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HIV Preventives Technology and Market Landscape

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List of Acronyms

3TC	Lamivudine
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
FDC	Fixed-dose combination
FHC	Female Health Company
FTC	Emtricitabine
GMP	Good Manufacturing Practice
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
MOVE	Models for Optimizing the Volume and Efficiency
MPP	Medicines Patent Pool
MRC	Medical Research Council
MTN	Microbicide Trials Network
NIH	National Institutes of Health (United States)
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 HIV transmission
PSI	Population Services International
R&D	Research and development
SCMS	Supply Chain Management System
SRA	Stringent Regulatory Authority
STI	Sexually transmitted infection
TAG	Technical Advisory Group for Innovations in Male Circumcision
TDF	Tenofovir disoproxil fumarate
TIA	Technology Innovation Agency
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNFPA	United Nations Population Fund
USAID	United States Agency for International Development
USFDA	United States Food and Drug Administration
VMMC	Voluntary medical male circumcision
VOICE	Vaginal and Oral Interventions to Control the Epidemic
WHO	World Health Organization
ZA	Zinc acetate
ZDV	Zidovudine

1. Executive summary

Introduction

This landscape report is part of an ongoing UNITAID initiative to describe and monitor the landscape for human immunodeficiency virus (HIV) commodities. It provides a broad overview of key HIV prevention tools, describing the market dynamics around 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) methods based on antiretroviral (ARV) drugs and (v) commodities needed in harm reduction programmes for people who inject drugs. The report also explores market-based interventions that could alleviate current market shortcomings in order to improve access, focusing on key emerging products and rapidly evolving product areas. The report focuses exclusively on commodities for HIV prevention and not on 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. The material presented in this report is current as of July 2014.

Public health problem

The HIV epidemic remains one of the world's most serious health challenges. Substantial progress has been achieved in preventing new HIV infections—which declined globally by 38% between 2001 and 2013 and by more than 75% in 10 countries. However, 2.1 million people were newly infected with HIV in 2013, underscoring the continued importance of HIV prevention. Acquired immunodeficiency syndrome (AIDS) is still the sixth leading cause of death globally and the number one cause of death in Eastern and Southern Africa. 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 falls sharply, long-term costs associated with the provision of lifelong antiretroviral therapy (ART) in low- and middle-income countries (LMICs) could soon become prohibitive, potentially threatening advances achieved to date by the global AIDS response.

Global context

In recent years, biomedical research breakthroughs have revolutionized the approach to HIV prevention and have dramatically expanded the array of available options. These breakthroughs—which include voluntary medical male circumcision, a broad range of ARV-based prevention methods and some progress in developing vaginal microbicides—have generated considerable optimism that it is now possible to alter sharply 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. 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, shortages of human resources, and inadequate support from international donors and national governments. Advocacy and demand for prevention have been limited compared to HIV treatment. Unlike treatment services, HIV prevention focuses on uninfected healthy people who may not always appreciate their HIV risk or the need to take prevention measures. Although the need for further innovations in prevention is substantial, global investment in prevention-related research and development declined by 4% in 2013.

The leading purchasers of biomedical HIV prevention tools are the Government of the USA (via the President's Emergency Plan for AIDS Relief [PEPFAR] initiative), the United Nations Population Fund (UNFPA), the United Kingdom's Department for International Development (DfID), and the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund). 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 influence markets, although some limited market-shaping activities are underway, such as efforts to support the roll-out 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 such as UNITAID to influence market conditions in order to expand access and accelerate scale-up.

Male circumcision devices

Background

Clinical trials have found that medical male circumcision reduced the likelihood of female-to-male sexual HIV transmission by about 60%. In 2007 the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommended prioritizing medical male circumcision services in countries with a high prevalence of HIV and a low prevalence of male circumcision. Thirteen countries in sub-Saharan Africa were identified as priority countries for scale-up of voluntary medical male circumcision (VMMC).

Commodity access

HIV programmes face challenges in implementing VMMC on a large scale through traditional surgical methods due to limitations in resources, including insufficient numbers of trained staff to perform the interventions. Although these challenges have slowed progress in scale-up, nearly 6 million procedures had been performed as of December 2013 amid signs that the pace of service delivery was quickening. Expansion of VMMC for HIV prevention should be viewed as a public health triumph.

Non-surgical VMMC devices offer an alternative to surgical circumcision. Recognizing their potential value, WHO issued information and guidance documents on circumcision devices in 2012. To date, uptake of non-surgical VMMC devices for adults has largely been limited to trials and demonstration projects in the WHO priority countries for VMMC.

Little, if any, progress has been made towards implementing the routine offer of circumcision for newborns, primarily because of the current prioritization of adult VMMC programmes before resources are allocated to programmes for newborns. This sequential prioritization stems from 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) and the lack of clear guidance on infant circumcision in public health programmes.

Technology overview

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 circumci-

sion currently exist, several (PrePex, Shang Ring, Unicirc, Simplecirc) have attracted the interest of global health experts.

PrePex, developed for the African market, is a relatively simple elastic collar compression device consisting of two plastic rings and one elastic ring. Due to the lack of injected anaesthesia and cutting of living tissue with the PrePex device, it is likely that nurse-based service delivery models in all countries would be feasible. Shang Ring is a clamp-and-latch device that consists of two concentric plastic rings and has been used extensively in China. Shang Ring prevents bleeding and averts the need for sutures; research is underway to examine a simplified technique and the use of a topical anaesthetic.

PrePex is manufactured in Israel and is the sole product of Circ MedTech, while Shang Ring is manufactured in China by WuHu SNNDA Medical Treatment Appliance Technology. WHO prequalified PrePex in May 2013. Prequalification of Shang Ring was expected in early 2014 but has been delayed. It is hoped that prequalification will occur by the end of 2014.

Unicirc and Simplecirc are time-saving surgical-assist tools used at the time of surgery and, unlike PrePex and Shang Ring, are used only at the time of surgery (i.e. single-visit devices) and are not worn for a period of time afterwards. Unicirc does not require injected anesthesia and can be used with topical anaesthesia. Simplecirc, which is adjustable and single-sized, offers a guide for suture placement. Unicirc and Simplecirc are at earlier stages of development than Shang Ring and PrePex.

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

Market landscape

While the target number of men to be circumcised in priority countries is 20 million by 2015, the total potential market size is much larger as efforts in adults and adolescents will extend after this date. On the basis of modelling, an additional 8.4 million circumcisions will be needed between 2016 and 2025 to maintain 80% coverage. Much remains unknown about the market dynamics of male circumcision devices. PEPFAR currently funds the overwhelming majority of VMMC procedures in sub-Saharan Africa, exceeding its cumulative target of 4.7 million procedures by the end of 2013 with an estimated 5.8 million procedures performed in the past five years. Likewise, the Global Fund has indicated an interest in increasing funding for VMMC scale-up, and a few countries have made national investments in VMMC programming already.

Market shortcomings and their reasons

Affordability: On the basis of the potential costs of manufacturing and raw materials, VMMC devices, including associated utilization costs, would in theory be cheaper than surgery. A price point of US$12 per PrePex unit was discussed in negotiations between the manufacturer, the Global Fund and PEPFAR. However, several modelling studies using PrePex costs in the range US$ 12–20 have failed to document cost savings with use of the device. ***Reasons:*** A monopolistic market exists with only one prequalified product (PrePex). Recovery of research and development costs appears to be a critical priority for the manufacturer of PrePex, a new company with a single major product line. In addition, to date, demand for VMMC has been inconsistent, resulting in periods of underutilization. The underutilization of capacity is a primary driver of unit cost in current surgical VMMC programmes, and will be a determining factor also when devices are used.

Quality: WHO has issued guidance on prequalification of male circumcision devices. One product has been prequalified and prequalification of a second is anticipated. No single product is yet prequalified for use in adolescents. ***Reasons:*** Prequalification of Shang Ring has been delayed due to technical reasons. Studies of use of both PrePex and Shang Ring in adolescents have been completed and data review is required before prequalification can be considered for this age group.

Acceptability: Devices are promising tools for circumcision as they avoid sutures and, in the case of PrePex, injected anaesthetic. However, while pilot studies have yielded favourable feedback from clients and providers regarding PrePex and Shang Ring, the acceptability of the devices as methods for VMMC and the programmatic implications of their introduction and integration remain to be seen.

Delivery: Increased or unforeseen demand could compromise the capacity of suppliers. Integration of devices in national programmes may encounter challenges, including challenges to ensure reliable and uninterrupted supplies at the country level. Shortages of lidocaine and other local anaesthetic products, required for device use, have been reported. ***Reasons:*** Reliability of manufacturing capacity to deliver at sufficient scale is unknown, and needs forecasts remain uncertain. There are limited numbers 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 adolescent male circumcision devices

Shortcoming	Adult and adolescent male circumcision devices	Potential market interventions
Affordability	Initially negotiated rate of US$ 12 for some programs for PrePex, while costs of production and raw materials are presumed to be low	■ Support demand creation for prequalified devices ■ Promote competition through incentives for additional manufacturers to enter market in each product category (e.g. support for research on other devices and their market entry) ■ Market aggregation: There is some concern that the entry of multiple products may fragment the market to such a degree that companies would have difficulty in amortizing R&D costs, achieving economies of scale, or making sufficient profit to remain economically viable. Potential purchasers may be interested in focusing on the most attractive devices and aiming to drive the cost lower through higher-volume purchases.
Quality	Availability of only a single product eligible for procurement by main donors, and restricted to adult use	■ Support prequalification of other devices (including Shang Ring) to offer purchasers options for selection on non-surgical devices ■ Support data-gathering to facilitate prequalification process for new innovative tools (e.g. single-visit devices) ■ Support articulation of clear regulatory pathways for VMMC devices at national level, clarify data required for approval of devices, including for adolescents and infants
Delivery	Limited uptake; slow scale-up	■ Support best practices for optimal demand creation ■ Support accurate forecasting and early dialogue with manufacturers

Infant circumcision

Market-based intervention for infant circumcision devices may be premature. However, monitoring of 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 of the AccuCirc device, as needed
Delivery	Slow scale-up	■ Closely monitor progress in development of infant circumcision programmes

Barrier methods

Male condoms

Male condoms remain a cornerstone of HIV prevention efforts, but the effectiveness of condom programming is potentially undermined by a global gap in the number of condoms available in LMICs.

Commodity access

Although international donors purchase the overwhelming majority of male condoms for use in resource-limited settings, the number of donor-provided condoms represents less than one third of what is deemed necessary for HIV prevention. In 2013, eight male condoms were available per year for each sexually active person in sub-Saharan Africa. Access to lubricants, recommended during anal intercourse, is limited to an estimated one in five of men who have sex with men.

Market overview

There is little indication that market shortages could be the source of the current access gap. The global condom market is highly competitive, with 26 manufacturers located in middle-income countries with lower production costs and prequalified by UNFPA. As countries move from low-income to middle-income status (as defined by the World Bank), donor funding for condom procurement may decline. To the extent that these countries transition from donor to domestic funds for condom procurement, they may opt for less expensive products of poorer quality that are not prequalified. For example, UNFPA found that around 85% of Viet Nam's condom supply comes from the private sector, and 47% of these fail quality control tests.

Potential market interventions

It is unlikely that a market intervention will lower the cost of male condoms 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. Likewise, strategies at country level should be designed to secure continued supply through improved linkage between quantification of need and timely financing, as well as to ensure and monitor the quality of condoms available for use.

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 (32 million female condoms vs. 3 billion male condoms in 2012).

Technology landscape

FC1, developed in the 1980s, was the first female condom approved by the United States Food and Drug Administration (USFDA) and prequalified by WHO. There are now three primary products of clear public health significance: FC2 (the successor to FC1), Cupid, and a third product that is at an advanced stage of development and clinical evaluation (the Woman's Condom). Additional products are undergoing evaluation by UNFPA for prequalification.

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 USFDA. Nearly all female condom purchases for LMICs have been for this nitrile product. 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.

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 likely to be procured by programmes supported by the Government of the USA as it is not approved by USFDA. A third female condom—the Woman's Condom, developed by the Program for Appropriate Technology in Health (PATH) and manufactured in China was expected to obtain WHO prequalification and USFDA approval, but delays have occurred, with approval now expected at some time in 2014 or 2015. The Woman's Condom is made of soft polyurethane and is inserted through a capsule that dissolves in the vagina. Dossier review is also underway for the prequalification of several other female condom products, offering the prospect that additional products will be prequalified in the future.

Market landscape

UNFPA and the Government of the USA are together responsible for nearly all international purchases of female condoms, with UNFPA alone accounting for nearly two-thirds of all female condoms purchased in 2011. UNFPA supplies condoms to national governments, other United Nations agencies and nongovernmental organizations, while the Government of the USA purchases condoms for use in USA-funded health programmes. 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.

Market shortcomings and their reasons

Availability: No ideal product exists to 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 area. 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 demand 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 product, such as difficulties with insertion and what some women perceive as the product's strange appearance.

Affordability: The price of the female condom is nearly 20 times higher than that of the male condom (unit price up to US$ 0.60 versus US$ 0.03), and 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 USA-funded programmes. ***Reasons***: The second product prequalified by WHO has not been submitted for approval to USFDA and hence is not likely to be procured through USA-funded programmes.

Delivery: Common stockout 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, weak forecasting and supply management capacity at country level.

Potential market interventions

The female condom is a potentially important additional HIV prevention tool that affords protection during sexual acts that are otherwise unprotected. Smart programming should accompany distribution to minimize the displacement of male condoms. It is not clear if additional products are needed in this relatively small market, as the emergence of additional products could potentially 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, backed by programming of the product that aims to achieve additional coverage of otherwise unprotected sexual acts.

The suggested market interventions for female condoms presented in Table 3 are linked and interdependent.

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 the price of FC2 could be halved if the number of units procured annually were to reach 3% of the total male condom market) ■ Analyse manufacturing processes for each of the prequalified products to assess potential for efficiency improvements ■ Support demand creation activities for female condoms
Quality	Limited number of products eligible for procurement by all donors	■ Encourage submissions to USFDA 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

Given the shortage of prevention methods that women may 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 ARV compounds, with a major clinical trial in South Africa in 2010 providing the first proof of concept for an ARV-based microbicide.

Two leading microbicide products have emerged, although there is an active pipeline of many additional experimental approaches in the earlier stages of clinical evaluation. The 1% tenofovir gel incorporates

an approved ARV drug manufactured by Gilead Sciences, which has provided a co-exclusive, royalty-free licence 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 results of the South Africa study electrified the HIV field, efficacy has yet to be confirmed in a second study, with evidence strongly suggesting that adherence has a critical effect leading to lower degree of protection. An arm of the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study examining 1% tenofovir used daily rather than pericoitally was stopped when no effect from 1% tenofovir gel was seen. This lack of effect has been blamed at least in part on poor adherence. An additional study is continuing to assess pericoital dosing of 1% tenofovir gel with results expected in 2015.

The second product is a vaginal ring that contains dapivirine, an ARV compound manufactured by Tibotec Pharmaceuticals, which has provided IPM with a royalty-free licence 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. The two large studies assessing the safety and efficacy of the dapivirine ring continue and are expected to give results in 2015 or 2016. Early studies examining the potential for longer-acting rings (up to 3 months) are underway.

Although 1% tenofovir gel and the dapivirine ring are the only products with a meaningful chance of becoming available for use in LMICs over the next few years, a robust microbicide pipeline could generate additional products in the future. Candidates currently being developed or studied include microbicides that incorporate more than one ARV 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. The major purchasers of microbicides are likely to be international donors, including the United Kingdom, USA and other high-income countries that have provided major funding for microbicide research.

Market shortcomings

Availability: No microbicide is currently ready for roll-out; all potential products are still in the development phase. Several questions remain unanswered about microbicides. These products, especially early ones, will offer only partial protection that might potentially be offset as a result of increases in risky behaviour. There is some concern about the potential for microbicides to facilitate drug resistance in individuals who seroconvert while using a microbicide or who were already HIV-infected when they used a microbicide, although recent studies have indicated that microbicides appear to act locally with little systemic exposure to the ARV drugs in the products. ***Reasons:*** Research challenges have emerged with respect to the development of new classes of product. Microbicide research and development efforts have proven to challenging adding to the development time required for these potential prevention products.

Acceptability: No ideal formulation has been developed. There are major concerns, reinforced by recent clinical trials, as to 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; however, women will still need to replace the ring with a new one every month and must avoid removing the ring or having it become dislodged during intercourse, urination or defecation.

Affordability: There is considerable uncertainty regarding the likely market prices for 1% tenofovir gel. The current price of the one-month dapivirine ring (presently up to US$ 8 per unit) may be too high for public health purposes. ***Reasons:*** With no marketable product currently available and with manufacturing and distribution partnerships yet to be fully established by product sponsors, precise pricing information for these products is not available. Current production costs, such as for the davipirine ring (manufactured

in Sweden), are high. At present, 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 that manufacturing capacity could potentially slow the uptake of new microbicides. ***Reasons:*** Capacity challenges appear especially pronounced for the dapivirine ring, given the generally limited global capacity for large-scale manufacture of intravaginal rings. Possibilities to expand capacity have not yet been realized.

Potential market interventions

Ongoing interventions aim to decrease the cost of candidate products. For instance, 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, and PATH is currently working to develop a paper applicator for tenofovir gel. Other opportunities for intervention might arise once products are proven effective and as evidence becomes available for widescale implementation.

Table 4. Summary of potential interventions for microbicides

Shortcoming	Microbicides	Potential market interventions
Affordability	Uncertainty about market price of tenofovir gel	Analyse the support needed to continue or accelerate development of a paper applicator for administration of vaginal gels, replacing more expensive plastic applicator
Delivery	Uncertainty about manufacturers' capacity to achieve scale-up	Make time-limited investments to assist microbicide developers in building manufacturing capacity to facilitate timely manufacturing scale-up, regulatory approval and expedited roll-out of forthcoming priority products

Other ARV-based prevention methods

Commodity access

Research has validated a number of ARV-based prevention methods, including ART 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 USA (the only country in which it is approved for use). Outside the USA, PrEP is largely limited to demonstration projects in a number of African countries, although in 2014 WHO formally recommended PrEP as an additional prevention strategy for men who have sex with men and proposed consideration of PrEP for the negative partner in serodiscordant couples.
- In LMICs, current coverage of PEP for occupational exposure or survivors of sexual assault is generally unknown.
- In 2013, 67% of pregnant women living with HIV received ARVs.

Technology landscape

The potential for strategic use of ARVs for HIV prevention has not been fully characterized. With respect to ART for prevention, for instance, questions remain regarding when to recommend initiation of therapy, although a clear trend is evident towards early initiation of ART for all populations. Questions also persist regarding PrEP, including how best to deliver the intervention in resource-limited settings, the magnitude of the demand for the intervention among HIV-uninfected people, and whether recipients of the intervention will adhere to the prescribed regimen. Adherence is a critical factor for the effectiveness of ARV-based prevention methods.

In addition to a combination of tenofovir and emtricitabine (TDF/FTC), the prophylactic regimen that has been approved for use in the USA, several early studies are underway on other PrEP options, including at least two Phase I or II trials investigating other single and combination ARV agents, including maraviroc, S/GSK1265744, ibalizumab, and a long-acting injectable formulation of ripilvirine.

In July 2014, WHO issued guidance recommending the availability of voluntary PEP to all eligible people from key populations following possible HIV exposure. WHO recommends the initiation of PEP within 72 hours of exposure, and continuation of the prophylactic regimen for 28 days. As with PrEP, adherence challenges have been reported for PEP.

Under WHO's 2013 consolidated ARV guidelines, countries are advised to provide the simplified one-pill once-a-day regimen recommended for first-line treatment and also for the prevention of transmission in serodiscordant couples, as well as for PMTCT.

Market landscape

For the current combination 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 zidovudine and lamivudine (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 USFDA. These include products manufactured in India, South Africa and Zimbabwe.

The market shortcomings and dynamics of antiretrovirals are extensively covered in UNITAID HIV medicines landscape, and UNITAID/MPP antiretroviral patent landscape, and are included here only to provide a comprehensive view of biomedical products for prevention.

