distinct delivery mechanisms, these topical agents are presented separately for the purposes of this discussion.

Commodity access

Worldwide, a woman is newly infected with HIV every minute. Women represent 49% of all adults living with HIV, including nearly 60% of prevalent HIV infections in sub-Saharan Africa. The search for a safe and effective microbicide has been motivated in large measure by the acute shortage of prevention tools that women and girls are able to initiate and/or control. Due to gender inequities, many women are unable to abstain from sex or negotiate condom use with their male partners. Already more physiologically vulnerable to HIV during sexual intercourse than men, women's HIV vulnerability is compounded by harmful gender norms.

From 2000 to 2008, global funding for microbicide R&D increased more than four-fold. However, as no microbicide has been approved for use in preventing HIV transmission, there currently is no access to any product beyond the limited number of women who have received them while participating in clinical trials.

Technology landscape

The term "microbicide" encompasses a wide variety of substances that may be inserted in the vagina or rectum to reduce the risk of sexual HIV acquisition. Although early microbicide development explored strategies for reducing the odds of both sexual HIV acquisition and transmission, newer products have focused exclusively on interrupting HIV acquisition. Theoretically, a microbicide could confer protection through any number of means, such as killing or disabling the virus upon exposure, preventing the virus from binding with vulnerable cells, or interrupting the viral replication process.

Use of a microbicide to prevent acquisition of HIV is biologically plausible. Studies show that individuals who experience mucosal HIV exposure have few infected cells three days after exposure, suggesting that some time is required for self-propagating infection to take hold. Timely intervention with proven antiretroviral compounds could inhibit the viral replication process, crippling the ability of HIV to move from a small number of exposed cells to establishment of disseminated infection. (147)

Microbicides are substances that are applied directly at the point of exposure (typically, the vagina) to reduce the risk of sexual HIV transmission. Candidate microbicides have been developed for delivery through various means, including gels, creams, tablets, films, slow-release vaginal rings or suppositories. (148)

Early, first-generation, microbicides were non-specific agents that exhibited activity against HIV (as well as other agents that cause other sexually transmitted infections) in preclinical studies, but ultimately proved to be ineffective in large efficacy trials. These early microbicides involved formulations of negatively charged long hydrocarbon chains or agents with surfactant activity, with the primary aim to inhibit HIV fusion and entry or disruption of the outer membrane of HIV. None of these candidates proved to be efficacious, with evidence suggesting that some of the first-generation candidates might actually have increased women's risk of acquiring HIV. (149) (150) In addition, issues with adherence emerged as a challenge for the products.

In 2010, for the first time, a clinical trial provided proof of concept for a vaginal microbicide to prevent HIV transmission. In a study involving 889 uninfected women in KwaZulu-Natal province, researchers with the Centre for the AIDS Programme of Research in South Africa (CAPRISA) found that use of a vaginal gel containing the antiretroviral agent tenofovir reduced the risk of HIV transmission by roughly 39%. (151) Unexpectedly, there was also a 51% reduction in acquisition of herpes simplex virus type 2 seen in this study. (152)

Second-generation microbicides incorporate antiretroviral drugs that specifically act against HIV. (147) Two second-generation products have emerged as leading candidates for microbicides to reduce the risk of sexual HIV transmission among women, tenofovir gel and dapivirine ring. Results from major clinical trials evaluating these candidate microbicides will continue to emerge in 2013 and 2014, potentially leading to the licensure and prequalification of one or more microbicides in the next several years. (153)

The microbicide pipeline is active. In addition to the two leading products, extensive R&D efforts are focusing on a wide range of antiretroviral formulations and combinations, as well as diverse delivery methods.

Leading Microbicide Candidates

1% Tenofovir Gel

Tenofovir is a leading antiretroviral drug used orally in the treatment of HIV. Part of a class of antiretrovirals known as nucleotide analogue reverse transcriptase inhibitors, tenofovir has demonstrated anti-transmission properties. After studies involving non-human primates indicated that tenofovir had potential as a microbicide, it was included in a 1% concentration in a clear, colourless gel (151) that, for vaginal use, is pre-measured in a disposable, plastic vaginal applicator.

In the CAPRISA trial, the protocol provided for peri-coital dosing of vaginal gel up to 12 hours before and as soon as possible within 12 hours after sex, with no more than two applications in a 24-hour period. There was evidence that some trial participants found it difficult to adhere to the regimen and that sub-optimal adherence significantly reduced the product's effectiveness. Among trial participants who were judged to have high adherence rates, the reduction in the risk of HIV acquisition was 54%—substantially higher than for the trial as a whole.

A subsequent trial in Uganda, South Africa, and Zimbabwe—VOICE (Vaginal and Oral Interventions to Control the Epidemic), sponsored by the Microbicides Trials Network (MTN)—examined *daily* use of 1% tenofovir gel and other prevention approaches, including a daily oral tenofovir (TDF) and daily oral combination of tenofovir and emtricitabine (TDF/FTC). In November 2011, the MTN discontinued the vaginal active gel and placebo gel arms early after data demonstrated futility and no efficacy in reducing HIV acquisition among participating women. (154) In 2013, VOICE researchers reported that none of the interventions examined demonstrated efficacy in reducing HIV infections and that sub-optimal adherence appeared to be responsible for the failure of all the interventions tested. (155) These disappointing results raise questions regarding the viability of all daily prophylactic tools for HIV-uninfected individuals.

Several other trials are ongoing to evaluate the 1% tenofovir gel. In 2013, results are anticipated from CAPRISA 008, an open-label follow-on implementation study to evaluate the effectiveness of the 1% tenofovir gel in the communities where the earlier CAPRISA trial occurred. By 2015, results are likely from Follow-on African Consortium for Tenofovir Studies (FACTS 001), a Phase III trial in South Africa investigating the effectiveness of the

1% tenofovir gel to prevent HIV and Herpes Simplex Virus Type 2 (HSV-2) in women; results from FACTS 001 will be used to confirm the findings of the CAPRISA trial. (153)

The US FDA has placed 1% tenofovir gel on the "fast track" for regulatory review. (156) In 2012, FDA released guidance to industry, detailing the types of clinical and non-clinical safety and efficacy studies needed for approval. (157) FDA has indicated that, in addition to CAPRISA, it requires a second and adequate well-controlled trial (presumably, FACTS 001) before it would entertain a New Drug Application for the 1% tenofovir gel. (158) FDA also highlighted the need for safety data on use of the gel by adolescents.

The need for additional evidence of effectiveness and clarity on the preferred dosing strategy has also been emphasized by WHO. (159) Like US FDA, WHO also cited the need for additional safety data.

Dapivirine Ring

The other leading microbicide candidate is the dapivirine ring. Dapivirine is a non-nucleoside reverse transcriptase inhibitor developed by Tibotec Pharmaceuticals (160) and is one of eight antiretroviral drugs for which the International Partnership for Microbicides (IPM) has obtained royalty-free licenses to develop for use as a microbicide. (161)

Dapivirine Ring – Microbicide

Andrew Loxley

IPM has used dapivirine to develop both a gel and a ring, although its formulation as a ring has generated the greatest excitement in the HIV prevention field. IPM has prioritized the dapivirine ring for development, due to its long-acting properties, favourable safety profile, ease of use, and relatively low manufacturing costs. (161)

The ring is inserted into the vagina and designed to last a month, at which point it needs to be replaced with a new ring. The ring is small, convenient and discrete. Unlike the 1% tenofovir gel, the vaginal ring is neither coitally dependent nor requires daily use.

Two major Phase III trials are underway to evaluate the effectiveness of the dapivirine ring. The first—The Ring Study, or IPM 027—aims to enroll 1,650 women in four to six centres. As of January 2013, IPM reported that half of the participants had been enrolled and that it anticipates the trial to be fully enrolled by mid-2013. As long-term safety monitoring is part of this study's design, all participants will be followed for at least two years to satisfy FDA safety requirements.