Potential market interventions

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

Harm reduction commodities

Commodity access issues

People who inject drugs accounted for an estimated 30% of all new HIV infections outside sub-Saharan Africa in 2013. 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 medication-assisted therapy, 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 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 medication-assisted therapy with methadone or buprenorphine (the recognized oral therapeutic substitutions for individuals with opioid dependence).

As international funding primarily supports programmes in low-income countries, external financing for harm reduction will become scarcer as countries move from low-income to middle-income classification, regardless of epidemiological need or the willingness of the national government to step in and cover the remaining funding gaps. This is a cause for concern as the majority of people who inject drugs (approximately 75%) live in middle-income countries.

Market shortcomings

Affordability: Monthly commodity costs for methadone are as low as US$ 7, but buprenorphine, an essential alternative to methadone that 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 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 are likely to enter the market in the near future warrant careful consideration. As new commodities are likely to emerge over the next few years, stakeholders interested in market interventions should continually monitor developments in the field and should anticipate how focused market interventions might enhance the long-term public health impact of prevention innovations.

KEY MESSAGES

Preventing new HIV infections remains one of the world's most important health priorities. *AIDS is the sixth leading cause of death worldwide and the leading cause of death in sub-Saharan Africa.*

A limited number of purchasers predominate for most HIV prevention technologies. *Although national governments are playing an increasingly important role in purchasing prevention commodities—especially as more middle-income countries move to self-finance their AIDS responses—procurement of prevention tools tends to be concentrated with the Government of the USA (through PEPFAR), the Global Fund, and (in the case of condoms) UNFPA.*

Consideration should be given to market interventions for new devices for voluntary medical male circumcision (VMMC), with particular focus on spurring competition and lowering the unit price of new products. *Two new devices for adults have generated interest in the global health field: PrePex and Shang Ring. With medical circumcision associated with a 60% reduction in the risk of female-to-male transmission of HIV, these devices have the potential to improve uptake and service efficiency for VMMC programmes, although much remains unknown about the effects of these products on VMMC-related demand and costs.*

Efforts to lower the cost of female condoms should be explored. *Female condoms offer protection against HIV acquisition to the same extent as male condoms do, although they are 20 times costlier than male condoms. Questions persist regarding demand for the product, the actual potential for price reductions for products that are more complicated to produce than male condoms, and the possibility that too many product entrants might fragment the market and inhibit makers from recouping investments in research and development.*

Although no microbicide is currently on the market, it may be prudent to explore interim steps to clarify future market dynamics. *The two leading products under investigation are tenofovir-based gels and a vaginal ring that includes dapivirine, although there is a robust pipeline of additional experimental products. Although efficacy of tenofovir gels has been demonstrated, most studies have generated disappointing results, primarily due to difficulties that users experience in adhering to demanding preventive regimens. The dapivirine ring, which is effective for a month, obviates the need for daily use and may have potential to alleviate adherence concerns. However, capacity to produce optimally affordable rings for rapid roll-out is uncertain, warranting analysis and exploration of potential options to ensure sufficient manufacturing capacity in the event that the product is found to be effective.*

2. Introduction

This landscape report is part of an ongoing UNITAID initiative to describe and monitor the landscape for human immunodeficiency virus (HIV) commodities. The report provides a broad overview of key HIV prevention tools, describing the market dynamics relating to 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) methods based on antiretroviral (ARV) drugs and (v) commodities needed for harm reduction. The report also explores market-based interventions that could alleviate current market shortcomings and improve access, focusing on key emerging products and product areas that are rapidly evolving.

This report is intended to inform the decision-making of 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 programmes 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 subnational contexts (*1*). Currently, numerous biomedical prevention tools have emerged, forming the backbone of effective combination HIV prevention (*2*). Although challenges and questions regarding these new products have not yet been fully addressed, there is a need to maximize the uptake and effectiveness of these emerging prevention tools. UNITAID's mission focuses on global health commodities and, therefore, a focus on biomedical prevention strategies—where well-defined, discrete commodities are available and needed—squarely aligns with UNITAID's mission.

This report is structured as follows:

- **Section 3** describes the methodology used to prepare the landscape.
- **Section 4** describes the focus of the report and provides an overview of HIV prevention strategies, noting current gaps and deficiencies in prevention approaches.
- **Section 5** describes the current global health architecture for HIV prevention.
- **Section 6** provides, for each category of preventive tools, an overview of:
  - ◊ the technology landscape, including the range of available and emerging technologies, the research and development (R&D) pipeline, and commodity access issues;
  - ◊ the market landscape;
  - ◊ the major market shortcomings and their causes; and
  - ◊ a potential range of interventions that could address the market shortcomings and increase access to the tools that are needed.
  - ◊ **Section 7** contains 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 of specific HIV prevention technologies.

The review of available literature involved several steps. First, published literature on HIV prevention generally, and on 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 the literature review, particularly in the case of late-breaking developments that had yet to be captured in peer-reviewed published literature.

Second, the authors conducted an extensive review of the market literature on each of the prevention technologies. Sources reviewed included analyses of specific markets (e.g. male circumcision devices, condoms), specific industries, financial and regulatory filing (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 to major regulatory agencies and submissions to the World Health Organization (WHO) prequalification programme were reviewed.

The desk review was supplemented by interviews with key informants for voluntary medical male circumcision (VMMC), microbicides, male and female condoms, and harm reduction commodities. In addition, authors interviewed relevant staff at key procurement agencies (e.g. the President's Emergency Plan for AIDS Relief [PEPFAR], the Global Fund to Fight AIDS Tuberculosis and Malaria [Global Fund], and the United Nations Populations Fund [UNFPA]).

The material presented in this report is current through 31 July 2014.

4. Public health problem

KEY MESSAGES

Preventing HIV transmission is one of the world's most important health challenges.

Important gains have been made in preventing new HIV infections, but progress has yet to reach all populations or all parts of the world.

Powerful new HIV prevention tools have emerged over the last decade, although bringing the use of these tools to scale remains a challenge.

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 (*3*, *4*).

Between 2001 and 2013, the annual number of new HIV infections worldwide declined by 38% (*5*). However, many countries do not appear to be on track to reach the global target of halving the number of new HIV infections by 2015 (*6*). Likewise, the world is not on track to reduce new infections among people who inject drugs by 50% by 2015 (*6*).

The toolkit to prevent HIV transmission has never been more robust. Antiretroviral treatment (ART), which significantly reduces the potential for sexual HIV transmission (*7*), is rapidly being brought to scale, with evidence indicating that the world is now on track to reach the global target of 15 million persons on ART by 2015 (*5*). Powerful new tools have emerged over the last decade, including VMMC and ARV-based prevention methods, as well as new non-technological approaches such as conditional cash transfer programmes for vulnerable young people (*2*).

Much greater progress in reducing the number of new infections will be required to ensure the viability and sustainability of HIV treatment programmes. Although 12.9 million people were receiving ART as of December 2013 (*5*), all of the more than 35 million people currently living with HIV will require lifelong HIV treatment at some point. Under WHO's consolidated ARV guidelines of 2013, only 37% of people eligible for ART were receiving HIV treatment services that year (*5*). There is growing evidence of the value of earlier initiation of therapy (*8*), and WHO now recommends earlier treatment—i.e. with initiation at higher CD4 counts (*9*). Yet in 2013, 22 million people living with HIV were not receiving ART (*5*). With a continually expanding queue for HIV treatment, mobilizing the resources required to support lifelong therapy for tens of millions of people worldwide will pose a long-term global challenge. These resource demands will intensify as people currently receiving first-line regimens will need more costly second- and

third-line regimens in future years. Unless the number of individuals entering the queue for HIV treatment falls sharply, the global push to ensure universal access to treatment 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 woman-initiated prevention methods, and clearly defined and well-validated structural interventions (i.e. policy interventions such as cash transfer programmes or legal changes) (*10*). Yet, even when new tools have emerged, their implementation has often been delayed. More than a decade elapsed following documentation of the prevention benefits of ARV drugs for newborns before ARV prophylaxis reached a majority of HIV-infected pregnant women. Although it is now nearly a decade since publication of results from the first trial showing the prevention benefits of adult medical male circumcision, progress of this intervention varies and has reached only 5% of the target number of uncircumcised adult men in some of the 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. An 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 to strategies that are most cost-effective and likely to have the greatest public health impact (*11*). Advocacy and demand for prevention have been limited compared to HIV treatment. Unlike treatment, which offers lifesaving benefits to people living with HIV, prevention focuses on uninfected healthy people who may not always appreciate their HIV risk or recognize the need to adopt prevention measures. 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 (*6*). Prevention approaches that are tailored to regional epidemiology and key populations at highest risk of infection will be most effective. A recently published model compared a uniform intervention strategy with a focused one that tailors interventions and the amount of resources to local epidemiology within Kenya. With tailored interventions, the prevention effect could be increased by 14% over 15 years, averting almost 100 000 extra infections (*12*).

5. Global architecture in the HIV prevention landscape

KEY MESSAGES

The USA is the leading funder of HIV prevention research, with numerous other countries and philanthropic groups making important contributions to build the evidence base for prevention programming.

The Global Fund and PEPFAR are the two most prominent funders of HIV prevention programming.

Signs suggest a flattening or decline in donor support for HIV programmes. Domestic spending in LMICs now accounts for a majority of HIV-related spending globally, with national governments tending to prioritize treatment programmes in their national HIV investments.

Prequalification by appropriate United Nations bodies (WHO or UNFPA) plays a key role in enabling access to HIV prevention commodities in LMICs.

This section describes how HIV prevention research and development (R&D) is funded, the key players in HIV prevention financing and programming, and the regulatory processes whereby new HIV prevention tools become available for use in LMICs.

Investments in R&D

In 2013, approximately US$ 1.26 billion was invested in R&D focused on HIV prevention technologies, a decline of 4% over amounts spent in 2012. This funding included US$ 818 million in spending on HIV vaccine research, US$ 210 million on microbicide R&D, US$ 36 million for pre-exposure antiretroviral prophylaxis (PrEP), US$ 32 million for VMMC, and US$ 117 million on ART as prevention (*13*).

Although most high-income countries have invested in HIV-related research, the USA has long been the global leader in HIV-related research investments. The USA's National Institutes of Health (NIH) played a central role in sponsoring studies that helped generate an array of HIV-related technologies, including ART, prevention of mother-to-child transmission (PMTCT), ART as prevention, and adult medical male circumcision. In 2013, NIH accounted for 62% of all HIV vaccine R&D spending, outstripping contributions by the second leading funder by more than five-fold. The NIH also accounted for more than half of all microbicide R&D spending in 2012 and for almost 95% of research expenditure related to PMTCT. Other United States government institutions also play prominent roles in financing HIV prevention research. With respect to HIV vaccine R&D, the United States Department of Defense and the Agency for International Development (USAID) represented the third and fourth most important funders in 2013. USAID was the second leading funder of microbicide research in 2013.

Other high-income countries also make notable investments in HIV prevention research. The European Commission was the sixth leading funder of HIV vaccine research in 2013, arms of the Government of the

United Kingdom were the fourth (DfID) and 13th (Medical Research Council [MRC]) leading funders of microbicide research in 2013. Other high-income countries such as Denmark, France, Ireland, Netherlands and Norway also contribute to HIV prevention research.

Emerging economies are increasingly investing in HIV prevention research. China was the ninth leading investor in HIV vaccine research (US$ 7.0 million) in 2013, and South Africa was the seventh leading investor in microbicide R&D (US$ 2.3 million). While providing limited direct financial support for HIV-related research, low-income countries with generalized epidemics provide substantial institutional support through regulatory approval and oversight for clinical trials.

The Bill & Melinda Gates Foundation is another leading funder of HIV prevention research. In 2013, the foundation invested US$ 160 million in HIV prevention research. The foundation was the second leading funder of HIV vaccine R&D (US$ 100.4 million) in 2013 and the third leading funder (US$ 19.2 million) of microbicide research. The Bill & Melinda Gates Foundation is currently providing financial support for pilot implementation and other studies of male circumcision devices, and is 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 field of HIV prevention. It explores how HIV prevention is financed, how prevention policy is developed, how stakeholders' approaches to HIV prevention may be evolving, and how various stakeholders have engaged in new prevention technologies.

PEPFAR: The USA is the leading funder of HIV programmes in LMICs. In 2013, the USA provided around two thirds (66.4%) of all HIV-related disbursements by donor governments (*14*). Although PEPFAR, when created, focused primarily on ARV 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 2014, PEPFAR took steps to ensure programme-wide compliance with a legislative mandate that at least 50% of all PEPFAR funding should support HIV treatment and care services.

In 2011, PEPFAR launched a new strategy to bring about what it calls an "AIDS-free generation". Under this new approach, PEPFAR now prioritizes funding for evidence-based interventions, including ART (together with HIV-testing and other related services), PMTCT and VMMC. Pursuant to its authorizing legislation, PEPFAR is required to spend at least 50% of its resources on ART-related activities. To implement its strategic blueprint, 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.

PEPFAR has shown flexibility in responding to advances in research and the emergence of new HIV prevention tools and strategies. Within a few weeks of the release of early results from the HIV Prevention Trials Network's HPTN 052 trial, for instance, PEPFAR convened its scientific advisory committee and agreed on programme adaptations to capture the prevention potential of ARV therapy. PEPFAR has also led global efforts to respond to clinical trials that demonstrate 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 was responsible for 28% of all international HIV assistance in 2012. The Global Fund supported the provision of ART to 6.4 million people in mid-2014, and the organization has also supported the uptake of PMTCT, HIV testing and counselling, and other HIV interventions (*15*). In the first six months of 2014, the Global Fund supported the distribution of 155 million condoms for HIV prevention. Through 2013, 30% of the Global Fund's HIV assistance supported HIV prevention, 29% went for treatment, 14% for health systems strengthening (including initiatives to address HIV/tuberculosis co-infection), 18% for building supporting environments, and 8% for care and support (*16*).

Non-USA bilateral donors: Leading non-USA donors in 2013 were the United Kingdom (10% of international HIV assistance), France (4.8%), Germany (3.4%) and Denmark (2.3%). The balance between

prevention and treatment in non-USA bilateral HIV support is unclear, as is the distribution of financing between different HIV prevention approaches (*14*).

National governments: An important trend is the increasing move among many LMICs to self-finance a larger share of their national AIDS responses. In 2013, countries themselves accounted for a majority (51%) of total HIV-related expenditures (US$ 19.1 billion) (*5*), although international sources still account for 75% or more of all HIV spending in 51 LMICs (*6*).

Increasingly, global experts are focusing on LMICs as potentially vital sources of funding for HIV programmes. Taking steps to develop national HIV investment cases, a number of high-prevalence countries are exploring innovative mechanisms to generate sustainable financing, such as dedicated tax levies, mandatory multiministerial budget earmarking and national trust funds for health (*17*).

In addition to allocating a larger share of domestic public-sector spending to HIV, countries will also need to strengthen their focus on HIV prevention. While domestic sources account for the bulk of global spending on ARV treatment, international sources account for the largest proportion 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 (*18*).

United Nations: United Nations 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 United Nations agencies (e.g. UNFPA, UNICEF). In the case of new technologies, donors and national governments look to United Nations agencies to develop programmatic guidance on their use of new tools, including the prequalification of products (medicines, condoms, vaccines and devices). United Nations-led technical support facilities exist in numerous regions to respond to national requests, including assistance for the roll-out and management of health technologies.

Regulatory processes

As in the case of drugs and diagnostics, prevention tools require appropriate regulatory approval to assure safety, efficacy and quality. Because the regulatory approval process is often weak or nonexistent in many LMICs, WHO (and, in the case of condoms, UNFPA) has developed processes to "prequalify" health commodities, effectively signaling to national governments and donors that particular products meet global standards of safety, efficacy and quality. Donors such as PEPFAR and the Global Fund tend to require prequalification by WHO (delegated to UNFPA in the case of condoms), or approval by a regulatory authority that has been designated as a Stringent Drug Regulatory Authority (SRA)[1]. Agencies of the United Nations that purchase health commodities for use in LMICs normally require that a product be prequalified before United Nations funds can be used for its procurement.

In the case of PMTCT or other ARV-based prevention methods, the pharmaceutical agents used are the same as those primarily approved and administered for treatment of HIV. In the potential case of introduction of new drugs to be used solely for prevention, such as microbicides, a similar process of stringent review will be required.

USAID and UNFPA are the primary purchasers of male and female condoms. These products are subject to review and approval by the USFDA and other regulatory bodies around the world. UNFPA also operates a prequalification scheme to ensure the quality of all products purchased. In the case of female condoms, USAID preferentially purchases products with USFDA approval. USFDA approval includes review of clinical data, which in the case of new designs of female condoms includes contraceptive efficacy studies. Because the USFDA requires contraceptive efficacy studies for completely new designs of female condoms,

1 An SRA is a regulatory authority which is (a) a member of the International Conference on Harmonisation (ICH) (as specified on its website:); or (b) an ICH Observer, being the European Free Trade Association (as represented by Swiss Medic), Health Canada and the World Health Organization (WHO) (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

some prequalified products such as the Cupid female condom are unlikely to become USFDA-approved because of the expense of contraceptive studies. It is therefore unlikely that the Cupid female condom and will be purchased by USAID, despite its lower price. UNFPA prequalification also includes clinical data review as well as site inspection to assure good manufacturing practice (GMP). Subject to certain conditions, UNFPA will consider the prequalification of new designs of female condoms on the basis of clinical functionality studies and will not require contraceptive studies.

Anticipating the introduction of male circumcision devices and surgical assist tools, WHO convened a meeting of a Technical Advisory Group (TAG) on Innovations in Male Circumcision to determine requirements for WHO prequalification of these products. The TAG outlined stringent clinical research criteria for prequalification, taking into account that these devices will be used in large numbers of healthy young people and that experience with the use of the devices in adults and adolescents is limited. USFDA approval for medical devices such as these can be based on similarity to an approved device (through a process known as 510(k)), thus requiring limited clinical data. Both the Global Fund and PEPFAR, the anticipated main purchasers of male circumcision devices, have opted to link eligibility for procurement to WHO prequalification.

Although WHO prequalification plays a pivotal role in facilitating access to new health tools, national regulatory authorities have the ultimate say as to whether a health commodity may be used in a particular country. Although some middle-income countries have robust national regulatory authorities, the regulatory picture across LMICs as a whole is highly variable, with many LMICs having extremely weak regulatory authorities. Ideally, national regulation strikes a reasonable balance between overly permissive approaches that allow substandard products to be used and overzealous approaches that effectively delay roll-out of priority health tools. Recognizing the need to build national regulatory capacity in LMICs while accelerating access to breakthrough health products, health experts are increasingly exploring potential regulatory strategies, such as adoption of a common regulatory submission, joint multinational review of data, and agreement on common use of laboratories for post-marketing surveillance (*19*).

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

KEY MESSAGES

Rapid scale-up of VMMC could avert 1 in 5 new HIV infections in priority countries in sub-Saharan Africa up to 2030.

Non-surgical devices for VMMC have the potential to improve the efficiency of circumcision services and reach men who resist surgical cutting.

The two most promising circumcision devices (at least for the foreseeable future) are PrePex (which has obtained WHO prequalification) and Shang Ring, although numerous other devices have been developed. Whether either of the leading devices will reduce the costs of circumcision services is unclear.

Interventions to reduce the price of devices, coupled with demand creation for VMMC in general, and with use of devices in particular, will be important for optimal uptake and pricing.

Lessons are needed on leveraging investments made in studies to support acceptance, regulatory approval, demand creation and affordable pricing of new products, especially in the absence of competition.

Although numerous devices have been validated for use in infants, little progress has been made in priority countries in rolling out the routine offer of infant circumcision.

Considerable international interest has focused on two devices to facilitate the scale-up of VMMC: PrePex and 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 reliance on surgeons or other advanced medical personnel in the delivery of VMMC. In addition, it has been suggested that the devices may help increase the demand for circumcision by potentially alleviating fears and anxieties associated with surgical cutting.

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 aged over 15 years having been circumcised (*20*). However, prevalence of circumcision varies widely within and between countries, with Muslims accounting for 70% of all circumcised males worldwide. National prevalence of circumcision among males 15 years of age and older in 2007 was 14% in Uganda and 35% in South Africa (*20*).