The second efficacy trial of the four-week dapivirine ring is A Study to Prevent Infection with a Ring for Extended Use (ASPIRE), conducted by MTN. ASPIRE aims to enroll 3,476 women in Malawi, South Africa, Uganda, Zambia and Zimbabwe, with results anticipated in late 2014 or early 2015. (162)

Other candidates in the Pipeline

Energized by the CAPRISA trial's proof of concept, the microbicide field is presently pursuing a range of active ingredients and product formulations in preclinical or early clinical development. Included in this pipeline are rectal gels and various vaginal products (e.g. gels, rings, films, tablets and rings with a combination of an antiretroviral agent and a hormonal contraceptive). Because these products are all in early development, efficacy trials are not expected to begin before 2015.[1]

Combination Products

Considerable efforts are focused on the development and evaluation of "combination" microbicides, i.e., products that combine more than one substance with anti-HIV properties. One potentially promising combination microbicide combines the antiretroviral drugs dapivirine and maraviroc, an antiretroviral marketed by Pfizer that operates as a CCR5 co-receptor agonist, affecting a different aspect of the HIV replication process. (163) The product is currently formulated as a vaginal ring. Its developer, IPM, joined with the MTN to launch a safety trial in 2011, slated to run through April 2013.

Another investigational microbicide combines the non-nucleoside reverse transcriptase inhibitor MIV-150 with zinc acetate (ZA) in a 3% carrageenan gel. Although ZA does not have antiretroviral properties itself, it appears to boost the antiviral effect of MIV-150. (164) An animal study found that a single dose of MIV-150/ZA provided 24 hours of protection against vaginal challenge, but less durable protection against rectal challenge. (164) The Population Council and USAID initiated a Phase I study of the product in 2012. (165)

Several combination vaginal ring candidates are currently in development. These include one that combines tenofovir and acyclovir.

Novel Delivery Methods

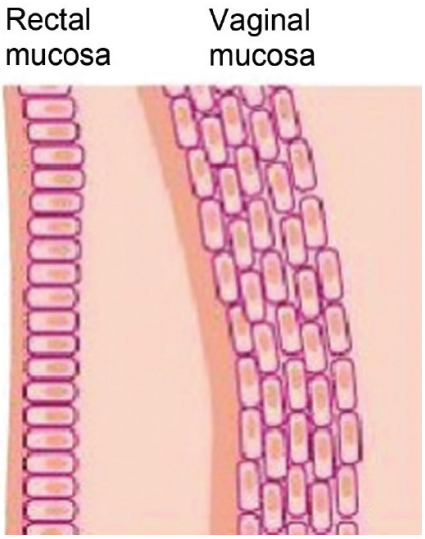
Although gels and rings have predominated to date with respect to microbicide development, researchers are actively investigating other delivery methods. CONRAD is currently evaluating the safety of a fast-dissolving vaginal tablet (165), and researchers are also investigating various injectable substances. Vaginal films that require no applicator are also under development, although such efforts are in the early stages.

1 See http://www.avac.org/ht/a/GetDocumentAction/i/49803 for a listing of the microbicide pipeline.

Rectal Application

As HIV-related risks are substantially higher during anal intercourse than for penile-vaginal intercourse (166), there has long been interest in the development of microbicides suitable for rectal application. Globally, it is estimated that 5-10% of the population engages in anal sex (167), although studies in various settings and different heterosexual populations have found a substantially higher prevalence of anal intercourse. The need for a rectal microbicide is especially acute for men who have sex with men, who experience HIV-related risks several times greater than other males, primarily due to the heightened risks associated with anal intercourse. (166)

Tissue Structure, Rectal and Vaginal Mucosa



Experts have long believed that unique formulations would be needed for rectal application. The surface space inside the anal cavity is substantially greater than in the vagina, and mucosal and other properties of the two cavities differ as well. (168) To date, research on rectal microbicides has largely been restricted to Phase I safety studies (169) and acceptability trials (170) (171) (172) although a Phase II trial of a candidate rectal microbicide is reported likely to launch in the near future. At present, the field is largely focused on microbicides that incorporate tenofovir, maraviroc or a combination of these two agents. A small phase I study that examined rectal use of vaginal 1% tenofovir gel demonstrated that the gel was not entirely safe and acceptable, suggesting the need for alternative rectal-specific formulations. (173)

Multipurpose Technologies

There are some indications of waning enthusiasm in the field for products that solely protect against HIV. Especially in light of evidence of women's potentially heightened risk of HIV acquisition when using hormonal contraception, (174) development of products that simultaneously prevent HIV and unwanted pregnancy has become an increasing focus of research efforts in the field. Some rings currently in development add hormonal contraception, with early work underway on integrating hormonal contraception in rings that contain tenofovir, dapivirine, or MIV-150.

Potential Limitations and Unanswered Questions

Although the leading microbicide candidates are still undergoing extensive investigation, even the most efficacious products are likely to offer only partial protection. Microbicides will need to be used in combination with other prevention options to ensure robust protection against HIV. One concern, especially for products intended to be used frequently, is that a microbicide might damage fragile mucosa and thereby increase the risk of transmission.

It is possible that the degree of protection offered by microbicides might be partially offset or entirely overridden as a result of risk compensation or the displacement of other prevention tools. In one survey of women in New York City, 50% said they would decrease condom use if they began using a vaginal microbicide. (175) Investigators in the CAPRISA trial reported encouraging evidence on risk compensation among trial participants (151), although the issue has yet to be rigorously studied and warrants further examination.

Available evidence indicates that adherence has an important effect on the degree of protection afforded by a microbicide. Leading microbicide candidates have different adherence challenges. The peri-coitally dependent dosing tested in the CAPRISA study is rather complicated and may not be feasible for many women in the real world, especially those who are unable to anticipate when they might have sex (although the relatively generous 12-hour window aids somewhat with regard to this constraint). As the VOICE trial results underscore, daily regimens are also associated with adherence challenges that have been well-documented for antiretroviral treatment. While the four-week dapivirine ring obviates the need for daily action, it nevertheless requires users to remove the product at periodic intervals and replace it with a new one. Even with this formulation that is less user-dependent, rings can be intentionally removed by women or inadvertently dislodged during sex or while urinating or defecating. Use of injectable, long-acting formulations of antiretroviral agents has drawn interest as a potential strategy to minimize adherence problems. A dose-finding study of long-acting injected rilpivirine has been conducted, and a phase II trial is planned.

Male perceptions of microbicide use are not fully understood and may have an effect on women's ability or willingness to use the product. At least two acceptability studies found evidence that many women would be uncomfortable using the product without the cooperation or agreement of their male partner. (176) (177)

Concerns persist regarding the potential for microbicides to induce drug resistance among users of the product who seroconvert while using a microbicide, or in those who have established, but perhaps undiagnosed, HIV infection and are inappropriately given a microbicide. (160) Recent studies have shown that microbicides appear to act locally with little systemic exposure. (178) Microbicide candidates aim to deliver an optimal dosage of the drug to prevent both HIV acquisition and the development of resistance in the case of breakthrough infections, although such optimal dosages have not been precisely determined and are the focus of active research. It is believed that combining two or more classes of antiretroviral agents in a single microbicide may reduce the potential for resistance to develop. To date, clinical trials have offered little cause for concern regarding the emergence of drug-resistant strains, although unlike real-world conditions, participants in microbicide trials are tested monthly and taken off the product as soon as HIV infection is detected, thereby limiting the amount of time that the virus is exposed to the antiretroviral agent in the microbicide.

Implications for HIV Prevention

Modelling exercises indicate that the actual population-level impact of microbicides for HIV prevention will depend on the degree of protection afforded by the products, the number of women who use them, and users' adherence to dosing regimens. One modelling study that analysed 1% tenofovir gel found that high coverage (i.e., use of the gel in 80% or more of sexual encounters) would avert 2.3 million new infections and 1.3 million AIDS-related deaths in South Africa over the next 20 years. (179) Low coverage (i.e. use of the product in 25% of sexual encounters) would prevent 500,000 new infections and avert 230,000 deaths over two decades. (179)

Analyses have generally found vaginal microbicides to be cost-effective and to compare favourably with other prevention tools, although cost-effectiveness determinations are highly sensitive to efficacy, coverage, product price and dosing periodicity. One modelling study determined that a 55% effective microbicide (at US$ 0.51 per use) used in 30% of sexual encounters would be cost-effective in South Africa. (180) At US$ 0.5 per dose, the tenofovir gel would be "highly cost-effective" even when used in only 25% of sexual encounters. (180) In another model among South African women, tenofovir gel reduced mean lifetime HIV risk from 40% to 27% and was highly cost effective, but was not cost saving, even assuming efficacy of 60%. (181) Whether vaginal

microbicides might offer uninfected male partners some protection against sexual transmission from an infected woman remains unanswered.

Important decisions will need to be made regarding optimal delivery methods for any new microbicide, with strategies probably needing to be tailored to the specific characteristics of individual products. Limiting distribution to health care settings could slow uptake, although the desire to minimize the development of drug resistance and ensure that products are used only by women who are HIV-uninfected may encourage programmes to retain some means of screening and monitoring microbicide users, at least in the early stages of product introduction.

For such a novel product, creative marketing strategies will be needed to promote acceptance and uptake and limit stigma potentially associated with a product solely intended for HIV prevention. Community leaders, women's networks and faith-based groups may play a potentially important role in accelerating roll-out and building demand for the product.

Products that combine a contraceptive with a microbicide (multi-purpose prevention technologies) may gain more acceptance since contraceptives are widely received and the product could be marketed primarily on a contraceptive claim.

Market landscape

As no microbicide product is currently available—and as sponsors of leading microbicide candidates are actively working to identify suitable manufacturing and distribution partners—it is difficult to accurately analyse likely market dynamics for the products most likely to emerge in the next several years including manufacturing strategies, delivery channels, prices and roll-out strategies. However, given the genuine prospect that one or more microbicides may be available for roll-out during the current decade, various initiatives have been undertaken to plan for expedited uptake (182) (183) and respond to potential access challenges for this high-priority HIV prevention tool.

Supply

1% tenofovir gel: Tenofovir is made by Gilead Sciences, which has provided a co-exclusive, royalty-free license to CONRAD (part of the Eastern Virginia Medical School in Norfolk, Va., USA) and IPM to develop the 1% tenofovir gel for use in LMICs. Currently, the gel is manufactured by DPT Laboratories, based in the state of Texas in the US. It is believed that DPT has the capacity to produce on a scale required for clinical trials and early launch of the product, but additional capacity would be required for scale-up.

Pursuant to its license agreement with Gilead, CONRAD has entered into a sub-license agreement with the South Africa-based Technology Innovation Agency (TIA) to pursue activities to ensure the affordability of the 1% tenofovir gel for use in resource-limited settings. Subsequently, it was announced that the gel would be registered, manufactured and distributed by Propreven, a joint venture involving TIA and Cipla Medpro. (184) No actual manufacturing capacity established under this agreement had been made public at the time of this report.

Dapivirine Ring: IPM currently uses QPharma to manufacture the dapivirine ring. QPharma is a Swedish-based company with a strong and successful history of supplying vaginal rings to the commercial and research worlds, including intravaginal rings for contraception and hormone replacement. There are currently two large pharmaceutical companies that conduct large-scale production of their own intravaginal ring products, although neither is expected to produce microbicide rings. While there are other contract companies that may have capability to manufacture microbicide intravaginal rings, capacity for large-scale production does not exist and will need to be developed, most ideally in a setting such as sub-Saharan Africa, China or India where labour costs are less expensive. IPM is actively working to identify potential production partners.

Demand

International donors are likely to be the primary purchasers of new microbicides, although it is possible that some middle-income countries may invest meaningful domestic resources in the purchase, distribution and promotion of microbicides. South Africa provided the third largest amount of funding globally in 2011 to support microbicide research, suggesting a strong national commitment to develop and use these products once they become available. (185) Currently, international donors account for the large majority of HIV prevention

spending worldwide, with the proportion of prevention spending deriving from international donors especially pronounced in countries with generalized epidemics. (12)

The US, through PEPFAR, is likely to be largest bilateral purchaser of microbicides. Both USAID and the National Institutes of Health have invested considerable resources towards microbicide R&D, representing the two top funders worldwide for microbicide R&D. (186)

Although US assistance is likely to predominate among international donors in terms of total amounts, the US will certainly be joined by other bilateral assistance agencies in supporting scale-up of microbicides. Development agencies from the UK, Netherlands and Ireland were among the top 10 funders of microbicide R&D in 2011, suggesting a likely interest among these agencies in supporting microbicide roll-out (185).

Having vied with the US Government in recent years as the leading purchaser of male and female condoms, UNFPA may also be an important potential purchaser of microbicides, although the organization's degree of support for a product that does not offer contraception is not clear. The Global Fund is likely to play a central role in future microbicide purchases, although consistent with the Global Fund's operating approach, much will depend on countries' willingness to include microbicide programming in national funding proposals.

In comparison to the public sector, the private market is likely to be minimal in the generalized epidemics where microbicides are most needed. Even assuming IPM's success in lowering manufacturing costs sufficiently to ensure a unit price of US$ 3 for a four-week dapivirine ring, such a monthly outlay is likely to be beyond the means of many women who need the product.

Demand drivers: For the public sector agencies that will probably purchase the overwhelming majority of microbicide products, at least two sets of issues are likely to drive their purchasing behaviours. First, donors and national programmes will need to be convinced that microbicide purchases represents a cost-effective use of finite HIV prevention resources and may wish to make comparisons of cost-effectiveness among available prevention methods. On the other hand, the urgent unmet need for HIV prevention methods that women may initiate and control would presumably encourage purchasers to invest in microbicide uptake, even if other interventions not directed specifically at women might be modestly more cost-effective.

The second factor that is likely to affect purchasers is the degree of actual demand for such a product in the real world. Extensive evidence suggests that diverse women find the notion of using a microbicide to be desirable and acceptable. (177) (187) (161) The body of evidence on microbicide acceptability, however, has been criticized on the grounds that many acceptability studies are based primarily on hypothetical questions asked participants following verbal descriptions of investigational products. (188) Initial behaviour also may not predict behaviour over the long run. In the face of such concerns, researchers have worked to design trials that more accurately measure users' actual experiential preferences. In one recent trial of 526 sexually active women in Burkina Faso, Tanzania and Zambia, participants were asked to use three different delivery methods—a vaginal film, a soft-gel capsule, and a tablet; women surveyed found each of the methods to be acceptable, with preferences among the different delivery modalities differing by country. (189)

Although acceptability studies provide critical information on possible future demand for a microbicide, gauging actual demand will need to await experience in the real world. Several factors are likely to influential, including the characteristics of the microbicides approved for distribution, the response of male partners, the reach and effectiveness of marketing efforts to promote microbicide use, available distribution channels (and consumers' ease in accessing the product), the enthusiasm with which health providers and community and national leaders promote microbicide use, and the degree to which social norms evolve to support use of intravaginal products.

Work is ongoing to estimate demand for microbicides. IPM, for example, has undertaken an analysis of demand for the dapivirine ring in 12 African countries with the largest eligible populations (Nigeria, Ethiopia, Democratic Republic of Congo, Sudan, Kenya, Tanzania, South Africa, Mozambique, Ghana, Uganda, Rwanda, Malawi). Accessible women aged 20-49 years in these markets was estimated to range between 47-85 million (mean 65 million). Adoption of product approximately 10 years after launch has been estimated at 1.5-6.6 million (mean 4 million). (190)

Procurement requirements and guidance: Data on both tenofovir gel and dapivirine ring will be submitted to FDA for approval, as this is a requirement for PEPFAR purchase. WHO prequalification has provided guid-

ance on the types of non-clinical and clinical data needed to support prequalification and has also convened consultations to consider various access issues. However, as no microbicide product is currently available for distribution, no international guidelines have been developed for microbicide-related programming. Given the high priority attached to microbicides for HIV prevention, it is likely that WHO would prioritize the guidelines development process assuming favourable research results on one or more of the leading microbicide products.