In the 1980s, epidemiological studies detected notably lower HIV prevalence in settings where male circumcision was common (*21*). 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 (*22*, *23*).

As this powerful evidence emerged, investigation focused on the 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 (*24*). 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) (*23*), which enhance the likelihood of HIV transmission and acquisition (*25*).

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 conducted in Kenya, South Africa and Uganda to evaluate whether circumcising adult males reduced their risk of becoming infected. The three trials showed remarkably consistent results, finding that VMMC reduced the risk of female-to-male HIV transmission by roughly 60% (*26–28*). 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 (*29–31*).

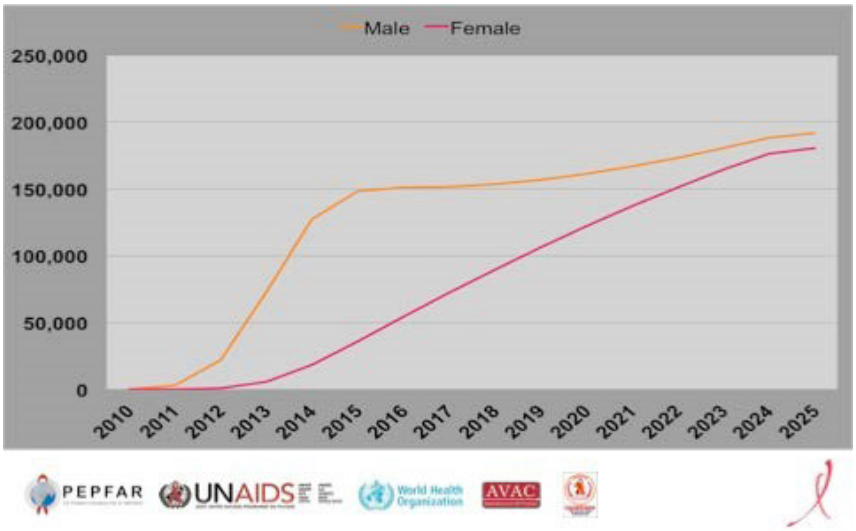
On the basis of these compelling findings from clinical trials, in 2007 WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) formally recommended the scale-up of VMMC in settings with high prevalence of sexually transmitted HIV and low prevalence of male circumcision (*32*). Initially this recommendation applied to only 13 countries (Botswana, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, the United Republic of Tanzania, Zambia and Zimbabwe), each of which added this intervention to national HIV prevention programmes. Subsequent to their initial recommendation, WHO and UNAIDS began encouraging and monitoring the roll-out of VMMC in parts of Ethiopia.

Modelling has determined that rapidly scaling up VMMC over a five-year period to reach 80% of uncircumcised males aged 15–49 years in the 13 original priority countries (Botswana, Gambelea region of Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, the United Republic of Tanzania, Uganda, Zambia and Zimbabwe) would reduce projected HIV incidence by more than 20% by 2025 (*33*). Although the direct prevention benefit from VMMC is to men, women will benefit as well from VMMC scale-up through reductions in the number of males infected with HIV and in the prevalence of other STIs. According to modelling, the long-term prevention benefit to women as a result of VMMC will be approximately equal to the benefit to men by 2025 Figure 1) (*33*).

More recent mathematical models suggest that optimal VMMC public health benefit is associated with the age at which males undergo circumcision. In an age-structured model for estimating the impact of VMMC, focus was on maximizing impact while minimizing effort. Using Zambia as a model, effectiveness by 2025 is optimized by circumcising men between 15 and 34 years of age. By targeting the 20–24-year-old age group > 60% of potential impact is achieved, with approximately 60% fewer procedures at approximately half the cost. By targeting the 15–24-year-old age group, approximately 80% of impact is achieved, with 40% fewer procedures at 30% lower cost (*34*). Countries have been encouraged to use the new modelling tools as guides to increase the efficiency of programming.

As an intervention that offers only partial protection, VMMC should be situated within the broader context of programmes that combine multiple HIV prevention interventions.

Figure 1. Total new HIV infections averted



The number of VMMC procedures needed to achieve 80% coverage varies considerably between priority countries, with more than 4 million circumcisions required in both South Africa and Uganda. The potential prevention benefit also varies between countries. While reaching the VMMC target coverage of 80% would prevent 9.2% of new infections projected to occur in Tanzania through to 2025, scale-up would avert an estimated 41.7% of new infections in Zimbabwe over the same period (*33*). 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 (*33*).

As an HIV prevention intervention, VMMC has particular advantages. Unlike many HIV prevention interventions—such as condoms or ARV-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 (*35–38*). 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 (*33*). A modelling exercise based on experience in South Africa concluded that VMMC is substantially more cost-effective than providing ART to all persons with HIV infection, regardless of CD4 count, with VMMC having a cost per infection averted of roughly one sixth that of early treatment as prevention (*39*).

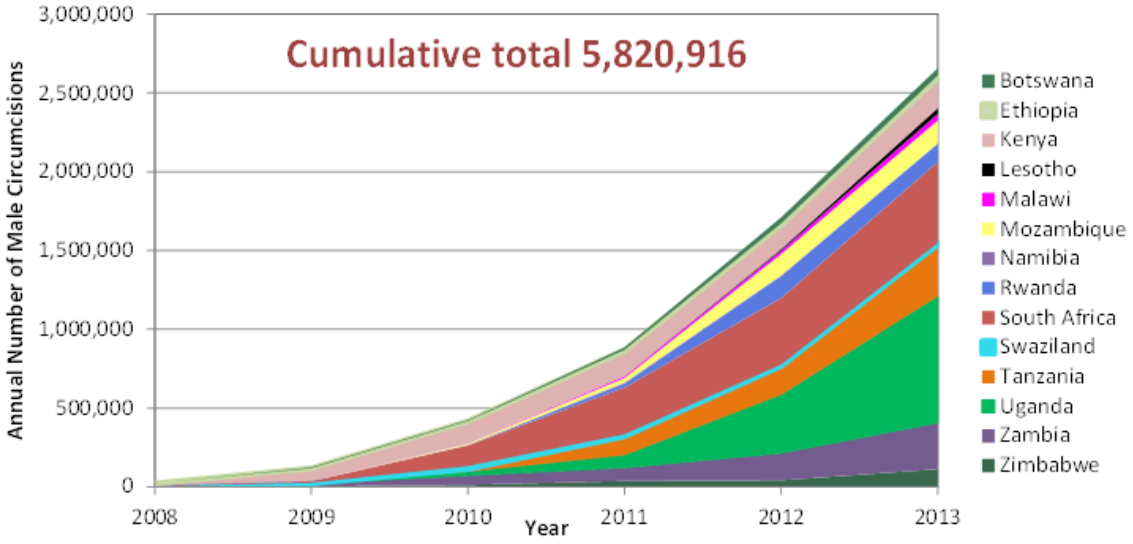
In addition to delivering the highly cost-effective circumcision procedure, VMMC programmes offer additional benefits to men, a population with historically poor health care-seeking patterns. Services facilitated through VMMC programmes include STI screening and treatment, HIV testing and referral to care, and sexual and reproductive health services (*40*).

Commodity access issues for surgical methods

Progress towards scale-up of VMMC after 2007, when WHO and UNAIDS recommended roll-out of VMMC in priority countries, was initially slow. In recent years, the pace of scale-up has accelerated, with PEPFAR meeting its goal of circumcising at least 4.7 million males by the end of 2013. However, the global target of 80% VMMC coverage in priority countries appears unlikely to be achieved by the end of 2015. As of July 2014, an estimated 5.8 million men in priority countries had been circumcised, bringing the 13 priority countries roughly 30% towards the goal of circumcising 20 million men by 2015 (*41*).

Progress varies in the priority countries (Figure 2). The greatest gains have been achieved in Kenya, where over 500 000 men (63% of the target) were circumcised between 2008 and 2013, mostly in Nyanza Province, where circumcision prevalence is much lower than the national average (*42*, *43*). Although initial efforts were slow in Uganda, the country has emerged as a leader. From 9052 procedures performed in 2010, numbers of VMMC procedures in Uganda rapidly increased to 57 132 in 2011, 352 039 in 2012 and 742 978 in 2013. The rapid acceleration is attributed to numerous factors, including policy, strategy, communication plan development, standardized data and reporting forms, development of dedicated sites and providers, increased provider training, centralized logistics and supply chain management, and continuous quality improvement (*44*). Elsewhere, progress has been much slower, with Ethiopia and Swaziland the only other countries to have reached at least 25% of their national VMMC targets as of December 2012 (*6*, *42*).

Figure 2. Number of male circumcisions performed in the 14 priority countries: 2008–2013

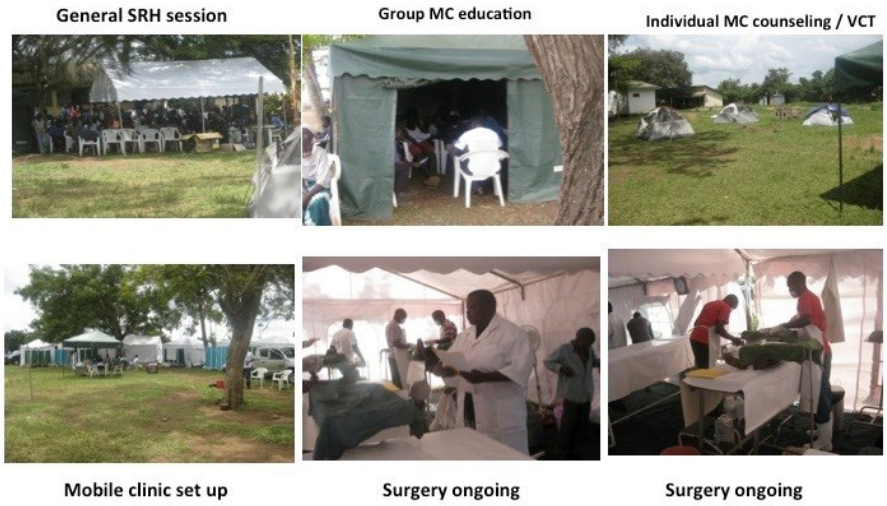


Demand has frequently been robust when services are first offered, although reports indicate that demand sometimes declines over time, especially among men aged over 25 years. In one relatively mature VMMC programme in the Iringa and Njombe regions of Tanzania, 82% of circumcisions have been conducted among males between the ages of 10 and 19 years (*45*, *46*). In Kenya, where VMMC scale-up has been most pronounced, the median age of VMMC clients is 17 years (*47*). 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, if sexually active, do not have a large number of sexual partners. Reasons why older men have been less likely than teenagers to seek VMMC may include reluctance to miss work (and potentially forfeit income), resistance to the recommended period of abstinence following the procedure, and perceived low risk because of being in a stable relationship. 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 in this area and awarded research grants for innovative demand-creation strategies in 2013.

Although numerous studies have found VMMC to be broadly acceptable in sub-Saharan Africa (*48–51*), actual demand for VMMC in the real world has been variable (*52*). Even in the generally favourable scientific literature on VMMC acceptability, more than one-third of uncircumcised men said they were not willing to be circumcised (*51*). If extended more broadly, 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 (*45*, *53*, *54*), demand elsewhere 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 the routine offer of male circumcision in priority countries, building in part on positive word-of-mouth feedback from the increasing number of men who have been circumcised.

Figure 3. 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 (Figure 3). Celebrities (such as the rap star Winky D in Zimbabwe) have been mobilized to encourage men to be circumcised. Many social marketing efforts use humour, such as 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 (*55*).

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 procedures to be performed. According to studies in Kenya and Zambia, trained medical staff require about 20 minutes to perform a standard surgical circumcision (*56*). Recognizing that limited health-care resources are slowing scale-up, WHO has recommended adoption of Models for Optimizing the Volume and Efficiency (MOVE) for male circumcision services (*57*). 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 strategic design of surgical settings in order to streamline patient flow, the use of optimally efficient surgical techniques, and the 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 (*52*). In countries that have implemented the MOVE model, task-shifting and other efficiency-promoting practices have contributed to swifter scale-up (*47*). Data from Kenya, South Africa, Tanzania and Zimbabwe confirm the efficiency benefits of utilizing elements of MOVE, such as task-sharing and use of electrocautery, as a way to decrease procedure time without decreasing quality of care (*58*). In several countries, weaknesses in the underlying health-care infrastructure are compounded by limited capacity within ministries of health to develop and manage VMMC programmes.

Commodity access issues for adult and adolescent male circumcision devices

Uptake of the VMMC devices to date has largely been limited to clinical and field trials. Rwanda is an exception, as in 2012 WHO advised phased roll-out of PrePex in Rwanda where there had been extensive study of the method. The Government of Rwanda envisages PrePex as central to the country's aim to circumcise 2 million adult men. The government 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 experience.

The implications that PrePex, Shang Ring and potentially other devices will have on HIV prevention are unclear. With the view that such devices may aid in scale-up of services, PEPFAR plans to make the devices part of its funded VMMC services and is currently working with national programmes in priority countries to integrate PrePex into service delivery.

Pilot implementation studies of the PrePex device are either underway or planned in most of the priority countries, indicating that national health authorities have an interest in this device. In most sites, nurses are performing the PrePex circumcisions. For example, as of the end of 2013, plans were underway for a scale-up pilot project of 35 000 men in Rwanda with the PrePex device (*59*).

However, with the MOVE model already providing strategies to sharply reduce the time required for performance of VMMC, the actual time that might be saved by the devices is unclear. Programmes will need to determine how best to strategically configure themselves in order to capitalize on the potential time-savings offered by the devices.

Commodity access issues for infant circumcision

Little, if any, progress has been made in rolling out infant circumcision in priority countries since the primary priorities to date have been adult and adolescent programmes and also because significant conversations with relevant stakeholders have not taken place and sources of reliable funding to support infant circumcision as a sustained activity have yet to be identified. However, some countries have limited infant male circumcision activities in place. Unlike the catch-up phase for adolescent and adult VMMC, which is envisaged as a time-limited vertical programme, circumcision of infants or young boys will need to be sustained and probably integrated into existing services such as maternal and child health programmes, vaccination programmes 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, and countries will need to decide how and when to develop infant programmes more fully.

Delivery of male circumcision in infants is arguably simpler than in adolescents and adults, in that newborn circumcision may be integrated into pre-existing neonatal care services. It has been assumed that neonatal male circumcision is safer than adult and adolescent VMMC and is likely to 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 (*60*).

Although data demonstrate that infant circumcision may be 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 some 15 years or more—i.e. 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 and several small pilot studies

have been initiated. Given variable uptake, sustained service delivery to both infants and adolescents may be needed to achieve desired levels of circumcision.

Technology landscape

Surgical methods

The surgical techniques recommended for adult male circumcision require suturing for haemostasis and wound closure, thus necessitating the availability of technical skills. With the exception of field trials and pilot implementation studies 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 (*61*): the *forceps-guided method* (using forceps to extend the foreskin until the incision line is beyond the end of the glans), the *dorsal slit method* (somewhat more skill-intensive, involving a single slit from the end of the foreskin to the point of intended incision which allows the surgeon to see the glans at all times), and the *sleeve resection method* (the most skill-intensive approach which involves two circumferential incisions around the penis and removal of the foreskin tissue between the two cuts).

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, if the circumcised man has HIV infection, transmission to sexual partners (*61*). According to a recent study, roughly one in four men who receive VMMC have sex during the healing period (*62*). 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 modelled HIV-related risks for female partners of recently circumcised men are highly sensitive to the prevalence of sex during the healing period (*62*).

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 as well as other complications such as bleeding, infection and even death. Men who obtain only partial circumcision through traditional rituals have an HIV risk comparable to that of uncircumcised men and are significantly more likely to acquire HIV than men who have been medically circumcised (i.e. with full removal of the foreskin) (*63*).

Devices for adult and adolescent males

Since VMMC scale-up emerged as a major global health priority, there has been interest in devices that may decrease the skills and time required for the procedure and that potentially 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.

On the basis of the mechanism of action of VMMC devices, WHO has developed a classification scheme with four categories (Table 5).

Table 5. Classification of VMMC devices for adults and adolescents

Type	Summary characteristics	Example
Surgical-assist male circumcision devices	Reusable metal or single-use disposable plastic devices employed during surgery and not worn by the client after the procedure	Unicirc SimpleCirc
Clamp and latch male circumcision devices	Disposable devices that use a clamping mechanism to hold the device in place and control bleeding at the site of incision and that are worn for about seven days after device placement and foreskin removal	Shang Ring Tara KLamp Ali's Klamp Smartklamp
Male circumcision devices with ligature compression	Disposable devices that use a ligature to hold the device in place for about seven days and control bleeding at the incision after device placement and foreskin removal	Zhenxi Ring
Male circumcision devices with elastic collar compression	Disposable devices that use an elastic ring to induce necrosis of the intact foreskin. The device and necrotic foreskin are removed at the same time, about seven days after placement	PrePex

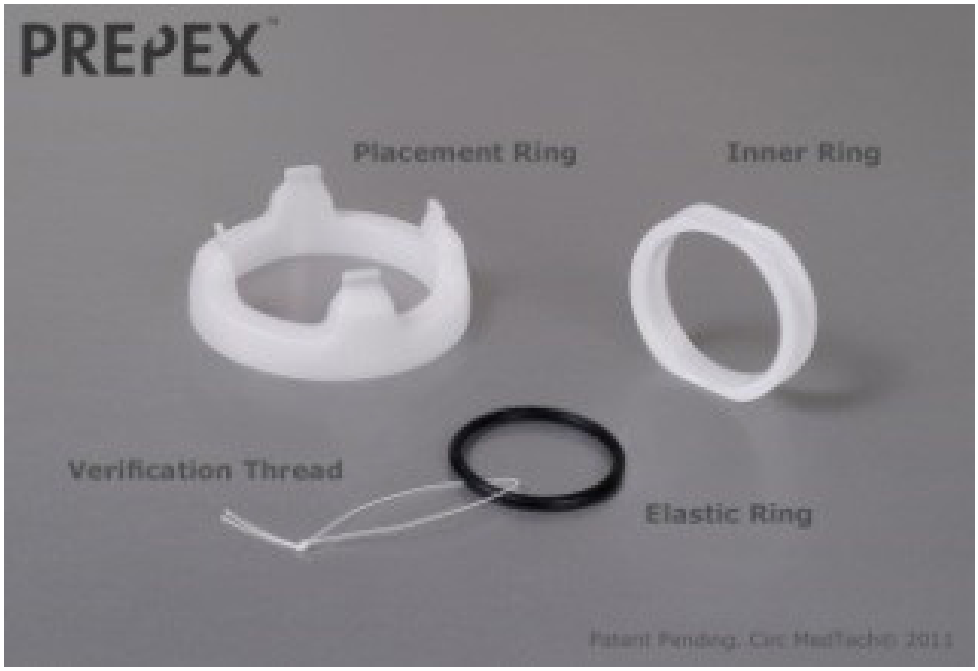
Of the devices available in sizes for adolescents and adults (*64*), PrePex and Shang Ring have particularly attracted the interest of health experts. Other devices have more recently emerged, including Unicirc and SimpleCirc.

Because of interest in the devices and emerging data, WHO has issued guidance on the use of devices in the context of VMMC programmes. WHO convened a meeting in November 2013 to address device-related issues (*59*, *65*).

PrePex

PrePex is a relatively simple *elastic collar compression device* consisting of two plastic rings and one elastic ring (Figure 4). PrePex devices are available in different sizes, allowing the health worker to choose the appropriate size by referring 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 (*64*).

Figure 4. The 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 complete the procedure, the health worker dresses the wound (*66*).

PrePex appears to have several advantages over many other circumcision methods. Intended for use in nonsterile 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 (*67*). Placement of PrePex by physicians has been documented to be safe (*68*). A recent study of use of PrePex in 590 men in Rwanda indicated 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 (*67*). Likewise, in a study in Zimbabwe, primary care nurses with no surgical training performed PrePex placements and removals successfully and safely.