Microbicides are a novel product, potentially increasing burdens on national regulatory agencies, which are often weak and have limited capacity in countries where demand for a microbicide is likely to be greatest. In addition, pharmacovigilance for adverse events and impact on HIV drug resistance will be needed after a microbicide is brought to market. Concerted efforts by WHO, regional associations of regulators, manufacturers and international donors will be needed to avoid potential regulatory delays to meaningful access.

No other prevention method currently available is likely to compete in the particular niche that microbicides will occupy. In the quest for discreet, female-initiated prevention methods, microbicides stand alone. From a practical standpoint, however, microbicides will compete with other prevention strategies (e.g. antiretroviral-based prevention, male circumcision, condom promotion) for the limited budgets of national programmes and donor agencies for the purchase of HIV prevention commodities.

Market shortcomings

Availability: No microbicide is currently on the market and ready for roll-out. Several questions remain unanswered with current pipeline microbicides. A healthy microbicide pipeline suggests that if current candidates show sub-optimal or no efficacy, back-up candidates that may be more efficacious are soon likely to follow. As a result, purchasers may one day have several microbicide products from which to choose, including one or more that offer dual protection against HIV and pregnancy. Over the next several years, however, it is likely that the microbicide field will be limited to one to two products available for roll-out. ***Reasons:*** Research challenges of development of new classes of products. Limited focus until recently.

Acceptability: No ideal formulation developed yet. Concerns regarding whether women will rigorously adhere to microbicide regimens are a major challenge, reinforced by data emerging from recent clinical trials. Female acceptability, and male perceptions of microbicide use are not fully understood, and how best to optimize user adherence remains unclear. ***Reasons:*** The VOICE trial results suggest that many healthy, uninfected women may find it challenging to take a daily prophylactic regimen. The monthly regimen for dapivirine may be less taxing than coital or daily dosing, although women will still need to replace the ring with a new one every month and avoid removing the ring or having it become dislodged during intercourse, urination or defecation.

Affordability: There is considerable uncertainty regarding likely market prices for 1% tenofovir gel. The unit price for a one-month dapivirine ring is about US$ 8, potentially a barrier for its scale-up use. ***Reasons:*** With no marketable product currently available and manufacturing and distribution partnerships yet to be fully established by product sponsors, transparent pricing for these still-in-development products is not available. It should be noted the sponsors of the leading microbicide candidates are mission-driven, not-for-profit entities that include affordable pricing in their operating approach.

For each of the leading microbicides, initial supply is likely to be concentrated in a single manufacturer. This appears to be expressly envisaged in the manufacturing and distribution regime established for tenofovir gel. Within each product category, it is unlikely that competition from multiple suppliers will exist in the early roll-out phase.

Currently productions costs in the case of davipirine ring as it is manufactured in Sweden, for instance, are high. Current packaging accounts for an estimated 90% of manufacturing costs of tenofovir gel.

Delivery: Manufacturing capacity is a potentially important concern for future microbicides. IPM's investigation of options to date has underscored worries about manufacturing capacity. ***Reasons:*** Capacity challenges appear especially pronounced for the dapivirine ring, given the generally limited global capacity for large-scale manufacture of intravaginal rings with few existing manufacturers globally. Possibilities to expand capacity have not yet delivered.

Potential market interventions

Although the disappointing results from the VOICE trial highlight the challenges facing the microbicide field, they also underscore the urgent need for researchers to pursue all promising avenues for development of new prevention technologies for women. Among participants in the VOICE trial, annualized HIV incidence was an astonishing 5.7%, vividly illustrating the extraordinarily high risk experienced by women in sub-Saharan Africa. (155)

Applicator used for vaginal administration of microbicide products

Several factors are likely to be influential in the uptake and market size of microbicides, including the characteristics of the microbicides approved for distribution, the response of male partners, the reach and success of marketing efforts to promote microbicide use, available distribution channels (and consumers' ease in accessing the product), the enthusiasm with which health providers and community and national leaders promote microbicide use, and the degree to which social norms evolve to support use of intravaginal products.

1% tenofovir gel: Currently, microbicidal gels come in wrapped in prefilled, single-use, plastic applicators, which wind up being the most expensive component of the product, accounting for 90% of the cost. (191) In an effort to reduce product costs, PATH has identified a manufacturer in the state of Alabama in the USA to produce a less expensive paper applicator that the user would fill. This approach might reduce the per-dose costs of microbicide roll-out (with a projected cost per dose with this applicator of US$ 0.17) (192) and provide a more environmentally suitable option than the plastic applicator. A bridging study jointly conducted by PATH, Profamilia and CONRAD found that the paper applicator delivered accurate doses of the gel and was equally safe, comfortable and easy to use as the plastic version. PATH is presently working with various stakeholders to explore use of paper applicators in roll-out plans for 1% tenofovir gel in South Africa and other countries. (193)

Dapivirine ring: With support from the Bill & Melinda Gates Foundation, IPM is presently studying how to expedite access to the dapivirine ring. Key elements to these access plans include development of national and global partnerships, timely scale-up of manufacturing capacity to meet anticipated demand, optimal pricing, and outreach and training for health care providers and community stakeholders. IPM have a goal to lower unit costs for the ring to US$ 2-4 as compared to the present cost of up to US$ 8. As manufacturing capacity for high volumes of a microbicide intravaginal ring does not currently exist, IPM is also studying possible manufacturing options in China, India and sub-Saharan Africa.

If studies of one or both of the candidate microbicide products are positive, time from study completion (2013-2014) to approval is uncertain, meaning that a product may not be available in the market until 2015 or 2016. Timelines for other microbicide candidates are longer as these products are still in preclinical or early clinical testing. Given the extended timeline and the high degree of uncertainty in this field, one could argue that this space should be followed closely without any market-based interventions planned for the near term. However, should studies prove favourable, some interventions could be undertaken in preparation for product launch.

Table 8. Potential Interventions for Microbicides

Shortcoming	Microbicides	Potential market interventions
Affordability	Uncertainty about market price of tenofovir gel.	Analyze support needed to continue or accelerate development of paper applicator for administration of vaginal gels to decrease their cost.
Delivery	Uncertainty about manufacturers' capacity to scale up.	Make time-limited investments to assist microbicide developers in identifying capable manufacturers to facilitate timely manufacturing scale-up and expedited roll-out once products are proven effective. Monitor capacity on South Africa local production through the Propreven partnership for tenofovir gel and applicator, as well as capacity of production for intravaginal rings.

6.4. Other Antiretroviral-Based Prevention Methods

In recent years, strategic use of antiretroviral drugs has transformed the HIV prevention landscape. (194) As the potential prevention applications of antiretrovirals have proliferated, leading global health experts have suggested it is now possible to lay the foundation for the eventual end of the epidemic (195) and could be argued that antiretroviral therapy now constitutes the centrepiece of effective HIV prevention.

The specific market dynamics for antiretroviral medicines are extensively covered in forthcoming complementary HIV/AIDS medicines landscape, and only included here to provide a comprehensive view of biomedical products for prevention.

6.4.1. Pre-Exposure Prophylaxis (PrEP)

PrEP is the use of antiretrovirals in an HIV-negative individual to prevent acquisition of HIV. In heterosexual, serodiscordant couples, daily use of either tenofovir (TDF) or tenofovir and emtricitabine (TDF/FTC) by the HIV-negative partner decreased the risk of HIV-1 transmission by 67% and 75%, respectively. (196) In 2013, study findings indicated that daily TDF reduced the risk of HIV acquisition by 49% among people who inject drugs. (197)

Commodity access issues

In 2012, the US FDA approved the combination of TDF/FTC for PrEP against HIV infection. Soon thereafter, the US Centers for Disease Control and Prevention (CDC) issued interim guidance to health care providers on administration of TDF/FTC for PrEP, addressing such issues as adherence counselling, a lack of evidence on long-term safety, and approaches needed for women of reproductive age. In the US, uptake has been slow, due to such factors as high drug costs, lack of clarity on reimbursement for PrEP by insurance providers, uncertainty regarding who should be eligible for the service, and low levels of awareness among subjects and providers. Efforts are now underway to obtain relevant information on optimal methods of targeting and delivering PrEP, although observers advise that projects to date are mostly ad hoc and have yet to coalesce into a meaningful strategic effort to inform programme implementation.

Technology landscape

Four international studies found that daily use of antiretrovirals by HIV-negative individuals substantially reduces the risk of HIV acquisition, with the greatest benefit seen with a combination of TDF/FTC. (198) (199) (200) In heterosexual, serodiscordant couples, daily use of either TDF or TDF/FTC by the HIV-negative partner decreased the risk of HIV-1 transmission by 67% and 75%, respectively. (196) In June 2013, study findings indicated that daily TDF reduced the risk of HIV acquisition by 49% among people who inject drugs. (197)

Two studies in women—the FEMPrEP and VOICE trials—found no benefit from TDF and TDF/FTC PrEP, likely due in large part to poor adherence with daily dosing. (201) (155) As in the case of the CAPRISA vaginal microbicide study, the benefit from PrEP is directly correlated with individual adherence to the daily regimen. (202) The crucial importance of adherence was further underscored by results from the VOICE trial in early 2013. This multi-country trial compared daily TDF, a daily combination of TDF/FTC, and daily 1% tenofovir microbicide gel. The trial found none of the products to be effective in reducing the risk of HIV acquisition, perhaps in part due to study participants' failure to adhere to the prescribed regimen. Although about 90% of trial participants told researchers they were taking the regimens daily, blood tests detected the presence of the antiretroviral agents only about a quarter of the time. (203) New research underlines the importance of adherence in the efficacy of PrEP, showing 70% efficacy for participants who had detectable levels of anti-HIV drugs in their blood, compared to an efficacy of 23% in people without detectable drug levels. Overall, the results show that the effectiveness of PrEP is closely tied to adherence. (197) (204)

In 2012, WHO advised that daily PrEP be considered for the uninfected partner in identified serodiscordant couples. (205) WHO recommended the implementation of development projects to identify optimal delivery methods and to expand the knowledge base on the clinical and real-world implications of PrEP. (205) Demonstration projects have been slow to get underway in LMICs, although one such PrEP project has been launched in Kenya and Uganda. Some are calling for additional demonstration studies in settings such as South Africa, where drug costs are relatively inexpensive, high-risk target populations have been identified and models have shown the intervention to be cost-effective. (206)

At least six large-scale clinical trials on tenofovir-based PrEP are currently underway, including two open-label trials that may generate valuable information on programme implementation and population-level effects. (207) In addition, several earlier studies are underway, including at least two Phase I or II trials that are investigating other single and combination antiretroviral agents including maraviroc, S/GSK1265744, ibalizumab, and a long-acting injectable formulation of ripilvirine. (208)

Although the evidence is clear that daily antiretrovirals reduce the risk of HIV acquisition, its relevance to practice in LMICs is unclear. Questions persist over how best to focus programmes and how best to deliver the intervention. The degree to which uninfected individuals will adhere to the daily prophylactic regimen outside the conditions of a clinical trial is unknown.

While there have been studies that have shown that the intervention may be cost-effective in some settings, even in low resource settings, the relatively higher cost compared to other less expensive interventions may affect uptake. (209) A recently published summary of PreP cost-effectiveness studies found that PrEP may be cost-effective in men who have sex with men in the US and in young women in South Africa, with cost-effectiveness of the intervention influenced by the degree of effectiveness (which in turn is affected by adherence), cost, and how PrEP is implemented. The analysis determined that PrEP does not currently result in cost savings. (210)

In addition, some HIV advocates in LMICs have sharply questioned the fairness of distributing antiretrovirals for HIV prevention when only less than 10 million people living with HIV are currently receiving it, despite estimated need being approximately 26 million people according to WHO revised guidelines (211).

Market landscape

As indicated above, further information of specific ARVs' market dynamics and shortcomings are subject of a complementary medicines landscape and not covered here in great detail.

The only marketed product currently approved for PrEP is TDF/FTC. Gilead, the originator company, offers the TDF/FTC combination to scores of LMICs at lower prices, with the list of eligible countries determined through a composite index that takes account of economic development and HIV prevalence (212). There are at least five generic manufacturers in India (four of them already WHO prequalified or tentatively approved by FDA), which market the dual fixed-dose combination at less than a third the price of the lowest-priced originator product (US$ 93 per person per year versus US$ 319-548 per person per year) (212).

Gilead has entered into a licensing agreement with the Medicines Patent Pool (MPP)[2] and some generic companies for TDF and its combinations, including this product, for a given list of eligible countries. Nonetheless, in some countries excluded from such licensing agreement, patents for these compounds or the combination might be granted and could prevent the use of lower priced generic versions (e.g. China, Mexico, Argentina and Brazil)[3]. Where granted, these patents would remain in force at least until 2018 for the compound patent for TDF and until 2024 for the combination.

Market shortcomings

Affordability: The high price of the required combination is a barrier to scale-up, contributing to the limited cost-efficacy of the intervention compared to other, more inexpensive, prevention interventions. ***Reasons:*** The cost is yet to decrease for the combination, the price of which is even higher in countries outside the licencing territory of Gilead and where no generic can be purchased.

Delivery: The security of supplies of antiretroviral formulations for prevention purposes is unclear. ***Reasons***: A lack of clarity exists on the demand for formulations specifically used for prevention (such as dual tenofovir fixed-dose combinations). With increasing efforts to achieve universal access to treatment and move to simplified treatment regimens, and recent recommendations from WHO on the use of one single-pill tenofovir-based regimen as first-line treatment across most population groups, triple fixed-dose combination pills are going to occupy the greatest market share, to the detriment of other alternative formulations with single or dual agents. This could compromise the continuity of supplies, warranting continued monitoring of supply of these formulations.

Potential market interventions

UNITAID and stakeholders are actively implementing a number of market-based interventions to reduce prices and increase availability of antiretroviral products. Given the persistent questions about the use of PrEP in LMICs, the timeliness of possible market-based interventions to expand PrEP access is unclear. While the new 2013 WHO guidelines aim to clarify international approaches for HIV treatment, policies for PrEP in LMICs remain poorly defined, with substantial uncertainty surrounding affordability, demand and acceptability of PrEP in these settings. A potential specific intervention in the case of PrEP could be to support investments in initial product introduction to inform policy and roll-out (e.g. in terms of the optimal target populations for intervention, magnitude of demand, and adherence issues).

2 See http://www.medicinespatentpool.org

3 See Medicines Patent Pool's patent database for Selected HIV Medicines available at: http://www.medicinespatentpool.org/patent-data/patent-status-of-arvs/

6.4.2. Post-Exposure Prophylaxis (PEP)

PEP is short-term use of antiretrovirals in HIV-negative people that have had a high risk exposure to HIV. According to WHO (213), people who are eligible for PEP must meet the following criteria: 1) exposure occurred within the past 72 hours; 2) the exposed individual is not infected or not known to be infected; 3) mucous membrane or non-intact skin was significantly exposed to an infectious body fluid, and 4) the source is known to be HIV-positive or the HIV status is unknown. The use of PEP should be in conjunction with other forms of HIV care, including counselling, testing and follow-up.

Commodity access issues

Since the 1980s, the CDC has recommended initiation of antiretrovirals within 72 hours for health care workers who experienced exposure to potentially infectious body fluids. (214) This approach was widely adopted in high-income countries and extended over time to other occupations in which exposure to blood or other body fluids might occur, including law enforcement and correctional personnel.