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 study, the average time for PrePex placement and removal (including time required for preparation) was 4 minutes 39 seconds (*67*). Healing after use of PrePex takes longer than that seen with surgical circumcision and device displacement and self-removals have been observed. In an analysis of the first 50 clients in a pilot implementation study conducted in Kenya, two displacements were observed and only 43% of men were completely healed by day 42. Additional studies on Prepex in Kenya and Uganda have been published (*69*, *70*).

Shang Ring

Another simple device, Shang Ring (Figure 5), is *a clamp-and-latch device* that consists of two concentric plastic rings and is available in multiple sizes from infant to adult. Before placing the device, a health-care worker measures the client's penis to determine the appropriate size of 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 (*56*, *64*). 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 (*56*).

Figure 5. The Shang Ring device

Studies have found Shang Ring to be safe and effective (*56*, *71*, *72*, *73*). Shang Ring has a rate of adverse events that it is comparable to experience with conventional surgical circumcision (*56*, *73*). According to a 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 (*56*). Clients who received Shang Ring reported levels of pain that were comparable to their surgically circumcised counterparts. A field study in over 1000 men found the device to be quite safe, with an adverse event rate of 1.6%, and acceptable to clients and providers (*56*, *74*).

In a study in the Rakai district of Uganda, 621 men were offered Shang Ring or surgery, of whom 82% chose Shang Ring. Shang Ring was provided to 504 men, among whom there were four failures of ring placement (0.8%) that required surgical haemostasis and wound closure. Adverse events with the device were 1.0%, compared with 0.8% among surgery recipients. The mean time for surgery was 6.1 minutes with the ring and 17.7 minutes with surgery. The mean time for ring removal was 2.2 minutes (*73*). In contrast to other studies where rates of adverse events associated with Shang Ring were quite low, a study in southwestern Uganda comparing Shang Ring to surgery showed a high rate of minor adverse events and emphasized the need for good training and standardized definitions for adverse events with use of the device (*7577*).

Like PrePex, VMMC with Shang Ring requires considerably less time to perform than standard surgical circumcision. The total time required for placement and removal of Shang Ring is roughly one third of the time required for surgical circumcision (*56*, *73*).

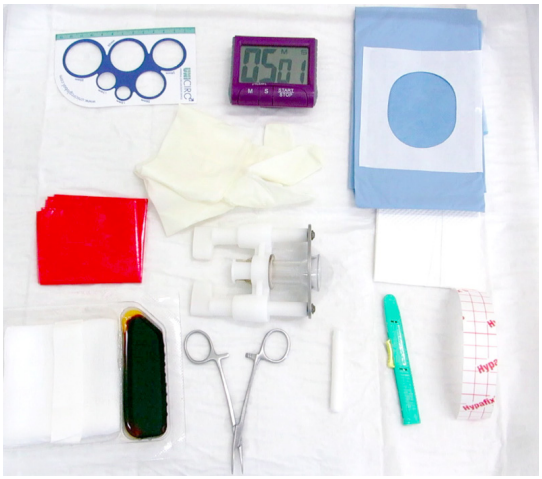
Shang Ring involves little, if any, blood loss, and no sutures are needed. A sterile setting is required. Local anaesthesia is administered prior to placement of the device, although a study is planned in Kenya to determine the feasibility of a topical anaesthetic (*64*). Field research in Kenya and Zambia suggests that the post-procedure healing period is somewhat longer for Shang Ring (44.1 days) than for conventional surgery (38.9 days), but may be shorter than for PrePex (*56*, *73*).

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, they are not the only circumcision devices. Most of these tend to be somewhat bulkier than PrePex or Shang Ring:

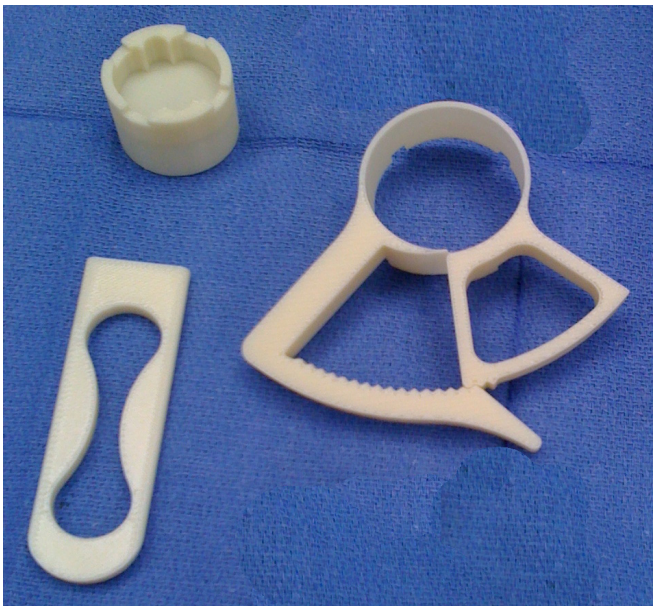
- *Unicirc*: Based on the Gomco clamp, a reusable instrument that has been in use for 80 years, Unicirc (Figure 6) is a recently developed disposable, single-use device that requires only a topical anaesthetic. With this device, the technique completes the circumcision at the time of surgery, requires no visits for device removal and could obviate potential problems with the use of PrePex and Shang Ring if men fail to return for removal. After application of a topical anaesthetic, the health worker places the device and tightens it to apply pressure to the tissue. After five minutes, the health worker cuts away the foreskin, removes the device and seals the skin with cyanoacrylate, a commonly used tissue adhesive (*78*). The use of tissue crush and adhesive to control bleeding eliminates the need for sutures or for the device to remain in place. In one study, Unicirc required less intra-operative time than surgery, with superior cosmetic outcomes and a preference by health workers for Unicirc over surgery. Adverse events were similar in the device and surgical groups, although some men in the Unicirc group required suturing in addition to the adhesive to control bleeding (*79*). Modifications to the device have since been made, and preliminary results have shown no further problems with bleeding (*79*). The sterile device is available in eight sizes for children, adolescents and adults.

Figure 6. The Unicirc device



- *SimpleCirc*: Like Unicirc, SimpleCirc is a surgical assist device that is applied and removed during a single visit (Figure 7). As with Unicirc, the foreskin is excised at the time of the visit. The tool consists of a cover for the glans, an adjustable outside ring, and a handle for removal of the glans protection. The tool has a suture guide that enables placement of stitches, and the outer ring size can be adjusted, obviating the need for different device sizes and thereby simplifying supply chain management. Few data are currently available for SimpleCirc, although data from a small study in the USA have been published (*80*).

Figure 7. The SimpleCirc device



- *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 (*64*). The average duration of VMMC with Ali's Klamp 3–4.5 minutes (*64*, *81*). A 58-person study in Kenya found VMMC with Ali's Klamp to be safe and well tolerated (*81*). 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 to displacement as a result of an erection (*64*).
- *Smartklamp:* Manufactured in Asia, Smartklamp is another clamp-and-latch device that operates much like Ali's Klamp. Smartklamp largely disappeared after liquidation of the Dutch company Circumvent BV (*64*), but it has re-emerged in Malaysia. Initially produced only in children's sizes, Smartklamp is now available in experimental adult sizes. Issuing a finding of "substantial equivalence" to other approved devices, the USFDA has approved marketing of Smartklamp for circumcision of "newborns and older males" (*82*).
- *Tara KLamp:* The Tara KLamp was the first single-use, clamp-and-latch device to be marketed (*64*). 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 (*64*). 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. However, 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, resulting in early termination of the trial (*83*). In 2012, the Treatment Action Campaign asked public prosecutors to investigate purchase of the Tara KLamp in South Africa (*84*, *85*).

Infant male circumcision devices

At least 12 devices are available for infant circumcision, including several that are also available for adults and adolescents. Only the *Gomco Clamp*, *Mogen Clamp* and *Plastibell* are listed for use in infant circumcision in the WHO/UNAIDS/Jhpiego *Manual for early infant male circumcision under local anaesthesia* (*85*). The manual recommends one surgical method (the dorsal slit) and the three devices for infant male circumcision. If clinical studies outlined by WHO find other infant devices to be safe, it is likely that WHO will expand the spectrum of approved infant circumcision devices.

Some of the devices to assist with infant male circumcision have been in use for over 50 years (the Gomco clamp has been used in the USA since the 1930s; the Mogen clamp and the disposable Plastibell since the 1950s), and several have been well studied, including in randomized clinical trials. Considerable clinical data is available on a number of devices that have been utilized for some time in Africa. A comprehensive review of 52 studies from 21 countries, including LMICs, of circumcision in infants and children, including circumcision performed by surgery and devices, found few severe complications following circumcision. 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 use of Plastibell (8%) (*86*).

The 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 together. A complication of the 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 size of device is used (*87*, *88*).

In an effort to avoid such safety concerns, developers designed a new device, *AccuCirc*, in a manner that shields the glans and employs an internal blade to cut the foreskin. A study examining this device has been conducted in Botswana while another is ongoing in Zimbabwe (*89*). In the Botswana study, 151 healthy full-term male infants were circumcised with AccuCirc in the first 10 days of life; no major adverse events were observed and parental satisfaction was high. The pre-assembled sterile AccuCirc kit has the potential to overcome obstacles related to supply chain management and on-site instrument disinfection that can pose challenges in resource-limited settings. Another study of AccuCirc in Kisumu, Kenya, that aims to follow 500 babies circumcised with AccuCirc, is in the planning stages. Optimal approaches to implementation of infant or young male circumcision in the context of HIV prevention are unclear, although the issue is under discussion, with a stakeholder consultation held by UNICEF in 2014. Similarly unclear is how sustained circumcision programmes for infants and young children will be funded. Given the long and established history of use of devices in babies and young boys, it is likely that devices will play a predominant role in this age group if and when sustained male circumcision programmes are developed in the high-priority countries.

Market landscape

Demand

Achievement of the current target for VMMC in the original 13 priority countries of sub-Saharan Africa (80% VMMC coverage by 2015 in men 15–49 years of age) would require delivery of VMMC services to around 20 million men (*33*). The 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, infant circumcision programmes have yet to be introduced, and countries may choose to sustain adolescent programmes. As a result, adult and adolescent VMMC will need to continue longer than originally anticipated, enlarging the potential market for these new devices. As national programmes move to embrace combination prevention, the integration of VMMC referral into programmes such as home-based testing may increase demand for services.

Main buyers: International donors account for the overwhelming bulk of financing of VMMC scale-up. Currently, PEPFAR is the major funder of VMMC services, supporting an estimated 80% of VMMC procedures in sub-Saharan Africa. PEPFAR exceeded its programme target of 4.7 million men with VMMC by the end of 2013 and will continue to support service provision, including use of devices and acceleration of scale-up.

National political and financial support for VMMC scale-up has varied, sometimes slowing the pace of scale-up (*52*). 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 (*90*). In the case of South Africa the investment has been sizeable, while the Government of Rwanda has expressed enthusiasm about rolling out PrePex in its VMMC programmes and has funded research on this device.

With respect to the purchase of non-surgical circumcision devices, there currently appear to be two main players—PEPFAR and the Global Fund—which are both prepared to purchase devices as they become prequalified by WHO in order to promote uptake of VMMC programmes in priority countries. PEPFAR has chosen to make devices part of its VMMC programmes and has made an initial purchase of 1.5 million PrePex devices at a negotiated price of US$ 12 per piece.

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 provided funding for pilot introductory studies aimed at examining prequalified devices in a programmatic context. As part of these studies, countries need to define the in-country regulatory pathway needed for device use. The studies are completed or ongoing in nearly all priority countries. Those in Kenya, Mozambique and Zimbabwe are completed, as is one of three South African studies, while several other studies are ongoing or in planning. In countries where pilot implementation studies have been completed, scale-up will take place with initial active surveillance to ensure safety and full reporting of adverse events. 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, though this situation may evolve as national health insurance programmes become more widespread.

Quality and safety requirements: In response to the growing interest in possible use of devices in the scale-up of adult and adolescent VMMC, WHO held consultations with stakeholders, established a TAG, and published *Framework for clinical evaluation of devices for adult male circumcision* (*91*) 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 the safety and acceptability of male circumcision devices. In addition, WHO prequalification has established a formal programme for of adult VMMC devices (*92*). The programme aims to provide technical information to other United Nations agencies and WHO Member States on each male circumcision device, as well as promoting and facilitating access to safe, appropriate and affordable devices of assured quality, and facilitating 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), and post-marketing surveillance for adverse events or device-related issues that should continue after device introduction. As current data for each of these devices solely address use of the device in men who are 18 years or older, prequalification will be limited to use in this population. However, adolescent studies for both Shang Ring and Prepex, as outlined by WHO, have been conducted and data will be reviewed by WHO in the coming months. It is expected that the prequalification of PrePex will be extended to adolescents, and the inclusion of adolescents is likely to accompany prequalification of Shang Ring or follow quickly thereafter. WHO has also issued formal guidance on the use of devices, plus proceedings of a meeting devoted to male circumcision devices (*59*, *65*, *93*).

PEPFAR will support the purchase of devices for adolescents and adults only after prequalification. The Global Fund allows use of its funds to purchase products from an applicable list of prequalified products, once such list is in place, if such products are in compliance with the quality standards applicable in the country where the product will be used.

Supply

PrePex: This device is manufactured in Israel and was developed by Circ MedTech, which is incorporated in the British Virgin Islands. In those trials where product was not donated, reported cost was 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 in global health issues. The Acumen Fund, a non-profit global venture fund that focuses on poverty reduction in East Africa and South Asia, announced in 2011 that it had invested in Circ MedTech to build the company's capacity for widescale roll-out of PrePex in sub-Saharan Africa (*94*). Circ MedTech has claimed to have capacity to produce 500 000 devices per month.

The USFDA and the European Union have approved PrePex. In addition, WHO granted prequalification to this product as of 31 May 2013 for use in men 18 years of age and older (with use recommended in settings where there is access to surgery within 6–12 hours in case there are complications that require surgical intervention) (*95*).

With manufacturing costs believed to be quite low for PrePex, it is expected that amortization of R&D investments is likely to make up 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 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 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 (*96*). Joint price negotiations of PEPFAR and the Global Fund with Circ MedTech could lead to an ex-work price point near US$ 12 per item.

Shang Ring is manufactured in China by WuHu SNNDA Medical Treatment Appliance Technology Co. Ltd. The company has submitted a dossier to WHO for prequalification, with initial manufacturing site visits conducted in 2013 and 2014. A follow-up visit occurred in August 2014. Shang Ring has been approved by the USFDA for marketing in the USA and has also been approved by the Shanghai FDA for use in China.

While manufacturing processes for Shang Ring have not been verified, inexpensive injection moulding techniques are probably 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. However, this will need to be verified. To date, about 600 000 Shang Ring devices have been sold in China.

The manufacturing cost of 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 (albeit modest) market for Shang Ring in China where 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 consideration of potential purchases is far less advanced for this device than for PrePex, but the price could be in the range of US$ 7 or even lower for the device alone. Interest by countries in this device and distribution channels in Africa have not yet been determined.

Other adult and adolescent devices: None of the other devices has been extensively tested in clinical or field trials consistent with WHO's *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 and there has been no additional research on these devices in the past few years. Research on Unicirc is continuing, with the aim of generating the needed clinical data for prequalification. A small series on SimpleCirc has been published but additional research is not currently underway.

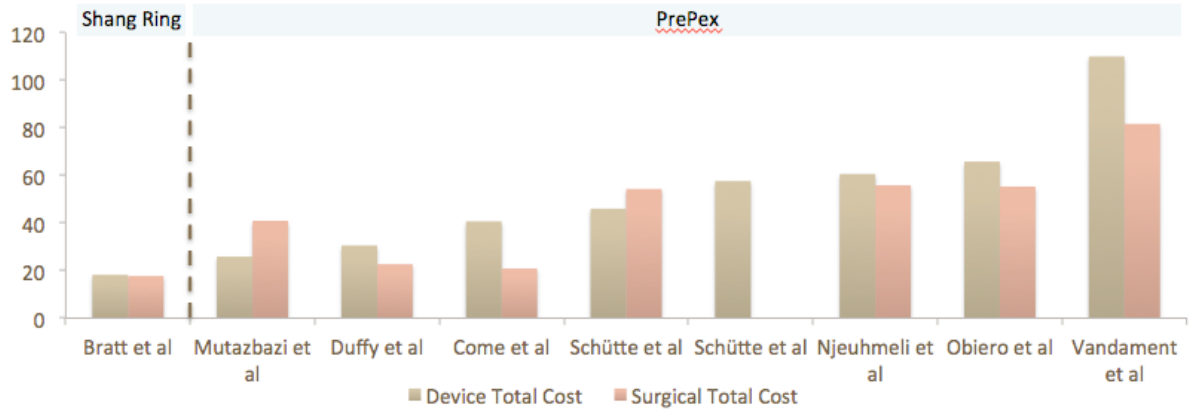
Infant devices: Gomco and Mogen Clamps are widely available from surgical suppliers, and there are multiple manufacturers of Plastibell. AccuCirc is supplied through Clinical Innovations, a small USA-based company. Six infant devices are USFDA-approved (Gomco clamp, Mogen clamp, Plastibell, Smartklamp, Shang Ring, AccuCirc), and one has a CE Mark (Ali's Klamp). Research on AccuCirc, using the WHO

clinical evaluation framework recommendations for study design, has been conducted in Botswana and a study is underway in Zimbabwe.

Market shortcomings and their reasons

Affordability: A price point of US$12 per PrePex unit was discussed in negotiations between the manufacturer, the Global Fund and PEPFAR. On the basis of the potential costs of manufacturing and raw materials, VMMC devices would in theory be cheaper than surgery, as well as their utilization, i.e., lower cadre health care staff may be qualified to apply and remove the device, lesser health facility infrastructure is required, less health care provider time is required for each case, although, potential cost savings could be offset initially by training costs needed to equip health-care workers with the skills needed to place, remove and monitor the device. However, several modelling studies using PrePex costs in the range US$ 12 to 20 have failed to document cost savings with use of the device as opposed to surgery (with the difference in cost-effectiveness found to be just 2% compared with the current surgical method) (*97–99*, *100*). Likewise, comparison of costs between Shang Ring and surgery showed no cost advantage with the device (*101*). ***Reasons:*** The cost of a disposable kit for surgery has recently declined by about one third, as reported by PEPFAR, to roughly US$ 13 since VMMC programming in priority countries began. For adult male circumcision devices, no competitive market exists, with only one product eligible for purchase by main donors following the WHO prequalification of PrePex. Recovery of research and development costs appears to be a critical priority for the manufacturer of PrePex, a new company with a single major product line.

Figure 8. Summary of the costing studies conducted to date on VMCC



Device	$18	$26	$31	$41	$46	$58	$61	$66	$110
Surgical	$18	$41	$23	$21	$54	N/A	$56	$55	$82

Source: BMGF Male Circumcision Devices Meeting, Sept 16-18, 2014

In addition, to date, demand for VMMC has been inconsistent, resulting in periods of underutilization. There is abundant evidence that demand is likely to be a critical driver of cost regardless of the method used while there are evidences of limited demand for male circumcision services in some locations. To maximize cost-effectiveness, VMMC sites will need to function at or close to capacity. With personnel and consumables the largest cost drivers of VMMC, both decreased consumable costs and reduced efficiencies in service delivery will be needed to optimize cost savings.

Quality: One product has been prequalified by WHO and prequalification of a second one is anticipated. No single product is yet prequalified for use in adolescents. A lack of clarity exists regarding national regulatory approval for the devices. ***Reasons:*** Clinical data on devices submitted to WHO for prequalification address solely the use of the device in men who are 18 years or older, which means that data with respect

to device use in adolescents must be generated and analysed before WHO will review the scope of the prequalification. WHO has outlined the additional studies that will be needed in order to assess device safety in populations such as adolescents, and studies of both PrePex and Shang Ring in adolescents have been completed with data submitted to WHO. Once a device category is endorsed by WHO and an initial device prequalified, similar "fast-follower" devices could emerge. WHO has not indicated whether all clinical studies it has recommended for a first-in-category device will be needed for other devices in the same category; this issue is to be addressed in planned future consultations. At country level, regulatory requirements for the licensure of new medical devices vary and in many African countries, medical devices are effectively unregulated.