In 1987, WHO joined with the International Labour Organization (ILO) to issue guidelines on PEP for occupational exposure and sexual assault. (213) These guidelines addressed needed policies and practices (including adherence to human rights principles), details regarding administration of PEP (including assessment of individual risk, selection of regimens, and duration of regimens), clinical management of occupational exposure, and appropriate approaches to managing HIV risk in individuals who have experienced sexual assault.

In high-income countries, use of PEP has sometimes extended beyond occupational exposure or instances of sexual assault. In 2005, the CDC issued guidelines on use of PEP after non-occupational exposures, including consensual sexual intercourse and injecting drug use. (215) The CDC recommends clinical evaluation of the appropriateness of PEP on a case-by-case basis, with the intervention indicated in cases where a significant risk of transmission exists.

In LMICs, current coverage of PEP for occupational exposure or survivors of sexual assault is unknown. Nor is information readily available on the degree to which PEP is made available to individuals who have experienced consensual exposures, although one may assume the number is relatively small.

Technology landscape

WHO recommends a 28-day course of PEP, with the first dose offered as soon as possible within 72 hours after exposure, and with choice of ARVs base on the country's first-line ART regimen for HIV. According to 2007 WHO guidelines for PEP not yet updated, standard PEP regimen should comprise two nucleoside-analogue reverse-transcriptase inhibitors, preferably zidovudine plus lamivudine. Three-drug regimens, comprising two nucleoside-analogue reverse-transcriptase inhibitors plus a boosted protease inhibitor, can be considered in situations where antiretroviral therapy resistance is known or suspected (213). The use of PEP should be in conjunction with other forms of HIV care including counselling, testing and follow-up.

Market landscape and market shortcomings

As indicated above, further information of the market dynamics and shortcomings of specific ARVs are the subject of a complementary medicines landscape and not covered here in great detail. For the dual combination traditionally used in PEP, ZDV/3TC, the market is highly competitive, with at least 15 products prequalified by WHO and/or approved/tentatively approved by US FDA, including products manufactured in India, South Africa and Zimbabwe.

Potential market interventions

As with other antiretroviral-based prevention methods, UNITAID and other stakeholders continue to engage in broader efforts to improve market conditions in LMICs for ARVs. For PEP, it is likely that programmatic issues and questions regarding prioritization of scarce resources may primarily determine access in resource-limited settings.

6.4.3. Prevention of Mother-to-Child Transmission (PMTCT)

HIV-positive pregnant women risk transmitting the infection to their children during pregnancy, the birthing process, or from breastfeeding after birth. (216) In the absence of any intervention, transmission rates range from 15-45%. (217) Antiretrovirals can help prevent transmission of most infections if taken by the mother during pregnancy and breastfeeding, and by the infant postpartum and while breastfeeding. (216) The use of PMTCT has been shown to reduce the risk of infection < 5% in breastfed infants and < 2 % in non-breastfed infants. (218)

Programmes to prevent mother-to-child transmission (PMTCT) are another form of treatment as prevention, although they are discussed separately here due to the uniqueness of the population they serve as well as their reliance on distinct delivery channels.

The Global Plan "Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive" provides for a four-pronged approach to prevent new HIV infections in newborns:

- Strengthen primary HIV prevention services for women and their partners;
- Meet the unmet need for family planning services among HIV-infected women;
- Deliver HIV testing and antiretroviral drugs in a timely manner to pregnant women living with HIV; and
- Provide HIV care, treatment and support for HIV-infected women and children, as well as their families. (219)

Commodity access

Globally, 22 countries (all but one of them in sub-Saharan Africa) account for more than 90% of new HIV infections in children, and the Global Plan for elimination of new HIV Infections focuses specifically on these countries. (216) These 22 priority countries are Angola, Botswana, Burundi, Cameroon, Chad, Côte d'Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, India, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia and Zimbabwe. (216)

Although progress in bringing PMTCT programmes to scale was extremely slow in the years immediately following the release of clinical trial results that demonstrated the efficacy of affordable preventive interventions for newborns, major strides have been made more recently. In 2012, 66% of pregnant women living with HIV worldwide received antiretroviral prophylaxis. (8) Among LMICs, the highest coverage was in the Caribbean (79%), with substantially lower coverage in South and Southeast Asia (18%) and the Middle East and North Africa (7%). (216) These gains are reflected in transmission trends, as the number of children newly infected with HIV in 2011 was 24% lower than in 2009. (4)

Important gains have also been made in promoting HIV testing and delivering antiretroviral therapy in antenatal settings. Progress is less apparent with respect to other components of PMTCT; no demonstrable progress has been made in reducing the number of women of reproductive age who are living with HIV (220) , and unmet need for family planning has changed little in recent years. (4) There are signs that the number of breastfeeding women receiving ARVs has increased, although to date relatively few countries have rigorously monitored this element of PMTCT. (4) Sub-optimal utilization of antenatal services in many countries also continues to undermine efforts to achieve universal access to PMTCT.

Technology landscape

As the evidence base on PMTCT has expanded, international normative standards have evolved. Single-dose nevirapine, an earlier mainstay of PMTCT programmes, is being phased-out due in part of evidence concerning the risk that drug resistance in the women who take it and subsequent negative impact on treatment outcomes in these women. (4) Increasingly, international consensus has recognized the clinical and programmatic value of adopting a single triple-drug combination antiretroviral regimen for both treatment of HIV in pregnant women and PMTCT. (216) In 2012, WHO recommended that clinicians consider prescribing lifelong antiretroviral therapy to HIV-infected pregnant women, regardless of CD4 count. (216) In addition, while prophylaxis was previously confined to pregnancy, WHO now recommends administration of ARVs to prevent HIV transmission during breastfeeding. (216)

In new WHO guidelines released on 30 June 2013 (10), a single first-line regimen, harmonized with regimens for the general population, is recommended for pregnant and breast-feeding women. Such a regimen can now include efavirenz, as prior concerns over the safety of efavirenz in pregnancy have been clarified. Nevirapine, and alternatively, zidovudine, are recommended for the infant in the current simplified approach to prophylaxis.

Market landscape, shortcomings and potential market interventions

As indicated above, further information on the market dynamics and shortcomings of specific ARVs is the subject of a complementary medicines landscape and not covered here in great detail. Ongoing efforts to decrease costs of antiretroviral agents and secure uninterrupted supplies, both for adults and children, will contribute to improved access in the context of PMTCT and enable its expansion.

6.4.4. Antiretroviral Treatment for prevention

Background

Treating patients that are HIV-positive with ART decreases viral load. High viral load is the greatest risk factor for HIV transmission, with studies suggesting the risk of HIV transmission is near zero when viral load is < 1500 copies/mm^3. (221) In 2011, investigators in the HPTN 052 trial reported that early antiretroviral therapy reduced the risk of HIV transmission within serodiscordant couples by 96%. (6) Two subsequent observational studies confirmed the population-level benefits of antiretroviral therapy within serodiscordant couples, although the observed reduction in the risk of HIV transmission (26% in one study, 38% in the other) was less pronounced than the effect observed in the controlled experimental conditions of HPTN 052. (222) (223) Diverse mathematical models have differed regarding the projected population-level effect of scaled-up antiretroviral treatment, although all have determined that scale-up would result in a significant reduction in new HIV infections. (224)

Many questions remain as to the best means of harnessing antiretroviral therapy for HIV prevention, including when to start therapy, which regimens are optimal to reduce the odds of onward transmission, and how best to target treatment initiatives to maximize their impact on HIV incidence. As of January 2013, at least six major clinical trials were underway, involving participants from at least five continents, to expand the knowledge base on antiretroviral therapy as prevention. (225) Among these trials is the continuation of HPTN 052, which seeks to ascertain the duration of the prevention benefit seen in the early 2011 results. (226)

The HPTN 052 results have already affected normative practice. In 2011, the PEPFAR Scientific Advisory Board recommended that PEPFAR accelerate treatment scale-up for all individuals with a CD4 count of 350 or lower. (227) In 2012, WHO issued guidelines recommending initiation of antiretroviral treatment to HIV-infected partners in serodiscordant couples, regardless of CD4 count. (228) (10)

With respect to international norms, key questions persist, especially regarding guidance on when to initiate treatment. For example, while the US recommends consideration of antiretroviral therapy for all HIV-infected individuals in the US, regardless of CD4 count, PEPFAR adheres to the prevailing WHO-recommended threshold for initiating therapy, with certain caveats where treatment should be started earlier, including for pregnant women, infected partners in serodiscordant couples, and those with certain medical conditions, including tuberculosis.