Acceptability: Devices are promising tools for circumcision as they avoid sutures and, in the case of PrePex, injected anaesthetic. However, while pilot studies have yielded favourable feedback from clients and providers regarding PrePex and Shang Ring, the acceptability of the devices as methods for VMMC and the programmatic implications of their introduction and integration remain to be seen.

Delivery:

- It is unknown whether manufacturers of PrePex or Shang Ring will be able to ensure adequate supplies, given uncertainties regarding the magnitude and trends of future demand. ***Reasons:*** Although information exists regarding device makers' 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 of 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 (*102*). As these costs may not be apparent at the level of service delivery, they may not always be incorporated into cost estimates. Many priority countries lack the technical capacity to forecast commodity needs, frequently submitting budgets for assistance that ignore supply chain management costs. SCMS, the supply chain contractor for PEPFAR, 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 expand.
- Ensuring the integration of male circumcision devices in national programmes and access at country level may be a potential challenge. ***Reasons:*** Countries will need to embrace the new devices and routinely offer them in VMMC or infant circumcision programmes. In addition, the pathways for in-country regulatory approval are not clear for all 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 health-care workers authorized to perform VMMC with one or more devices, appropriate training, capacity-building and ongoing supervision will be needed, which could be an obstacle to scale-up. In Rwanda, nurses receive a three-day training course in performance of VMMC with PrePex (*67*).
- 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 surgical VMMC services due to an inability to provide adequate pain control. ***Reasons:*** Causes of the supply problem include a limited number of manufacturers, discontinuation of production of certain 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 for the main producer of lidocaine (*103*). Lidocaine administration is a component of the protocol for VMMC with Shang

Ring, while placement of PrePex and Unicirc involves use of a topical anaesthetic that may also be affected by this shortage.

Potential market interventions

Market interventions for male circumcision devices (Table 6) should aim to ensure accessibility and to decrease the price for optimal devices. 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 will have a substantial impact on future pricing. Efficient use of resources depends not only on a reasonable price for all VMMC supplies, including devices, but also on maintaining sufficient demand at the service delivery points to maximize provider efficiency. Programmes will need to determine how to best integrate circumcision devices, taking account of forecasting supply needs, supply chain management, training of providers and community awareness. In addition, care will be needed to ensure that device-related community education does not diminish demand for surgery or confidence in available surgical methods.

Table 6. Potential interventions for adult and adolescent male circumcision devices

Shortcoming	Adult and adolescent male circumcision devices	Potential market interventions
Affordability	Initially negotiated rate of US$ 12 for some programs for PrePex, while costs of production and raw materials are presumed to be low	■ Support demand-creation for prequalified devices ■ Increase volumes (it is not clear what size could trigger a greater reduction in the price than current level of price). ■ Promote competition through incentives for additional manufacturers to enter the market in each product category (e.g. support for research for other devices and their market entry, including prequalification) ■ Market aggregation: Competition exerts downward pressure on prices. In the case of non-surgical VMMC devices, however, there is some concern that the entry of multiple products may fragment the market to such a degree that companies would have difficulty in amortizing R&D costs, achieving economies of scale, or making sufficient profit to remain economically viable. Potential purchasers may be interested in focusing on the most attractive devices and aiming to drive the cost lower through higher-volume purchases .
Quality	Single product eligible for procurement by main donors, and restricted to adult use	■ Support prequalification of other devices (including Shang Ring) to offer purchasers options for selection on non-surgical devices (assuming all, including WuHu SSNDA and other potential producers, seek to market their products for use in VMMC programmes in sub-Saharan Africa) ■ Support data-gathering to facilitate the prequalification process for new potentially innovative tools (e.g. single-visit devices) ■ Support articulation of clear regulatory pathways for VMMC devices at national level and clarify data required for approval of devices, including for adolescents and infants
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; ◊ ensuring financial, logistical and technical support to ensure a functional distribution network for supply of devices. ■ Support accurate forecasting information to facilitate effective coordination of supplies, demand and providers

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 (Table 7). Guidance from WHO and funders regarding requirements needed for recommendation and purchase will be important in determining the next steps. While clinical data on the Gomo Clamp, Mogen Clamp and Plastibell are sufficient, clinical studies of AccuCirc are needed to evaluate the acceptability, feasibility and safety of the device in priority-country settings. Attention is needed to policies and plans for the sustainability of male circumcision programmes and to the role that infant male circumcision will play.

Table 7. 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 AccuCirc device, as needed
Delivery	Slow scale-up	■ Closely monitor progress in the development of infant circumcision programmes

6.2. Barrier methods

KEY MESSAGES

Male condoms are highly effective in preventing HIV transmission, but there is little reason to believe that market issues are responsible for persistent uptake challenges, as a competitive market exists for this affordable commodity.

Female condoms have similar efficacy and effectiveness to male condoms, but they are 20 times more expensive than male condoms.

The FC-2 condom accounts for the overwhelming majority of female condom purchases for global health programmes, although a number of additional female condom products have emerged, including Cupid and the Woman's Condom.

Questions persist regarding the probable demand for female condoms, and some commentators have suggested that more focused targeting of promotional efforts would be more cost-effective than programme strategies that have been pursued to date.

Although female condoms are likely to remain more expensive than male condoms due to their comparatively more complex manufacturing requirements, interventions may be warranted to lower product costs.

6.2.1. Male condoms

Studies have repeatedly demonstrated the effectiveness of male condoms in reducing the likelihood of sexual HIV transmission. Laboratory tests have determined that HIV and pathogens that cause several other STIs cannot penetrate male latex condoms (*104*). A meta-analysis of available studies determined that consistent condom use reduces the chance of HIV acquisition among heterosexual couples by 80% (*105*). 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 major part 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 (*106*). In recent years, trends in condom use have been mixed, with use on the rise in some high-prevalence countries but declining in others (*6*).

Condom use remains disappointingly low, partly due to lack of acceptance. 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 perception that condoms diminish the intimacy of sexual intercourse. In an effort to make condoms more acceptable, the Bill & Melinda Gates Foundation has funded projects aimed at creation of a next generation of female and male condoms that include novel designs and materials (*107*).

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 (*6*). 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 (*6*).

Too often, however, there are not enough condoms for those who need or want them. In 2012, an estimated 3.1 billion condoms were purchased for use for HIV and STI prevention in LMICs—far short of the 13 billion target for 2015 *(229)*. In 2013, eight male condoms were available per year for each sexually active person in sub-Saharan Africa (*6*). 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 be an approximate match to 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 (*109*).

Sexual lubricants have emerged as an important factor in determining the 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 5800 men who have sex with men found that, while almost 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, which is a simple, readily available and inexpensive raw material. The male condom is straightforward to manufacture through a simple dipping process. It is exceedingly inexpensive compared to other HIV prevention commodities, costing less than US$ 0.03 per unit in 2012 according to the UNFPA 2012 procurement catalogue. Indeed, the simplicity and affordability of condoms 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.

The 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 programmes. 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 (*110*). Advocates have recently approached the NIH in the USA and have asked the agency to develop and implement a comprehensive research agenda to assess the safety of sexual lubricants.

Market landscape

Demand

Total donor purchase of male condoms has trended upwards (from US$ 66-76 million per year in 2008—2010 to US$ 97-110 million per year from 2011-2013). In general, European donors devote a larger share of their HIV prevention assistance to male condom programming than the USA does (*112*). The Global Fund represents an additional important source of funding for male condom procurement; in 2011 and 2012, the Global Fund funded the purchase of 278 million and 343 million male condoms, respectively (almost 10% of all donor-procured units) *(229)*. 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 (*113*).

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 (*114*). As of June 2013, UNFPA, managing the prequalification schemes for male latex condoms and intrauterine contraceptive devices (IUD) for the United Nations system, had prequalified 26 different manufacturing sites for male condoms (*115*).

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 probably related to its proximity to the rubber plantations that supply the critical raw ingredient. Lower manufacturing costs in China, India and other countries where major producers of condoms are based are also probably a factor in the geographical distribution of condom manufacturing.

As countries transition from low-income to middle-income status (as defined by the World Bank), the availability of donor assistance to condom procurement and distribution activities in these countries may diminish. To the extent that such countries compensate for the loss of donor support with increased domestic outlays, they may opt for less expensive but poorer-quality products that are not prequalified. For example, UNFPA found that roughly 85% of Viet Nam's condom supply comes from the private sector, and 47% of these condoms fail quality control tests (*116*).

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 on a region where the raw material is produced and where manufacturing costs tend to be lower. 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 rates of condom use.

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 a protection against pregnancy that is comparable to the protection offered by male condoms (*117*). Numerous randomized trials have found that integration of female condoms into HIV prevention programmes offers protection against STI transmission that is at least as great as that seen in programmes that distribute male condoms alone (118–121). According to several stud-

ies, adding the female condom to condom distribution programmes results in an overall increase in the proportion of protected versus unprotected sex acts (*119*, *122–125*).

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 (*126*). A cost-effectiveness analysis found that expanding distribution of the female condom product FC2 (described below) to 10% of current male condom distribution in South Africa would prevent more than 9500 new infections, at a saving of US$ 985 per infection averted (*127*).

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 (*128*). 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 (*129*). Altogether, available evidence indicates that female condoms are a meaningful 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 may 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 seek permission from their male partners before using the female condom (*130*). Indeed, by its design, covert use of the product is quite difficult, underscoring the fact that in most situations male knowledge and consent is likely to be needed for a female condom to be used. Some women, however, report use of female condoms in situations where they lack the means to negotiate the use of a male condom (*131*). A recent study involving sex workers along the Mexico-USA 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 (*132*).

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 study in Kenya 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 (*133*).

The scientific literature on female condoms includes vigorous debates regarding the optimal programmatic approaches to accelerating product uptake. 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 United Nations 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 into national monitoring and evaluation mechanisms.

Given some health providers' discomfort with the female condom (*133*, *134*), it has been suggested that roll-out strategies should include training for both providers and end-users (*135*). 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 a comparable footing and promote them as equally effective in preventing sexual transmission (*135*). In an effort to make female condoms more acceptable to users, the Bill & Melinda Gates Foundation has funded the development of novel female condom products (*107*).

According to studies, knowledge of the female condom is strongly correlated with actual use of the product (*136*, *137*), as are discussions about female condom use within social networks (*138*). Despite this, in data from a South African national cross-sectional population survey conducted in 2008, knowledge of the female condom among sexually active females over the age of 15 years was high at 77.8 % but use was low at 7.2 % (*139*).

Some programmes have used social marketing approaches to increase the acceptance and uptake of the female condom (*140*, *141*). 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 (*142*). To promote uptake of FC2, the Female Health Company (FHC) and local social marketing organizations have trained barbers, hairdressers and other community stakeholders how to educate community members about the female condom and has also forged public-private partnerships for promotion and distribution of the product (*143*).

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 (*121*, *144*). In a notable study conducted at STI clinics in the state of Alabama, USA, 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 (*145*).

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 works to reduce commodity costs and proactively prevent displacement of the male condom (*146*). 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 2013, 40 times as many male condoms than female condoms were purchased by international donors and in 2011 nine male condoms were available for every man in sub-Saharan Africa between the ages of 15 and 49, compared to only 0.1 female condoms for every female ages 15–49 years (*141*). In 2010, in only one country in sub-Saharan Africa (Zimbabwe) was there at least one female condom available for every adult woman (*147*).

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 (*146*). From 2005 to 2009, global distribution of female condoms more than tripled. It is the opinion of many experts that there is room for growth in the distribution of this product (*148, 149*). Substantial advocacy is focused on further accelerating female condom uptake.

Technology Landscape

Female condom products offer dual protection against HIV and other STIs as well as pregnancy.

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

FC1, developed in the 1980s, was the first female condom approved by the USFDA and prequalified by WHO. It remained the mainstay of female condom distribution programmes worldwide until 2007, 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/UNFPA.

A plethora of female condoms has since been developed, although FC2 accounts for the bulk of those purchased for female condom programming for HIV prevention in LMICs. To date, only two female condoms are prequalified by WHO/UNFPA, a prerequisite to widespread scale-up in disease prevention and family planning programmes: FC2 since 2007 and renewed in 2012 and since 2012, Cupid. Applications for prequalification have been submitted to UNFPA for additional products at varying stages of development, including the Woman's Condom, Cupid, version 2, Velvet, VA w.o.w. Pleasure More and Phoenurse. (*150*, *151*)

FC2

Prequalified by WHO in 2006 and approved by the USFDA in 2009, FC2 is a nitrile product that has a similar design and appearance to FC1 (Figure 9). 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 FHC, ceased manufacturing FC1 in 2009 (*152*).

Figure 9. FC2—Female condom

FC2 has a soft sheath, with an external ring of rolled nitrile and an internal ring of polyurethane (*153*). 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 (*153*). (Insertion without the internal ring is possible if the condom is placed on the erect penis prior to intercourse.)

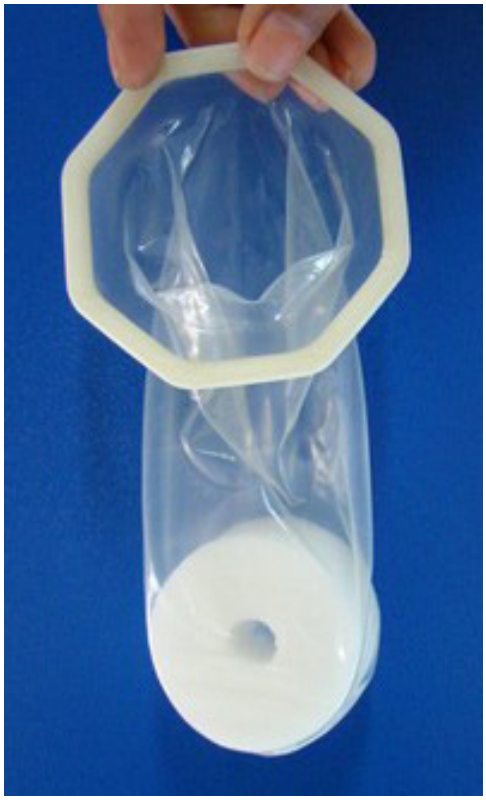
According to FHC, the synthetic latex nitrile polymer with which FC2 is made is stronger than the natural rubber latex found in most male condoms. Another claimed benefit of FC2's primary raw material is that it transfers heat, potentially contributing to a more natural and enjoyable sexual experience. Unlike natural latex, no allergies have been reported for nitrile polymer. FC2 comes lubricated, and it is recommended for a single sex act (*153*).

Some users of FC1 reportedly complained about the crinkling sound that the product emitted during sexual intercourse (*117*). 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 prelubricated, has an octagonal outer frame, and includes a sponge to anchor the condom inside the vagina (Figure 10). The product is currently distributed in 18 countries including India, Brazil and Indonesia (*154*).

Figure 10. Cupid (version 1)—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 to the segment of users who have reactions to latex. An estimated 1–2% of people are allergic to latex (*155*). Because Cupid has recently been prequalified, it has not been included in public-sector purchases of female condoms to date; as of the end of 2013, the product had not been included in purchases by USAID and UNFPA, the main public-sector purchasers of female condoms (*111*). Because of cost implications for required contraceptive studies, it does not appear that the manufacturer of Cupid will seek approval from the USFDA. Cupid version 2 is currently being evaluated for prequalification. Like Cupid version 1, Cupid version 2 is made of natural rubber latex and has an octagonal outer frame with a medical-grade sponge that holds it in place during use (Figure 11). Compared to Cupid version 1, version 2 has a shorter pouch and thinner sponge.

Figure 11. Cupid—Female condom

Version 1 (left) and version 2 (right)

Other products

Several other female condoms have been developed, although none now figure prominently in HIV prevention and family planning programming in LMICs. Some of the leading alternative female condoms include:

Woman's Condom

Manufactured in Shanghai and promoted by the Program for Appropriate Technology in Health (PATH), the Woman's Condom (Figure 12) has yet to be prequalified by WHO, although it has been approved for marketing in China by the Shanghai FDA and has received approval for marketing in the European Union (*154*, *156*). Clinical evaluation of the product is completed, including studies on contraceptive efficacy, with WHO prequalification and approval by the USFDA in the United States expected in 2014–2015. 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.

Figure 12. Woman's Condom—Female condom

PATH developed the product in an effort to enhance ease of use, increase comfort for both partners and address concerns regarding acceptability (*157*). Short-term studies have found the product to be acceptable to potential users (*158*, *159*). 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 (*159*).

The product is made of soft polyurethane, with the pouch enclosed in a 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, there are initial efforts to introduce the Woman's Condom in China and South Africa (*160*).

VA w.o.w. (worn of women)

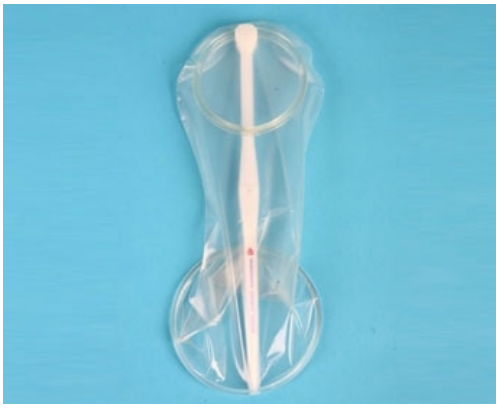
A natural latex condom made by Hindustan Lifecare Ltd., this product was formerly known as V-Amour, Protectiv or Reddy. It is made of natural rubber latex with a triangular outer frame, is prelubricated and uses a sponge to secure the condom in the vagina (Figure 13) (*154*).

Figure 13. VA w.o.w.—Female condom

Phoenurse

The Phoernurse female condom (Figure 14) is a polyurethane, comes with an insertion tool and is a pre-lubricated product that has limited distribution in China, although the company is reportedly seeking to enter the Brazilian and South African markets (*154*). 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 (*161*).

Figure 14. Phoenurse—Female condom



Pleasure More

This prelubricated natural latex rubber product is made in China by Guilin HBM Healthcare. Like FC2 and Velvet, the Pleasure More female condom has both an inner and outer ring (Figure 15).

Figure 15. Pleasure More—Female condom

Pipeline

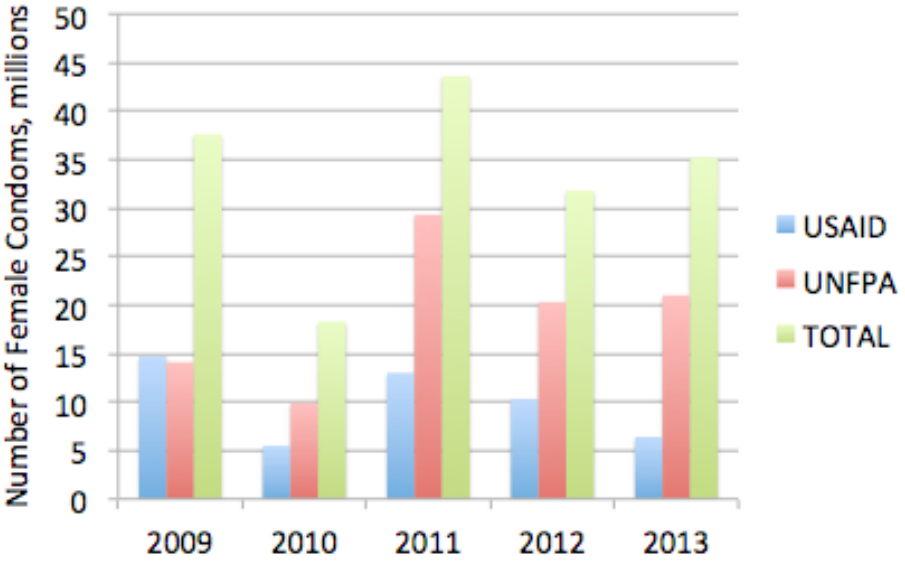
The female condom has been specifically designed for insertion into the vagina to protect against unwanted pregnancy or disease transmission during penile-vaginal intercourse. Although no existing female condom has been designed for use during anal intercourse—and no evidence exists that it is safe and effective for such use—men who have sex with men have experimented with off-label use of the female condom during anal intercourse (*162*). 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 India (*163*), Zimbabwe (*130*) 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" (*147*).