Market landscape and market shortcomings

Existing shortcomings for preferred antiretroviral regimens for treatment of the general population would also affect the roll out of potential strategies to treat for prevention. Key shortcomings include cost and supply capacity, as well as the availability and acceptability of products for use in resource- limited settings. These shortfalls are covered separately in the forthcoming UNITAID medicines landscape.

Potential interventions

There is ongoing research to identify opportunities for efficiency in delivery of treatment including through less expensive regimens, new and less expensive monitoring tests, and more efficient models for delivery of care and treatment. Opportunities for additional market-based interventions may arise from this work.

6.5. Harm Reduction Commodities

Background

Globally, people who inject drugs are 22 times more likely to be living with HIV than those who do not. (4) Injecting drug use is driving or significantly worsening national epidemics in many parts of the world, most notably in Eastern Europe and Central Asia, where HIV incidence is on the rise. (4) UNAIDS has estimated that injecting drug use accounts for 5-10% of all new HIV infections worldwide and for one in three new infections outside sub-Saharan Africa. Substantial evidence indicates that rates of new infections among people who inject drugs may be sharply reduced through implementation of an approach known as harm reduction. (4)

Commodity access

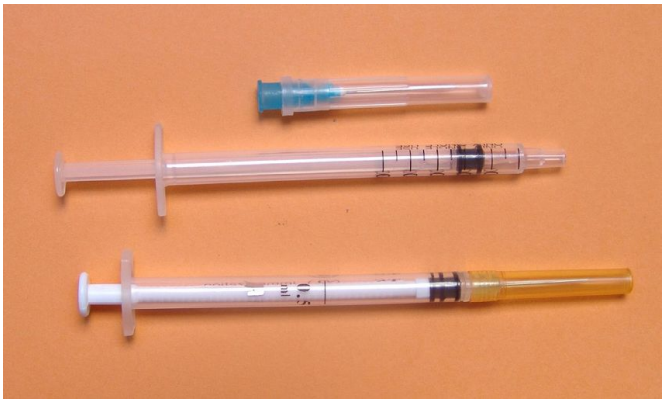
In 2011, WHO reported that among 107 countries reporting HIV programme data, only 42 had needle and syringe programmes in place. (227) Globally, only two needle-syringes were distributed each month for each person who injects drugs. (229) Of all episodes of injecting drug use worldwide, it is estimated that only 5% involve sterile injecting equipment. (230) Only 37 of 107 countries reporting data to WHO in 2011 said that opioid substitution therapy was available. (227)

National legal and policy frameworks further diminish harm reduction uptake by deterring individuals from seeking services. (231) Measures that discourage utilization of harm reduction include legal provisions in some countries that require health care providers to report drug users to law enforcement authorities, as well as compulsory detention and treatment regimes in a number of countries.

Technology landscape

Harm reduction consists of a package of interventions, including access to sterile injecting equipment, opioid substitution therapy and other drug treatment interventions, and a range of essential health services, including antiretroviral therapy. (232) With respect to commodities, key components include sterile syringes, as well as the leading compounds used as opioid substitution therapy, i.e., methadone and buprenorphine.

Auto-Disable Syringe



As a mainstay of medical practice, syringes are among the medical supplies most commonly produced throughout the world. The cheapest disposable device costs only about US$ 0.03 per unit, although WHO recommends use of more expensive auto-disable syringes in national vaccination programmes and other health services, primarily to reduce the risk of transmission of HIV and other blood-borne pathogens as a result of unsafe injection practice. These devices, which prevent reuse and reduce the risk of needlestick injury, cost about US$ 0.15 per unit. (233) Harm reduction advocates have criticized this WHO policy on the grounds that, while well-intentioned and appropriate to address issues of injection safety in health care settings, the agency may be needlessly

discouraging use of the less costly syringes preferred by people who inject drugs. In particular, harm reduction advocates argue that drug injection outside medical settings typically involves more than one retraction of the needle plunger, rendering auto-disable syringes inappropriate for drug use. (234)

Buprenorphine

Both methadone and buprenorphine, available for use in opioid substitution therapy, have been included in the WHO List of Essential Medicines since 2005. (235) Methadone was the first widely promoted therapeutic substitute for opiate dependence. Methadone may not work for everyone, underscoring the need for multiple drug substitution therapies. Buprenorphine is a distinct compound used as an alternative to methadone in opioid substitution therapy, which is available in sublingual tablets approved since 2009.

Market Landscape

Supply

Numerous suppliers—in Europe, North America, Eastern Europe, Central Asia, the Middle East, and Asia—currently produce and supply opioid substitution medicines. (236) Methadone prices vary considerably, though monthly commodity costs can be as low as US$ 7 (237). According to the WHO commodity pricing database (238), citing 29 different suppliers, the range is broad from US$ 14 to US$ 842 for the oral tablets on a daily dose of 80 mg.

On the other hand, treatment with buprenorphine sublingual tablets typically costs more than 10 times higher that of methadone (with a wide range from US$ 175 to US$ 2,999 per month for a daily dose of 16 mg, as reported to WHO by 14 different manufacturers).

Demand

In 2011, an estimated US$ 500 million was spent on harm reduction programmes worldwide. (13) Experts advise that current outlays for harm reduction services are inadequate. UNAIDS recommends that annual funding for harm reduction programmes should rise nearly five-fold by 2015 (US$ 2.3 billion). (13)

The Global Fund is the leading international funder of harm reduction programs, having committed US$ 430 million in multi-year funding toward them. In 2012, the Global Fund was supporting 120 harm reduction programmes in 55 countries. (239)

The global leader in HIV prevention assistance, the US Government, has a much more modest role with respect to harm reduction than for programmes to prevent sexual transmission. In part, this reflects PEPFAR's programmatic emphasis on sub-Saharan Africa, where injecting drug use plays a lesser role in national epidemics than in many parts of Eastern Europe and Asia. However, US policies also impede PEPFAR from playing a greater

role in preventing drug-related HIV transmission. In 2011, the US Congress enacted legislation prohibiting the use of US Government funds to support needle and syringe exchange; as a result, PEPFAR is legally prohibited from supporting syringe exchange, although PEPFAR funding may still be used for non-exchange components of harm reduction.

In funding, like policy, national governments have been resistant to embracing harm reduction programs. In 2010-2011, of all HIV resources spent on persons who inject drugs, 92% came from international donors. (4) In Eastern Europe and Central Asia—where national HIV epidemics are rapidly growing, primarily due to transmission during drug use—domestic public sector sources supplied only 15% of HIV spending focused on people who inject drugs in 2010-2011. (4)

Market shortcomings

Affordability: Monthly commodity costs for methadone can be as low as US$ 7, but buprenorphine, an essential alternative to methadone which can be taken sublingually, often costs more than 10 times as much. ***Reasons:*** Due to the fragmented and low-level nature of global funding for harm reduction programmes, purchasers may currently lack the market power to obtain optimal prices for buprenorphine. (240)

Delivery: Products are unavailable at the country level in certain cases. ***Reasons:*** These medicines are included in the list of controlled medicines and are not available in many countries due to related procurement challenges.

Potential market interventions

There is a crucial need to build support for harm reduction funding—among both national governments and international donors—in order to reverse the global neglect of this proven HIV prevention strategy. In the meantime, marketplace interventions—such as demand aggregation and support for increased purchases of buprenorphine to drive down unit costs—may be warranted to extend the programmatic reach of harm reduction programs. Such an approach would help overcome the difficulties in this fragmented market in terms of negotiating lower prices and helping to bring unit costs of buprenorphine therapy more in line with methadone.