Figure 16. Female condom procurement, 2009–2013



Of female condoms shipped to LMICs, the vast majority are purchased by donors and 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 (*147*). A number of middle-income countries—including Botswana, Brazil, India and South Africa—use domestic funds to purchase female condoms (*147*).

In 2013, UNFPA shipments of female condoms for use in LMICs totaled 49.7 million *(111)*. Although donor purchases of female condoms have steadily increased in recent years, procurement of female condoms represented just 0.19% of total HIV-related donor expenditure in 2011 (*108*).

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 (*147*). UNFPA is the largest purchaser of female condoms and there is an increasing trend in the number of female condoms purchased by UNFPA, from 3.5 million in 2008 to 20 million in 2012, (though this trend has not consistently increased each year as there is year-to-year variation). 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. The PEPFAR blueprint, released in November 2012, calls for the promotion of female condoms as "an essential part of an overall condom strategy" (*164*). USAID and UNFPA now jointly purchase female condoms. Countries are able to avail themselves of the lower price by using the USAID/UNFPA joint purchasing mechanism. 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 authorized to use grant funds to procure female condoms only if the products are compliant with the specifications indicated in the WHO/UNFPA guidelines.

PEPFAR purchases of female condoms focus on FC2 which is approved by the USFDA. Although the Cupid female condom has been prequalified by WHO, the Government of the USA may not purchase the product unless it receives approval by the USFDA. An additional contraceptive efficacy clinical trial will be needed before the USFDA will consider approval of Cupid, and there do not appear to be plans for the company to support such a study (*141*).

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 VA w.o.w, citing such issues as ease of use, feel, appearance and overall fit. In a study in nearly 600 women in China and South Africa who used and compared FC2, Woman's Condom, VA w.o.w and Cupid condoms, no difference in failure rates was observed (*165*). A second study using FC2 as a control with comparison to Cupid version 2 and Velvet has been recently completed and analysis is underway. 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.

Information from acceptability studies also suggests that certain characteristics of female condoms may deter some from using them. 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 per year, with capacity (expanded in 2013) to produce 100 million units annually. FHC's production site in India is much smaller, with capacity to generate 7.5 million units annually (*153*). Since FC2's predecessor (FC1) was approved by the USFDA in 1993, FHC has manufactured and sold some 332 million female condom products (*153*). FHC has sole and exclusive rights to the nitrile polymer formulation that serves as FC2's main ingredient (*153*).

For the fiscal year ending September 2013, 54.8 million units of FC2 were sold, generating net revenues of US$ 31.5 million (*166*). As the global demand for female condoms has grown, FHC has begun returning a profit, and in 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 that the use of a less costly material that allowed for automated manufacturing played an important role in FC2's lower price in relation to FC1 (*167*). FC2 is made by a dipping process that allows for large-volume production and utilizes equipment similar to that used for the production of medical gloves. The unit price for FC2 in 2013 was US$ 0.60.

Cupid: The Cupid female condoms, versions 1 and 2, are manufactured by Cupid, Ltd., which is based in Mumbai, India. The company reports annual turnover of US$ 6 million, as well as manufacturing facilities that have been certified as adherent to GMP (*168*). Production capacity for the Cupid female condoms 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 (*168*). 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$ 0.45 in 2013.

Woman's Condom: The Woman's Condom is manufactured by the Dahua Medical Apparatus Company in Shanghai, China. The first professional manufacturer of disposable medical supplies in China, Dahua has

a GMP-compliant factory that occupies 35 000 square metres. The manufacturing process for the Woman's Condom is more complex than for FC2 or Cupid, involving welding of the polyurethane sheath (*169*). At present, Dahua has limited (although not quantified) capacity to manufacture the Woman's Condom, although a key step in the manufacturing process is currently being automated, which may expand capacity to some extent. 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 may 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 (*170*).

Market shortcomings

Availability: No ideal product exists that meets all target characteristics for the female condom. 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 regarding the potential market may 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 use of such a product is difficult to gauge, with studies reporting a range of users' concerns, such as difficulties with insertion and aversion to the product's 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 (typically ranging towards US$ 0.60), suggesting that female condoms are currently nearly 20 times more expensive than male condoms. [*111*, *170*). ***Reasons:*** Because it is a larger, more complicated device than the male condom, the female condom will always be costlier than male condoms. Currently, the number of buyers and producers is limited (with a single producer currently dominating the market). The cost for female condom training and education are estimated to be at least 4- 5 times higher than such programming costs for male condoms (*111*). 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 (*147*).

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

Delivery: According to civil society analyses, stockouts of female condoms are common (*171*). In Mozambique, for example, UNFPA estimates that only one in four female condoms procured by USAID and UNFPA actually reached end-users in 2008 (*147*). ***Reasons:*** Weaknesses in forecasting and supply chain management at the country level diminish the efficiency and effectiveness of condom programming.

Potential market interventions

The female condom is a potentially important additional HIV prevention tool that affords protection of sexual acts that are otherwise unprotected. Smart programming should accompany distribution to minimize the displacement of male condoms and to focus promotion and distribution of female condoms on strategically selected population segments. 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 (Table 8).

- **Increase volumes:** Increasing demand may be the most important factor in reducing prices of the female condom. FHC, 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 the quantity of male condoms purchased (*172*). Similarly, Cupid's marketer indicates that a price of US$ 0.35 is available for a volume purchase of 1 million (*170*). 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 profitability will ultimately depend 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 (*141*). 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 to 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 relubricated for future use. The feasibility, acceptability and frequency of reuse of the female condom are unknown.

Table 8. Potential interventions for female condoms

Shortcoming	Female condoms	Potential market interventions
Affordability	Price up to 20 times higher than price of male condom	■ Determine price points for differing manufacturing volumes (e.g. it is suggested that the price of FC2 could be halved if the number of units procured annually were to reach 3% of the total male condom market) ■ Analyse manufacturing processes for each of the prequalified products to assess potential for efficiency improvements ■ Support demand creation activities for female condoms
Quality	Limited number of products eligible for procurement by all donors	■ Encourage submissions to USFDA for approval of currently prequalified products not yet USFDA-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

KEY MESSAGES

The lack of prevention methods that women may control is an important gap in HIV prevention efforts.

Vaginal microbicides offer a potentially important new prevention option for women.

The two leading microbicide candidates are tenofovir-based gels and dapivirine ring.

Although a tenofovir-based gel has proven efficacious, difficulties that users have in adhering to the prophylactic protocol represent a major challenge to effectiveness.

The dapivirine ring, which must be replaced monthly, offers a potential way to alleviate adherence concerns, although the efficacy of the product continues to be evaluated.

Questions regarding global capacity to meet the demand for the dapirivine ring, should it prove to be effective, warrant early exploratory work to enable timely creation of sufficient manufacturing capacity to avoid delays in roll-out.

Increasingly, second-generation microbicides are regarded as a form of ARV 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, with a subsequent section specifically devoted to oral PrEP.

Commodity access

Worldwide, a woman is newly infected with HIV every minute. Women represent roughly half 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. Women are already more physiologically vulnerable to HIV during sexual intercourse than men are, and women's HIV vulnerability is compounded by harmful gender norms.

From 2000 to 2008, global funding for microbicide R&D increased more than fourfold. However, as no microbicide has been approved for use in preventing HIV transmission, there currently is no access to any product for women 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 acquisition of HIV. Although early microbicide development explored strategies for reducing the chances 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 an ARV-based 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 ARV 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 (*173*).

Microbicides are substances that are applied directly at the point of exposure 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 and suppositories.

Early first-generation microbicides were non-specific agents that exhibited activity against HIV (as well as other agents that cause other STIs) in preclinical studies but ultimately proved to be inefficacious in large clinical trials. These early microbicides involved formulations of negatively-charged long hydrocarbon chains or agents with surfactant activity, with the primary aim of inhibiting HIV fusion and entry or disrupting the outer membrane of HIV. Evidence suggested that some of the first-generation candidates might actually have increased women's risk of acquiring HIV (*174*, *175*). In addition, concerns about adherence emerged as a challenge.

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 the KwaZulu-Natal province of South Africa, researchers with the Centre for the AIDS Programme of Research in South Africa (CAPRISA) found that the use of a vaginal gel containing the ARV agent tenofovir reduced the risk of HIV transmission by roughly 39% (*176*). Unexpectedly, there was also a 51% reduction in acquisition of herpes simplex virus type 2 (HSV-2) seen in this study (*177*).

Second-generation microbicides incorporate ARV drugs that specifically act against HIV (*173*). Two second-generation products (tenofovir gel and dapivirine ring) have emerged as leading candidates for microbicides to reduce the risk of sexual HIV transmission among women. Results from major clinical trials evaluating these candidate microbicides will continue to emerge in the coming months, potentially leading to the licensure and prequalification of one or more microbicides in the next few years (*178*).

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

Leading microbicide candidates

1% tenofovir gel

Tenofovir is a leading ARV drug used orally in the treatment of HIV. Part of a class of ARVs known as nucleotide analogue reverse transcriptase inhibitors, tenofovir has demonstrated anti-transmission properties. After studies involving nonhuman primates indicated that tenofovir had potential as a microbicide, it was included in a 1% concentration in a clear colourless gel (*176*) that, for vaginal use, is premeasured in a disposable plastic vaginal applicator.

In the CAPRISA trial, the protocol provided for pericoital 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 suboptimal 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 South Africa, Uganda and Zimbabwe—called VOICE (vaginal and oral interventions to control the epidemic) and 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 a 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, with no efficacy found in reducing HIV acquisition among participating women (*179*). In 2013, VOICE researchers reported that none of the interventions examined demonstrated efficacy in reducing HIV infections and that suboptimal adherence appeared to be responsible for the failure of all the interventions tested (*180*). These disappointing results raise questions about the viability of all daily prophylactic tools for HIV-uninfected individuals.

Several other trials to evaluate 1% tenofovir gel are ongoing. Results are anticipated from CAPRISA 008, an open-label follow-on implementation study to evaluate the effectiveness of 1% tenofovir gel in the

communities where the earlier CAPRISA trial took place. By 2015, results are likely from the Follow-on African Consortium for Tenofovir Studies (FACTS 001), a Phase III trial in South Africa investigating the effectiveness of the 1% tenofovir gel in preventing HIV and HSV-2 in women. Results from FACTS 001 will be used to confirm the findings of the CAPRISA trial (*178*).

The USFDA has placed 1% tenofovir gel on the "fast track" for regulatory review. In 2012, the USFDA released guidance to industry, detailing the types of clinical and nonclinical safety and efficacy studies needed for approval. The USFDA has indicated that, in addition to CAPRISA, it requires a second and adequate well-controlled trial (presumably FACTS 001) before it will entertain a new drug application for 1% tenofovir gel. The USFDA 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 (*181*). Like the USFDA, WHO cited the need for additional safety data.

Dapivirine ring

The other leading microbicide candidate is the dapivirine ring (Figure 17). Dapivirine is a non-nucleoside reverse transcriptase inhibitor developed by Tibotec Pharmaceuticals (*182*) and is one of eight ARV drugs for which the International Partnership for Microbicides (IPM) has obtained royalty-free licences to develop the drug for use as a microbicide (*183*).

Figure 17. Dapivirine ring—microbicide

Photo: 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 because of its long-acting properties, favourable safety profile, ease of use and relatively low manufacturing costs (*183*).

The ring is inserted into the vagina and is 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 not coitally dependent and does not requires daily use (*184*).

Two major Phase III trials are underway to evaluate the effectiveness of the dapivirine ring. The first—the Ring Study, or IPM 027—has enrolled 1650 women in 4–6 centres. The study is fully enrolled and, as long-term safety monitoring is part of the study design, all participants will be followed for at least two years to satisfy USFDA 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 has enrolled 2629 women in Malawi, South Africa, Uganda, Zambia and Zimbabwe, with results anticipated in late 2015 or 2016 (*185*, *186*).

Other candidates in the pipeline

Energized by the CAPRISA trial's proof of concept, the microbicide field is currently pursuing a range of active ingredients and product formulations in preclinical or early clinical development (Figure 18). Included in this pipeline are rectal gels and various vaginal products (e.g. gels, rings, films, tablets and rings with a combination of an ARV agent and a hormonal contraceptive). These products are all in early development, and efficacy trials are expected to begin in 2015.[2]

Combination products

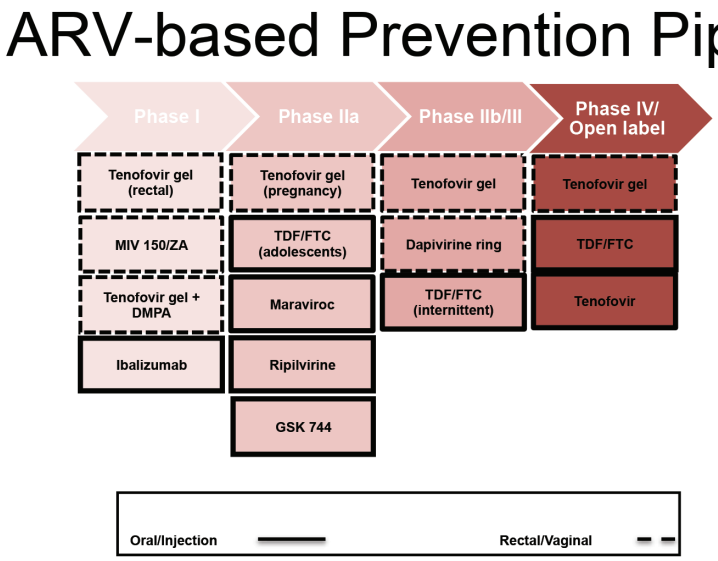
Considerable efforts are focused on the development and evaluation of "combination" microbicides—i.e. products that combine more than one substance with anti-HIV properties. One potentially promising combination microbicide combines dapivirine and maraviroc, an ARV marketed by Pfizer that operates as a CCR5 coreceptor agonist, affecting a different aspect of the HIV replication process (*187*). The product is currently formulated as a vaginal ring. Its developer, IPM, joined with MTN to conduct a safety trial in 48 women and found no safety concerns. Laboratory tests on tissue samples indicated that the dapivirine component of the ring was able to block HIV infection, though levels of maraviroc were not sufficient to have a similar effect (*188*).

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 ARV properties itself, it appears to boost the antiviral effect of MIV-150 (*189*). 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 (*189*). The Population Council is currently conducting a Phase I study of the product (*178*).

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

2 See http://www avac org/ht/a/GetDocumentAction/i/49803 for a listing of the microbicide pipeline (accessed 12 August 2014).

Figure 18. ARV-based prevention pipeline



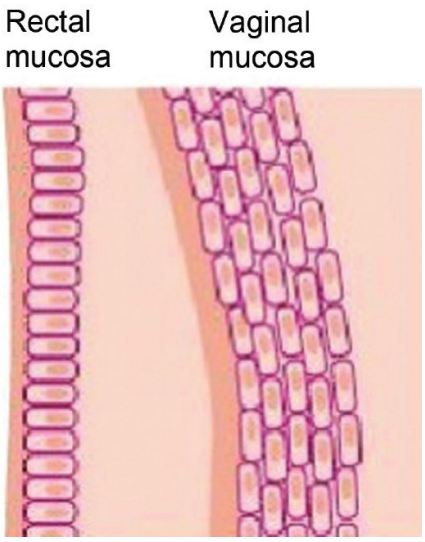
Novel delivery methods

Although gels and rings have predominated microbicide development to date, researchers are actively investigating other delivery methods. CONRAD is currently evaluating the safety of a fast-dissolving vaginal tablet (*190*), 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.

Rectal Application

As HIV-related risks are substantially higher during anal intercourse than for penile-vaginal intercourse (*191*), 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 (*192*), 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 (*193*).

Figure 19. Tissue structure: rectal and vaginal mucosa



Experts have long believed that unique microbicide formulations would be needed for rectal application. The surface space inside the rectal cavity is substantially greater than in the vagina, and mucosal and other properties of the two cavities differ as well (*194*) (Figure 19). Research on rectal microbicides has largely been restricted to Phase I safety studies (*195 – 197*). 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. A study of rectally-applied tenofovir reduced-glycerin 1% tenofovir gel in approximately 180 men is underway to examine the safety of a reformulated gel.

Multipurpose technologies

There are some indications of waning enthusiasm in the field for products that protect solely against HIV. Especially in light of evidence of women's potentially heightened risk of HIV acquisition when using hormonal contraception (*198*), the 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 levonorgestrel 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 also 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 (*199*). Investigators in the CAPRISA trial reported encouraging evidence on risk compensation among trial participants (*176*), although the issue has yet to be rigorously studied and warrants further examination.

With microbicide efficacy highly dependent on adherence, leading microbicide candidates have different adherence challenges. The pericoitally-dependent dosing tested in the CAPRISA study is rather complicated and may not, in fact, be feasible for many women—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 ART. 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 may be intentionally removed by women or inadvertently dislodged during sex or while urinating or defecating. Use of injectable, long-acting formulations of ARV 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.

As previously noted, 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 (*200*, *201*).

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 (*182*). Recent studies have shown that microbicides appear to act locally with little systemic exposure (*202*). 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 ARV 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 ARV agent in the microbicide.

Implications for HIV prevention

Modelling exercises indicate that the 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 (*203*). 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 (*203*).

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 used in 30% of sexual encounters (at US$ 0.5 per use) would be cost-effective in South Africa (*204*). At US$ 0.5 per dose, the tenofovir gel would be "highly cost-effective" even when used in only 25% of sexual encounters (*204*). 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% (*205*). Whether vaginal microbicides might offer uninfected male partners some protection against sexual transmission from an infected woman remains unclear.

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 of 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 to 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 (multipurpose prevention technologies) may gain more acceptance since contraceptives are widely used 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 analyse accurately the probable market dynamics for the products most likely to emerge in the next few years, including manufacturing strategies, delivery channels, prices and roll-out strategies. However, given the possibility 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 (*206*, *207*) and to respond to potential access challenges for this high-priority HIV prevention tool.

Supply

1% tenofovir gel: Gilead Sciences has provided a co-exclusive, royalty-free licence for tenofovir 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, USA. It is believed that DPT has the capacity to produce the gel on a scale required for clinical trials and early launch of the product, although additional capacity would be required for scale-up.

Pursuant to its licence agreement with Gilead, CONRAD has entered into a sub-licence 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. It was subsequently announced that the gel would be registered, manufactured and distributed by Propreven, a joint venture involving TIA and Cipla Medpro (*208*). 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 Sweden-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 other contract companies may have the capability to manufacture a limited quantity of 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 production 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 is a leading funder of microbicide research, suggesting a strong national commitment to development and use of these products once they become available. 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 (*6*).

Both USAID and the NIH have invested considerable resources in microbicide R&D, and are the two top funders worldwide for microbicide R&D (*209*).

Development agencies from a number of European countries have made significant contributions to microbicide R&D, suggesting a probable interest among these agencies in supporting microbicide roll-out.

Having vied with the Government of the USA 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 with the public sector, the private market is likely to be limited 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 may 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 represent a cost-effective use of finite HIV prevention resources and may wish to make comparisons of cost-effectiveness between available prevention methods. However, 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 influence 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 (*201*, *210*, *211*). The body of evidence on microbicide acceptability, however, has been criticized on the grounds that many acceptability studies are based primarily on hypothetical questions posed to participants following verbal descriptions of investigational products and do not accurately predict behaviours in the efficacy trials that have been conducted (*212*). Initial instincts also may not predict behaviour in the long term. In the face of such concerns, researchers have worked to design trials that more accurately measure users' actual experiential preferences. In one 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 differing by country (*213*).

Although acceptability studies provide critical information on possible future demand for a microbicide, gauging actual demand will need to await actual experience. Several factors are likely to be 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 the use of intravaginal products. In follow-up interviews with women who participated in one of the PrEP studies, reasons for nonadherence included lack of support or discouragement from others, concerns about toxicity, and low HIV risk perception (*214*, *215*). Similar reasons may extend to microbicides.

Work is continuing on estimation of demand for microbicides. IPM, for instance, has undertaken an analysis of demand for the dapivirine ring in 12 African countries with the largest eligible populations (Democratic Republic of Congo, Ethiopia, Ghana, Kenya, Malawi, Mozambique, Nigeria, South Africa, Sudan, Rwanda, Uganda, Tanzania). The number of accessible women aged 20–49 years in these markets was estimated to in the range of 47–85 million (mean 65 million). Adoption of a product approximately 10 years after the launch has been estimated at 1.5 million to 6.6 million (mean 4 million) (*183*).

Procurement requirements and guidance: Data on both tenofovir gel and the dapivirine ring will be submitted to the USFDA for approval, as this is a requirement for PEPFAR purchase. WHO prequalification has provided guidance on the types of nonclinical and clinical data needed to support prequalification and WHO 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 if there are 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 the 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 that is currently available is likely to compete in the particular niche that microbicides will occupy. In the quest for discrete female-initiated prevention methods, microbicides currently stand alone. From a practical standpoint, however, microbicides would compete with other prevention strategies (e.g. ARV-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: Several questions remain unanswered with regard to current pipeline microbicides. A healthy microbicide pipeline suggests that if current candidates show suboptimal 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 few years, however, it is likely that the microbicide field will be limited to one to two products at most that are available for roll-out. ***Reasons:*** There are considerable challenges involved in the development of new classes of product. Compared to many other longstanding prevention methods, intensive scientific work on microbicides remains relatively recent.

Acceptability: No ideal formulation has been developed as yet. On the basis of data emerging from clinical trials, questions persist regarding whether women will adhere rigorously to microbicide regimens. Women's acceptability of the product, as well as 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, which is a potential barrier to 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 that 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 with 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, production costs for the davipirine ring, manufactured in Sweden, 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 been realized.

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 (*180*).

The size of the market and the pace of uptake will be heavily influenced by actual demand for a new microbicide.

1% tenofovir gel: Currently, microbicide gels come wrapped in prefilled single-use plastic applicators (Figure 20) which constitute the most expensive component of the product, accounting for 90% of the cost (*216*). 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) (*217*) 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 currently working with various stakeholders to explore the use of paper applicators in roll-out plans for 1% tenofovir gel in South Africa and other countries (*218*).

Figure 20. Applicator for vaginal administration of microbicide gel products

Dapivirine ring: With support from the Bill & Melinda Gates Foundation, IPM is currently studying how to expedite access to the dapivirine ring. Key elements in 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 aims to lower the unit costs for the ring to US$ 2–4 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 (2014 or 2015) to approval is uncertain, which means that a product may not be available on the market until 2016 at the earliest. 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 progress should be followed closely without any market-based interven-

tions planned for the near term. However, should studies prove favourable, some interventions could be undertaken in preparation for product launch (Table 9).

Table 9. Potential interventions for microbicides

Shortcoming	Microbicides	Potential market interventions
Affordability	Uncertainty regarding market price of tenofovir gel	Analyse support needed to continue or accelerate development of paper applicator for administration of vaginal gels in order 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 ARV-based prevention methods

KEY MESSAGES

ARV-based prevention commodities now represent a critical pillar of efforts to prevent new HIV infections.

Recommended uses of ARVs for HIV prevention include PrEP, PEP, PMTCT and ART as prevention.

Each of these ARV-based prevention methods is associated with implementation challenges, including (in the case of PrEP and PEP) how best to target the intervention.

Market interventions to enhance the affordability and accessibility of ARVs are already being pursued by UNITAID and other partners. They are not being addressed at length in this landscape but in complementary reports; the specific market dynamics for ARV medicines are extensively covered in UNITAID HIV medicines landscape, and are included here to provide a comprehensive view of biomedical products for prevention.

In recent years, strategic use of ARV drugs has transformed the HIV prevention landscape (*219*). As the spectrum of potential prevention applications of ARVs has expanded, leading global health experts have suggested it is now possible to lay the foundation for the eventual end of the epidemic (*220*). It could be argued that ARV-based methods now constitute the centrepiece of effective HIV prevention.

6.4.1. Pre-exposure prophylaxis (PreP)

PrEP is the use of ARVs in an HIV-uninfected individual to prevent acquisition of HIV. In heterosexual serodiscordant couples, daily use of either TDF (the oral form of tenofovir) or TDF/FTC by the HIV-uninfected partner decreased the risk of HIV-1 transmission by 67% and 75% respectively (*221*). A separate multicountry study concluded that PrEP reduced the risk of HIV acquisition among men who have sex with men by 44% (*222*). In 2013, study findings indicated that daily TDF reduced the risk of HIV acquisition by 49% among people who inject drugs (*223*).

Commodity access issues

In 2012, the USFDA approved the combination of TDF/FTC for PrEP against HIV infection. Soon thereafter, the Centers for Disease Control and Prevention (CDC) in the USA issued interim guidance to health-care providers on administration of TDF/FTC for PrEP, addressing such issues as adherence counselling, lack of evidence on long-term safety, and approaches needed for women of reproductive age. In 2014, the USA's Public Health Service released comprehensive clinical practice guidelines for PrEP to broaden use of the

intervention in the USA, recommending PrEP to anyone with a substantial risk of acquiring HIV infection, including those with an HIV-infected sexual partner, recent bacterial STI, a high number of sex partners, history of inconsistent or no condom use, or those involved in commercial sex work (*224*). In 2014, WHO formally recommended PrEP as an additional prevention option for men who have sex with men, as well as consideration of PrEP for HIV-negative partners in serodiscordant couples (*225*).

In the USA, uptake has been slow, probably due to such factors as high drug costs, lack of clarity on reimbursement by insurance providers, uncertainty regarding who should be eligible for the service, and low levels of awareness among the target populations 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 ARVs by HIV-uninfected individuals substantially reduces the risk of HIV acquisition, with the greatest benefit seen with a combination of TDF/FTC and among heterosexual women. Two studies among women—the FEM PrEP and VOICE trials—found no benefit from TDF and TDF/FTC PrEP, apparently due primarily to poor adherence with daily dosing (*180*, *226*).

The benefit from PrEP is directly correlated with individual adherence to the daily regimen (*227*). The multicountry VOICE trial compared daily TDF, a daily combination of TDF/FTC, and daily 1% tenofovir microbicide gel. Although about 90% of trial participants told researchers they were taking the regimens daily, blood tests detected the presence of the ARV agents only about a quarter of the time (*228*) (Figure 21).

In 2012, WHO advised that daily PrEP be considered for the uninfected partner in identified serodiscordant couples (*221*). WHO also 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 (*221*). 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.

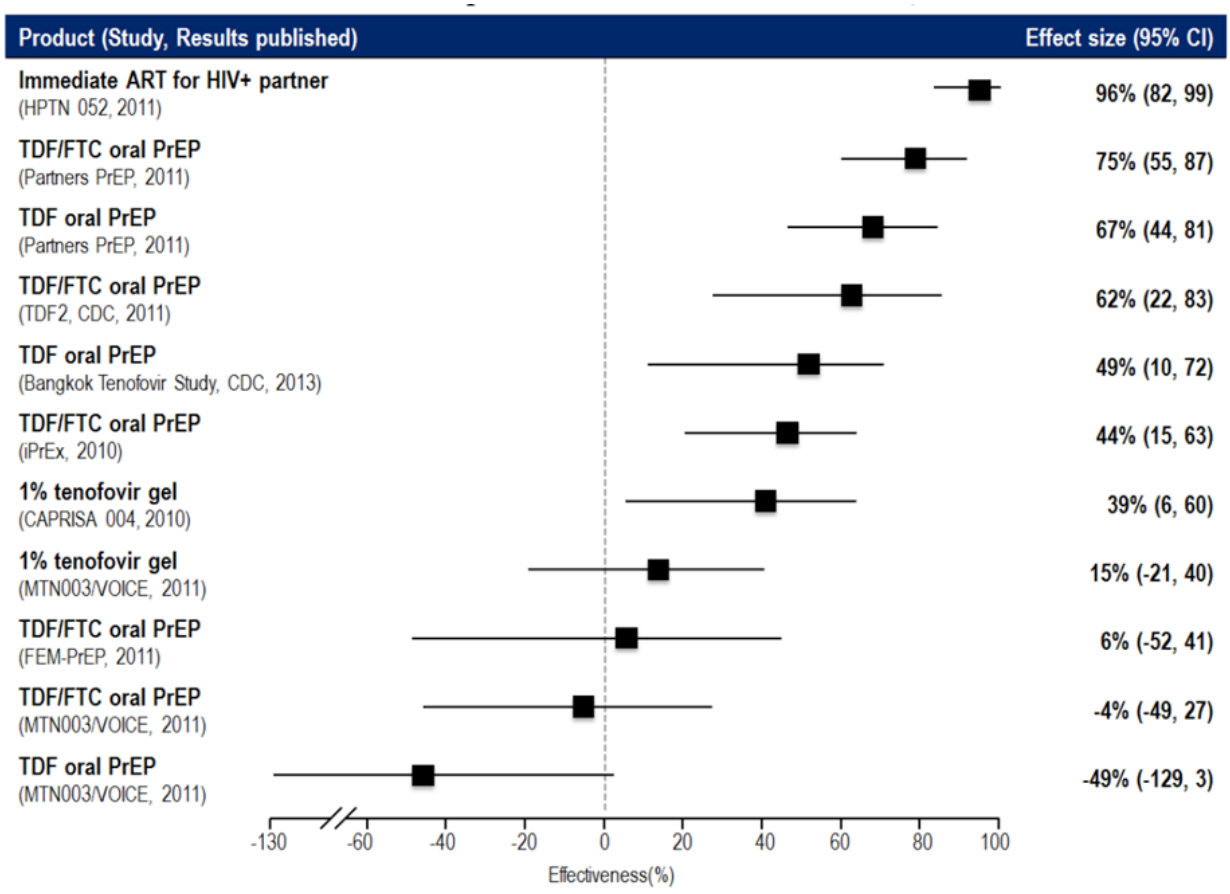
At least six large-scale clinical trials on TDF-based PrEP are currently underway, including two open-label trials that may generate valuable information on programme implementation and population-level effects (*178*). In addition, several earlier-stage studies are underway, including at least two Phase I or II trials that are investigating other single and combination ARV agents, including maraviroc, S/GSK1265744, ibalizumab, and a long-acting injectable formulation of ripilvirine (*230*).

Although the evidence is clear that daily ARVs reduce the risk of HIV acquisition, the 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, this does not mean that the intervention is affordable, especially in the lowest-income countries. The relatively higher cost compared to other less expensive interventions may affect uptake (*231*). 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 USA 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 *(232)*.

In addition, some HIV advocates in LMICs have sharply questioned the fairness of distributing ARVs for HIV prevention. In particular, these critics cite the persistent gaps in access to treatment among people living with HIV who have a direct and immediate need for ARV drugs to protect and preserve their own health (*4*).

Figure 21. Antiretroviral-based prevention study results



Source: Bekker L-G, Tenofovir based PrEP technologies in women: what do we currently know? IAS 2013.

Market landscape

As indicated above, further information on specific ARV market dynamics and shortcomings are the subject of a complementary medicines landscape[3] and are therefore not described here in great detail.

Gilead, the originator company for TDF/FTC (the only marketed product currently approved for PrEP) 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 (*233*). There are at least five generic manufacturers in India (four of them already WHO prequalified or tentatively approved by USFDA) which market the dual fixed-dose combination (FDC) for up to less than a fourth of the lowest price of the originator product (US$ 71 per person per year versus US$ 319–548 per person per year) (*233*).

Gilead has entered into a licensing agreement with the Medicines Patent Pool (MPP)[4] and some generic companies for TDF and its combinations, including this product, for a given list of eligible countries. Nonetheless, in some countries that are excluded from the licensing agreement, patents affecting the tenofovir disoproxil ester and salt, or the combination TDF/FTC, might be granted and could prevent use of lower-priced generic versions (e.g. Argentina, Brazil, China, Mexico).[5] Where granted, these patents would remain in force at least until 2018 for the compound patent for TDF and until 2024 for the combination.

3 See http://www.unitaid.eu/images/marketdynamics/publications/HIV-Meds-Landscape-March2014.pdf, accessed 13 August 2014.
4 See http://www.medicinespatentpool.org, accessed 13 August 2014.
5 See: Patents and licences on antiretrovirals: a snapshot. UNITAID/MPP, April 2014, and MPP's patent database for Selected HIV Medicines. (http://www.medicinespatentpool.org/wp-content/uploads/Patents_And_Licences_On_ARVs_Snapshot_web.pdf, accessed 13 August 2014)

Potential market interventions

UNITAID and stakeholders are actively implementing a number of market-based interventions to reduce prices and increase availability of ARV 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 WHO's 2013 guidelines aim to clarify international approaches to HIV treatment, policies for PrEP in LMICs remain poorly defined, with substantial uncertainty regarding 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).

6.4.2. Post-exposure prophylaxis (PEP)

In July 2014, WHO recommended the availability of voluntary PEP for eligible persons from key populations following possible HIV exposure. WHO advised that it intends to update PEP guidelines for all populations later in 2014 (*226*).

PEP involves short-term (28-day) use of ARVs in HIV-uninfected people who may have been exposed to HIV, with the intervention to be initiated within 72 hours of exposure. Originally developed to reduce the risk that health care workers would contract HIV following percutaneous injury, PEP is now recommended, subject to certain criteria, in persons who have experienced a non-occupational exposure. According to WHO and the International Labour Organization (ILO) (*234*), 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; 3) mucous membrane or non-intact skin was significantly exposed to an infectious body fluid, and 4) the source is known to be HIV-infected or the HIV status is unknown. The use of PEP should be in conjunction with other forms of HIV care, including counseling, testing and follow-up. As in the case of microbicides and pre-exposure prophylaxis, adherence to PEP has proven challenging (*235*).

Commodity access issues

Since the 1980s, CDC in the USA has recommended initiation of ARVs within 72 hours for health-care workers who experience exposure to potentially infectious body fluids (*236*). 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 ILO in issuing guidelines on PEP for occupational exposure and sexual assault (*234*). 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, the use of PEP has sometimes extended beyond occupational exposure or instances of sexual assault. In 2005, CDC issued guidelines on the use of PEP after non-occupational exposures, including consensual sexual intercourse and injecting drug use (*237*). 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 and 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 non-occupational 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 within 72 hours after exposure, and with the choice of ARVs based on the country's first-line ART regimen for HIV. According to the most recent (2007) WHO PEP guidelines, standard PEP regimens should comprise two nucleoside-analogue re-

verse-transcriptase inhibitors, preferably zidovudine (ZVD) plus lamivudine (3TC). Three-drug regimens, comprising two nucleoside-analogue reverse-transcriptase inhibitors plus a boosted protease inhibitor, may be considered in situations where ARV therapy resistance is known or suspected (*234*).

Market landscape and market shortcomings

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. 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 USFDA, including products manufactured in India, South Africa and Zimbabwe.

Potential market interventions

As with other ARV-based prevention methods, UNITAID and other stakeholders continue to engage in broader efforts to improve market conditions for ARVs in LMICs. For PEP, it is likely that programmatic issues and questions regarding prioritization of scarce resources, not market shortcomings, may primarily determine access in resource-limited settings.

6.4.3. Prevention of mother-to-child transmission (PMTCT)

HIV-infected pregnant women risk transmitting the infection to their children during pregnancy, during the birthing process, or from breastfeeding after birth (*238*). In the absence of preventive intervention, transmission rates range from 15% to 45% (*239*). ARVs help prevent transmission of most infections if taken by the mother during pregnancy and breastfeeding, and by the infant postpartum and while breastfeeding (*238*). The use of PMTCT has been shown to reduce the risk of infection to < 5% in breastfed infants and < 2 % in non-breastfed infants (*240*).

PMTCT is a form of treatment as prevention, although discussed separately here due to the uniqueness of the population served as well as the 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, namely:

- 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 ARV 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 (*241*).

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. The *Global plan* focuses specifically on these countries (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).

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 2013, 67% of pregnant women living with HIV worldwide received ARV prophylaxis (*5*). Since 2009, provision of ARVs to HIV-infected pregnant women has averted an estimated 900 000 new infections among children (*5*).

Important gains have also been made in promoting HIV testing and in delivering ARV 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 (*242*), and the unmet need for family planning has changed little in recent years (*6*). 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 (*6*). Suboptimal 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 to evidence on the risk of drug resistance and the associated negative impact on treatment outcomes among women (*6*). Increasingly, international consensus has recognized the clinical and programmatic value of adopting a single triple-drug combination ARV regimen for both treatment of HIV in pregnant women and PMTCT (*238*). In addition, the earlier exclusive programmatic focus on antenatal and postnatal care settings has expanded to recognize the need for preventive intervention during breastfeeding.

WHO's 2013 consolidated antiretroviral guidelines recommend immediate initiation of lifelong ART for all pregnant women living with HIV, regardless of their CD4 count. WHO recommends a single first-line regimen, harmonized with regimens for the general population, for pregnant and breastfeeding 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, the market dynamics and shortcomings of specific ARVs are the focus of a complementary medicines landscape and are not covered here in great detail. Ongoing efforts to decrease the costs of ARV agents and secure uninterrupted supplies for adults and children will contribute to improved access in the context of PMTCT and enable its expansion.

6.4.4. ART for prevention

Background

High viral load is the greatest risk factor for HIV transmission, with studies suggesting that the risk of transmission is near zero when the viral load is < 1500 copies/mm^3 (*243*). ART typically decreases the viral load in HIV-infected individuals to extremely low levels. In 2011, investigators in the HPTN 052 trial reported that early ART reduced the risk of HIV transmission among serodiscordant couples by 96% (*7*). Two subsequent observational studies confirmed the population-level benefits of ART among 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 (*244*, *245*). Diverse mathematical models have differed regarding the projected population-level effect of scaled-up ARV treatment, although all have determined that scale-up would result in a significant reduction in new HIV infections (*246*).

Many questions remain as to the best means of harnessing ART for HIV prevention, including when to start therapy, which regimens are optimal for reducing the likelihood of onward transmission, and how best to target treatment initiatives in order to maximize their impact both on HIV incidence and on early treatment for the individual receiving ART. As of August 2014, more than 50 trials were underway on issues related to ART as prevention, including three Phase III trials and two Phase IV trials (*190*). 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 (*247*).

The HPTN 052 results have already affected normative practice. In 2013, WHO recommended much earlier initiation of ART; people living with HIV whose CD4 count is 500 or lower are recommended for therapy, and WHO now recommends initiation of ART, regardless of CD4 count, for pregnant women, children

under 5 years, seropositive partners in serodiscordant couples, and people with HIV-related tuberculosis or hepatitis B (*9*). As of July 2014, seven countries had national ART guidelines calling for treatment initiation for all people living with HIV, regardless of CD4 count (*248*).

Market landscape and market shortcomings

Existing shortcomings for preferred ART regimens for the general population will inevitably 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, particularly second- and third-line regimens and newer ARVs. These shortfalls are covered separately in the medicines landscape.

Potential interventions

Research is ongoing to identify opportunities to enhance the efficiency of treatment delivery, including 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

KEY MESSAGES

People who inject drugs are 22 times more likely to be living with HIV than non-injecting drug users and account for an estimated 5 – 10% of HIV infections worldwide, including 30% of all new infections outside sub-Saharan Africa.

Harm reduction—an approach that has proved to be highly effective in reducing HIV incidence among people who inject drugs—involves a package of interventions, including access to sterile needles and syringes, medication-assisted therapy, and health-care services.

Of the two drugs commonly used as medication-assisted therapy for opiate-dependent individuals—methadone and buprenorphine—the latter is substantially more costly than the former. Many people who inject drugs need access to buprenorphine to reduce their dependence on opiates.

Consideration should be given to interventions to lower the cost of buprenorphine.

Background

Globally, people who inject drugs are 22 times more likely to be living with HIV than those who do not (*6*). 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 (*6*). UNAIDS has estimated that injecting drug use accounts for 5–10% of all new HIV infections worldwide and for 30% of new infections outside sub-Saharan Africa (5). 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 (*6*).