6.6. Longer-Term Pipeline for HIV Prevention Commodities

In addition to the HIV prevention technologies already available or likely to emerge in the foreseeable future, efforts are underway to develop other new HIV prevention tools. The time horizon for emergence of the prevention options discussed in this section appears to be substantially more distant than for the other new prevention tools discussed earlier (e.g. male circumcision devices and vaginal microbicides).

6.6.1. Vaccines

When US Health and Human Services Secretary Margaret Heckler publicly announced the discovery of HIV in 1983, she predicted that a preventive vaccine would be tested in two years. (241) Thirty years after Heckler's announcement, no vaccine is in sight, although meaningful progress has been made in obtaining answers to key questions that have hindered earlier stages of the search for a vaccine. (242)

Although disappointing, the record to date on HIV vaccine R&D is in line with the history of vaccine development. Among all vaccines that have been developed, only in two cases (hepatitis B and rotavirus) were vaccines developed within 30 years of the discovery of the causative agent. (243) In the case of HIV, vaccine development is complicated by the lack of an appropriate animal model, the need to protect against multiple strains of virus and against both mucosal and blood exposure, and the complexity of the virus itself.

Early efforts to generate immunity against HIV solely through the generation of antibodies—a common approach to vaccine development—proved unsuccessful, with antibody responses proving inadequate to neutralize the virus. (244) Developers then tried a new approach, seeking to elicit a cellular response sufficient to protect the body against infection. The STEP trial (a 3,000-person trial sponsored by the US National Institute of Allergy and Infectious Diseases and by Merck in Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico and the US) evaluated the most promising candidate of this type, manufactured by Merck. In 2007,

the STEP trial was terminated, with evidence emerging that the vaccine might have actually increased the risk of infection among trial participants. (245)

In 2009, for the first time, clinical trial results suggested that an experimental vaccine might offer some protection against HIV. In the RV144 trial in Thailand, a live recombinant adenovirus vaccine was boosted with a second vaccine. Recipients of the candidate vaccine were 31% less likely to become infected than the control group, although there were indications that the benefits of the vaccine waned over time. (246) The partial protection afforded by the vaccine appeared to derive from a combination of non-neutralizing antibodies (i.e. antibodies to the virus that were insufficient on their own to clear infection) and cellular responses.

Following the first proof of concept in HIV vaccination, the HIV vaccine field focused its efforts on building on the results of RV144. Novartis has joined with Sanofi in an effort to develop a product that is able to sustain over time the protective effect documented for RV144. (247) However, progress in building on RV144 has been slow. Although the Novartis/Sanofi candidate was originally scheduled to enter large-scale clinical trials in 2014, the start date for the trial has reportedly been pushed back to 2016. Even with the earlier start date, it had been projected that no vaccine would be available for use until 2022, assuming favourable research results. (247)

One of the most encouraging signs in HIV vaccine research has been the progress made in identifying broadly neutralizing antibodies. (248) In recent years, the NIH, the International AIDS Vaccine Initiative, and other research leaders have isolated a range of broadly neutralizing antibodies, including the first such antibodies isolated from the global South. (249) To facilitate these breakthroughs, leading researchers joined together in an international consortium focused on identifying and characterizing antibodies with the potential to neutralize the virus.

In 2012, about 30 clinical trials were underway to evaluate various HIV vaccine candidates. Nearly all of these were in very early stages, although a Phase IIb efficacy trial testing a combination of a DNA-based and adenovirus 5-based vaccine was terminated early in April 2013 for non-efficacy, two years ahead of schedule. (249) (250)

The public health impact of an HIV vaccine will depend in large measure on its particular characteristics and effectiveness. Ideally, a vaccine would be inexpensive, require a minimal number of doses, require no refrigeration or other special handling, and be easy to deliver. According to modelling commissioned by the International AIDS Vaccine Initiative, a vaccine with 50% efficacy that achieved 30% coverage would avert nearly 20% of all infections projected to occur between 2020 and 2030. (251)

6.6.2. Treatment for Herpes Simplex Virus Type 2 (HSV-2)

HSV-2 and HIV operate synergistically, encouraging viral replication and increasing the odds of transmission. (252) HSV-2 infection increases the risk of HIV acquisition by two to seven times, and studies have identified HSV-2 as an important co-factor in the continued transmission of HIV in sub-Saharan Africa, where HSV-2 prevalence is higher than in other regions. (252)

Given the strong epidemiologic evidence supporting a significant role for HSV-2 in HIV acquisition, efforts to mobilize HSV-2 suppression therapies for prevention have been aggressively—yet unsuccessfully—pursued. In two clinical trials where HSV-2 suppression was used as means to decrease risk of HIV acquisition, no effect was seen in those treated with acyclovir for HSV-2 suppression compared to those given placebo. (253) (254) A third large clinical trial found no benefit when HIV/HSV-2 co-infected individuals in serodiscordant couples were provided with acyclovir in an effort to decrease viral load and prevent transmission of HIV from the infected to uninfected partner. (255) In all of these studies of HSV-2 suppressive therapy, there were demonstrable declines in the incidence of genital ulcers in the study population. (252) Explanations for these disappointing research findings include the failure of doses of acyclovir to prevent HSV-2 reactivation, the persistence of HIV-susceptible cells (even following the disappearance of HSV-2 lesions), and possible non-adherence among trial participants. (252)

Many still believe that an effective primary HSV-2 prevention intervention would play an important role in the prevention of HIV. Research options include a vaccine against HSV-2, as well as confirmation that tenofovir gel protects not only against HIV, but also against HSV-2. (252)

In the study involving discordant couples, in which the HIV-infected partner received HSV-2 suppressive therapy, there were small but statistically significant antiretroviral effects of acyclovir on HIV load and HIV-associated clinical endpoints, raising the question of whether the antiretroviral effects of HSV-2 suppressive drugs could be used as an adjunct to current HIV treatment, or as bridging therapy until initiating standard treatment. Studies are currently evaluating antiretroviral effects of valacyclovir, another HSV-2 suppressant with potential promise. (252) (253)

7. Concluding remarks

Observed delays in roll-out of new HIV prevention technologies have stemmed from numerous factors, including insufficient financial and human resources, inadequate political support, technical uncertainty regarding optimal programme implementation, and systemic weaknesses, including problems with commodity procurement and supply management. As the discussion of specific prevention tools in this report reveals, market factors also often play a role in impeding scale-up. These factors include unfavourable commodity prices and insufficient demand.

This landscape report of HIV prevention commodities offers various possible strategies to enhance the effectiveness of stakeholders' efforts through strategic market-based interventions, with a focus on products currently available or expected to be available near-term.

By addressing market factors that impede access, UNITAID and stakeholders can play a catalytic role in maximizing the impact of efforts underway to achieve broader scale-up of prevention commodities and reduce the number of new HIV infections.

Table 9. Summary Table of Preventive Commodities

Priority Level for Intervention	Categorization of Commodity	Opportunities
Key emerging commodities	• VMMC • Female Condoms • Microbicides	Novel products are emerging, or are expected to emerge in the nearer term, in these areas of HIV prevention. Opportunities for nearer-term intervention in these categories are therefore most robust. In some cases, further evidence is required before wide-scale implementation can take place (e.g. microbicides).
Other available commodities	• Male Condoms • Harm Reduction • ARV-based methods (PrEP, PEP, PMTCT, treatment for prevention)	Some of these strategies have played a longstanding key role in HIV prevention efforts. However, market interventions could potentially be valuable in improving the affordability and access to certain key commodities. Most commodities have been available for some time, although in some cases evidence has emerged regarding new prevention uses for longstanding commodities (antiretrovirals). UNITAID and stakeholders are already addressing market shortcomings related to antiretroviral products used in for HIV treatment.
Long-term pipeline commodities	• Vaccines • Treatment of HSV-2	These advances are considerably upstream, with new technologies unlikely to emerge for a number of years.

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