Commodity access

In 2011 WHO reported that, of 107 countries reporting HIV programme data, only 42 had needle and syringe programmes in place (*242*). In 2013, the global supply of needles was inadequate, inevitably contributing to unsafe injecting practices such as sharing of needles; only 90 needles were available per person per year, compared to the recommended 200 (*5*). Of all episodes of injecting drug use worldwide, it is estimated that only 5% involve sterile injecting equipment (*249*). In 22 of 26 countries reporting data to UNAIDS in 2013, coverage of medication-assisted treatment for opioid users was under 10% in 2012 (*6*).

National legal and policy frameworks further diminish harm reduction uptake by deterring individuals from seeking services (*250*). 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, medication-assisted treatment and other drug treatment interventions, and a range of essential health services, including ART (*251*). With respect to commodities, key components include sterile syringes and the leading compounds used for medication-assisted treatment (i.e. methadone and buprenorphine).

Figure 22. 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 the 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 bloodborne pathogens as a result of unsafe injection practice (Figure 21). These devices, which prevent re-use and reduce the risk of needlestick injury, cost about US$ 0.15 per unit (*111*). Advocates of harm reduction have criticized this WHO policy on the grounds that, while well-intentioned and appropriate for addressing injection safety concerns in health-care settings, it may limit availability of the less costly syringes preferred by people who inject drugs. In particular, advocates argue that drug injection outside medical settings typically involves more than one retraction of the needle plunger, rendering auto-disable syringes unusable for injecting drug use (*252*).

Figure 23. Buprenorphine

WHO has included both methadone and buprenorphine, available for use in medication-assisted treatment, in the WHO List of Essential Medicines since 2005 (*253*). Methadone was the first widely promoted therapeutic substitute for opiate dependence. Methadone may not work for everyone, underscoring the need for multiple agents for medication-assisted treatment. Buprenorphine is a distinct compound used as an alternative to methadone in medication-assisted treatment and is available in sublingual tablets approved in 2009 (Figure 22). Methadone is a more potent and effective drug than buprenorphine in the treatment of opioid dependence and remains the preferred agent. An exception to this may be in the case of a pregnant woman as the frequency of opioid withdrawal occurring in the newborn may be less than with methadone.

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 (*254*). Methadone prices vary considerably, though monthly commodity costs can be as low as US$ 7 (*255*). According to the WHO commodity pricing database (*256*), 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 treatment with methadone (with a wide range from US$ 175 to US$ 2999 per month for a daily dose, as reported to WHO by 14 different manufacturers).

Demand

In 2011, an estimated US$ 500 million was spent on harm reduction programmes worldwide (*257*). 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) (*257*).

The Global Fund is the leading international funder of harm reduction programmes, having committed US$ 430 million in multiyear funding toward them. In 2012, the Global Fund was supporting 120 harm reduction programmes in 55 countries (*258*).

The global leader in HIV prevention assistance, the Government of the USA, has a much more modest role with respect to harm reduction than with 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, the USA's policies also impede PEPFAR from playing a greater role in preventing drug-related HIV transmission. In 2011, the USA Congress enacted legislation prohibiting the use of USA 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 the non-exchange components of harm reduction.

In funding, like policy, national governments have been resistant to embracing harm reduction programmes. In 2010–2011, of all HIV resources spent on persons who inject drugs, 92% came from international donors (*6*). In Eastern Europe and Central Asia—where national HIV epidemics are rapidly growing, chiefly 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 (*6*). As international funding primarily supports low-income counties, external funding for harm reduction will become even scarcer as countries move from low-income to being classified as middle-income. This is cause for concern since the majority (approximately 75%) of people who inject drugs live in middle-income countries and donors have to date accounted for the vast majority of funding for harm reduction services (*259*).

Market shortcomings

Affordability: Monthly commodity costs for methadone can be as low as US$ 7, but buprenorphine, an essential alternative that 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 (*255*).

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 difficulties of procurement.

Potential market interventions

There is a crucial need to build support for funding harm reduction—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 in order to extend the programmatic reach of harm reduction programmes. 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 those of 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 other new prevention tools discussed earlier (e.g. male circumcision devices and vaginal microbicides).

6.6.1. Vaccines

When USA's 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 (*260*). Over 30 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 (*261*).

While disappointing, the record to date on HIV vaccine R&D is in line with the history of vaccine development. Of all vaccines that have been developed, only in two cases (hepatitis B and rotavirus) were the vaccines developed within 30 years of the discovery of the causative agent (*262*). 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 the 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 (*263*). Developers then tried a new approach, seeking to elicit a cellular response sufficient to protect the body against infection. The STEP trial (a 3000-person trial sponsored by the USA's National Institute of Allergy and Infectious Diseases and by Merck in Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico and the USA) evaluated the most promising candidate of this type, manufactured by Merck. In 2007, the STEP trial was terminated, with evidence emerging that the vaccine may in fact have increased the risk of infection among trial participants (*264*).

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 persons in the control group, although there were indications that the benefits of the vaccine waned over time (*265*). 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, efforts were focused 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 (*266*). 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 (*266*).

One of the most encouraging signs in HIV vaccine research has been the progress made in identifying broadly neutralizing antibodies (*267*). In recent years, the USA's 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 (*268*). To facilitate these breakthroughs, leading researchers joined together in an international consortium aimed at identifying and characterizing antibodies with the potential to neutralize the virus.

As of August 2014, 33 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 (*268*, *269*).

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 would 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.

6.6.2. Treatment for Herpes simplex virus type 2 (HSV-2)

HSV-2 and HIV operate synergistically, encouraging viral replication and increasing the chances of transmission (*270*). HSV-2 infection increases the risk of HIV acquisition by 2–7 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 (*270*).

Given the strong epidemiological 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 of decreasing risk of HIV acquisition, no effect was seen in those treated with acyclovir for HSV-2 suppression compared to those given placebo (*271*, *272*). 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 to the uninfected partner (*273*). In all of these studies of HSV-2 suppressive therapy, there were demonstrable declines in the incidence of genital ulcers in the study population (*270*). 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 (*270*).

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.

In the study involving serodiscordant couples, in which the HIV-infected partner received HSV-2 suppressive therapy, there were small but statistically significant ARV effects of acyclovir on HIV load and HIV-associated clinical endpoints, raising the question as to whether the ARV effects of HSV-2 suppressive drugs could be used as an adjunct to current HIV treatment or as bridging therapy until initiation of standard treatment. Studies are currently evaluating the ARV effects of valacyclovir, another HSV-2 suppressant with potential promise (*273*).

7.0 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 such as problems with commodity procurement and supply management. As the discussion of specific prevention tools in this report reveals, market factors such as unfavourable commodity prices and insufficient demand also often play a role in impeding scale-up.

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

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

Table 10. Summary 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 the case of microbicides, further evidence is required before widescale implementation can take place.
Other available commodities	■ Male condoms ■ Harm reduction ■ ARV-based methods (PrEP, PEP, PMTCT)	Some of these strategies have played a longstanding key role in HIV prevention efforts. However, market interventions could potentially be valuable in improving affordability and access to certain key commodities. Most commodities have been available for some time, although in some cases evidence has emerged on new prevention uses for longstanding commodities (ARVs). UNITAID and stakeholders are already addressing market shortcomings related to ARV products used for 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.

References

1. Combination HIV prevention: tailoring and coordinating biomedical, behavioural and structural strategies to reduce new HIV infections. Geneva: Joint United Nations Programme on HIV/AIDS; 2010.
2. Maartens G, Celum C, Lewin SR. HIV infection: epidemiology, pathogenesis, treatment, and prevention. Lancet, 2014.
3. The 10 leading causes of death by broad income group, 2008. Geneva: World Health Organization; 2008.
4. Global update on HIV treatment 2013: results, impact and opportunities. Geneva: World Health Organization/ Joint United Nations Programme on HIV/AIDS/United Nations Children Fund, 2013.
5. The gap report. Geneva: Joint United Nations Programme on HIV/AIDS; 2014.
6. UNAIDS report of the global AIDS epidemic 2013. Geneva: Joint United Nations Programme on HIV/AIDS; 2013.
7. Cohen MS et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493 – 505.
8. A cure, in essence, for HIV in some adults. New York Times (editorial), 18 March 2013.
9. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach, June 2013. Geneva: World Health Organization; 2013
10. Baird SJ. Effect of a cash transfer programme for schooling on prevalence of HIV and herpes simplex type 2 in Malawi: a cluster randomised trial. Lancet. 2012;379(9823):1320 – 9.
11. Amico P et al. Pattern and levels of spending allocated to HIV prevention programs in low- and middle-income countries. BMC Public Health. 2012;12:221.
12. Anderson S-J et al. Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: a modelling study. Lancet. 2014;384(9939):249 – 56.
13. HIV prevention research & development investment in 2013. HIV Vaccines & Microbicides Resource Tracking Working Group; 2014 (http://hivresourcetracking.org/sites/default/files/RTWG2014.pdf, accessed 13 August 2014).
14. Kates JW. Financing the response to HIV in low- and middle-income countries: international assistance from donor governments in 2013. Washington (DC): Kaiser Family Foundation; 2014.
15. Mid-2014 results. Geneva: The Global Fund to Fight AIDS, Tuberculosis and Malaria: 2014.
16. Funding and spending. Geneva: The Global Fund to Fight AIDS, Tuberculosis and Malaria; 2014 (http://www.theglobalfund.org/en/about/fundingspending/, accessed 13 August 2014).
17. Smart investments. Geneva: Joint United Nations Programme on HIV/AIDS; 3013.

18. UNAIDS report on the global AIDS epidemic 2012. Geneva: Joint United Nations Programme on HIV/AIDS; 2012.

19. McNerney R et al. Improving access to new diagnostics through harmonized regulation: priorities for action. Afr J Lab Med. 2014;3.

20. Male circumcision global trends and determinants of prevalence, safety and accessibility. Geneva: World Health Organization; 2007.

21. Cameron DW et al. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. Lancet. 1989;2(8660):403 – 7.

22. Bailey RC, Egesah O, Rosenberg S. Male circumcision for HIV prevention: a prospective study of complications in clinical and traditional settings in Bungoma, Kenya. Bull World Health Organ. 2008;86(9):669 – 77.

23. Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. AIDS. 2000;14(15):2361 – 70.

24. Szabo R, Short RV. How does male circumcision protect against HIV infection? BMJ. 2000;320(7249):1592 – 4.

25. The role of STD detection and treatment in HIV prevention – CDC fact sheet. Atlanta (GA): Centers for Disease Control and Prevention; 2010 (http://www.cdc.gov/std/hiv/stdfact-std-hiv.htm, accessed 12 August 2014).

26. Bailey RC et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet. 2007;369(9562):643 – 56.

27. Auvert B et al. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med. 2005;2(11):e298.

28. Gray RH et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007;369(9562):657 – 66.

29. Auvert B et al. Association of the ANRS-12126 male circumcision project with HIV levels among men in a South African township: evaluation of effectiveness using cross-sectional surveys. PLoS Med. 2013;10(9):e1001509.

30. Kong X et al. Assessment of changes in risk behaviors during 3 years of posttrial follow-up of male circumcision trial participants uncircumcised at trial closure in Rakai, Uganda. Am J Epidemiol. 2012;176(10):875 – 85.

31. Mehta S et al. The long term efficacy of medical male circumcision against HIV acquisition. AIDS. 2013;

32. WHO and UNAIDS announce recommendations from expert consultation on male circumcision for HIV prevention. Geneva: World Health Organization; 2007.

33. Njeuhmeli E et al. Voluntary medical male circumcision: modeling the impact and cost of expanding male circumcision for HIV prevention in eastern and southern Africa. PLoS Med. 2011;8(11): e1001132.

34. Aawad S. USAID brown bag presentation on male circumcision. Washington (DC): United States Agency for International Development; 2013.

35. Galarraga O et al. HIV prevention cost-effectiveness: a systematic review. BMC Public Health. 2009;9(Suppl 1):S5.

36. Gray RH et al. The impact of male circumcision on HIV incidence and cost per infection prevented: a stochastic simulation model from Rakai, Uganda. AIDS. 2007;21(7):845 – 50.

37. Kahn JG, Marseille E, Auvert B. Cost-effectiveness of male circumcision for HIV prevention in a South African setting. PLoS Med. 2006;3(12):e517.

38. Uthman OA et al. Economic evaluations of adult male circumcision for prevention of heterosexual acquisition of HIV in men in sub-Saharan Africa: a systematic review. PLoS One. 2010;5(3):e9628.

39. Barnighausen T, Bloom DE, Humair S. Economics of antiretroviral treatment vs. circumcision for HIV prevention. Proc Natl Acad Sci U S A. 2012;109(52):21271 – 6.

40. Kikaya V et al. Voluntary medical male circumcision programs can address low HIV testing and counseling usage and ART enrollment among young men: lessons from Lesotho. PLoS One. 2014;9(5):e83614.

41. Scale-up of voluntary medical male circumcision for HIV prevention in Africa. Geneva: World Health Organization; 2014.

42. Sgaier SK et al. Achieving the HIV prevention impact of voluntary medical male circumcision: lessons and challenges for managing programs. PLoS Med. 2014;11(5):e1001641.

43. Push to meet 2013 male circumcision targets. IRIN humanitarian news and analysis, Kenya. Nairobi: Integrated Regional Information Networks; 2013.

44. Nanteza B, Uganda Minstry of Health. Personal communication, November 2013.

45. Mahler HR et al. Voluntary medical male circumcision: matching demand and supply with quality and efficiency in a high-volume campaign in Iringa Region, Tanzania. PLoS Med. 2011;8(11):e1001131.

46. Ashengo TA et al. Voluntary medical male circumcision (VMMC) in Tanzania and Zimbabwe: service delivery intensity and modality and their influence on the age of clients. PLoS One. 2014;9(5):e83642.

47. Progress in voluntary medical male circumcision service provision – Kenya, 2008 – 2011. MMWR Morb Mortal Wkly Rep. 2012;61(47):957 – 61.

48. Lukobo MD, Bailey RC. Acceptability of male circumcision for prevention of HIV infection in Zambia. AIDS Care. 2007;19(4):471 – 7.

49. Ngalande RC et al. Acceptability of male circumcision for prevention of HIV infection in Malawi. AIDS Behav. 2006;10(4):377 – 85.

50. Wambura M et al. Acceptability of medical male circumcision in the traditionally circumcising communities in Northern Tanzania. BMC Public Health. 2011;11:373.

51. Westercamp N, Bailey RC. Acceptability of male circumcision for prevention of HIV/AIDS in sub-Saharan Africa: a review. AIDS Behav. 2007;11(3):341 – 55.

52. A call to action on voluntary medical male circumcision: implementing a key component of combination prevention. New York (NY): AVAC – AIDS Vaccine Advocacy Coalition; 2012.

53. Lissouba P et al. Adult male circumcision as an intervention against HIV: an operational study of uptake in a South African community (ANRS 12126). BMC Infect Dis. 2011;11:253.

54. Mwandi Z et al. Voluntary medical male circumcision: translating research into the rapid expansion of services in Kenya, 2008 – 2011. PLoS Med. 2011;8(11):e1001130.

55. Kong X et al. Male circumcision coverage, knowledge, and attitudes after 4-years of program scale-up in Rakai, Uganda. AIDS Behav. 2014;18(5):880 – 4.

56. Sokal DC et al. Randomized controlled trial of the shang ring versus conventional surgical techniques for adult male circumcision: safety and acceptability. J Acquir Immune Defic Syndr. 2014;65(4):447 – 55.

57. Considerations for implementing models for optimizing the volume and efficiency of male circumcision services. Geneva: World Health Organization; 2010.

58. Rech D et al. Surgical efficiencies and quality in the performance of voluntary medical male circumcision (VMMC) procedures in Kenya, South Africa, Tanzania, and Zimbabwe. PLoS One. 2014;9(5):e84271.

59. Use of devices for adult male circumcision for HIV prevention in East and Southern Africa. Geneva: World Health Organization; 2014.

60. Binagwaho A et al. Male circumcision at different ages in Rwanda: a cost-effectiveness study. PLoS Med. 2010;7(1):e1000211.

61. Manual for male circumcision under local anaesthesia. Geneva: World Health Organization/Joint United Nations Programme on HIV/AIDS/Johns Hopkins Program for International Education in Gynecology and Obstetrics - JHPEIGO; 2009.

62. Hewett PC et al. Sex with stitches: assessing the resumption of sexual activity during the postcircumcision wound-healing period. AIDS. 2012;26(6):749 – 56.

63. Maughan-Brown B et al. A cut above the rest: traditional male circumcision and HIV risk among Xhosa men in Cape Town, South Africa. J Acquir Immune Defic Syndr. 2011;58(5):499 – 505.

64. Morris BJ, Eley C. Male circumcision: an appraisal of current instrumentation. Intech; 2011.

65. Guideline on the use of devices for adult male circumcision for HIV prevention. Geneva: World Health Organization; 2013.

66. PrePex user manual. Circ MedTech; 2013.

67. Mutabazi V et al. One-arm, open-label, prospective, cohort field study to assess the safety and efficacy of the PrePex device for scale-up of nonsurgical circumcision when performed by nurses in resource-limited settings for HIV prevention. J Acquir Immune Defic Syndr. 2013;63(3):315 – 22.

68. Bitega JP et al. Safety and efficacy of the PrePex device for rapid scale-up of male circumcision for HIV prevention in resource-limited settings. J Acquir Immune Defic Syndr. 2011;58(5):e127 – 34.

69. Feldblum PJ et al. Safety, effectiveness and acceptability of the PrePex device for adult male circumcision in Kenya. PLoS One. 2014;9(5):e95357.

70. Galukande M et al. Adverse events profile of PrePex a non-surgical device for adult male circumcision in a Ugandan urban setting. PLoS One. 2014;9(1):e86631.

71. Barone M et al. Randomized trial of the Shang Ring for adult male circumcision with removal at one to three weeks: delayed removal leads to detachment. J Acquir Immune Defic Syndr. 2012;60(3):e82 – 9.

72. Barone M et al. The Shang Ring device for adult male circumcision: a proof of concept study in Kenya. J Acquir Immune Defic Syndr. 2011;57(1):e7-12.

73. Kigozi G et al. The acceptability and safety of the Shang Ring for adult male circumcision in Rakai, Uganda. J Acquir Immune Defic Syndr. 2013;63(5):617 – 21.

74. Barone M et al. A field study of male circumcision using the Shang Ring, a minimally-invasive disposable device in routine clinical settings in Kenya and Zambia. 7th International AIDS Society Conference on HIV Pathogenesis and Treatment. Kuala Lumpur; 2013.

75. Kanyago S et al. Shang Ring versus forceps-guided adult male circumcision: a randomized, controlled effectiveness study in southwestern Uganda. J Acquir Immune Defic Syndr. 2013;64(2):130 – 3.

76. Kanyago S, Riding DM, Siedner MJ. Authors' reply: Proper surgical training and grading of complications for Shang Ring circumcision are necessary. J Acquir Immune Defic Syndr. 2013;64(2):e12.

77. Lee R et al. Proper surgical training and grading of complications for Shang Ring circumcision are necessary. J Acquir Immune Defic Syndr. 2013;64(2):e11.

78. Millard PS et al. Rapid, minimally invasive adult voluntary male circumcision: a randomised trial. S Afr Med J. 2013;103(10):736 – 42.

79. Millard PS et al. Rapid, minimally invasive adult voluntary male circumcision: a randomised trial of Unicirc, a novel disposable device. S Afr Med J. 2014;104(1):52 – 7.

80. Hotaling JM et al. Simple circumcision device: proof of concept for a single-visit, adjustable device to facilitate safe adult male circumcision. Fertil Steril. 2014;101(5):1266 – 70.

81. Musau P et al. The safety profile and acceptability of a disposable male circumcision device in Kenyan men undergoing voluntary medical male circumcision. J Urol. 2011;186(5):1923 – 7.

82. 510(K) summary – Smartklamp. Silver Spring (MD): Food and Drug Administration; 2003.

83. Lagarde E et al. High rate of adverse events following circumcision of young male adults with the Tara KLamp technique: a randomised trial in South Africa. S Afr Med J. 2009;99(3):163 – 9.

84. Shelembe M. TAC voices Tara KLamp circumcision concerns. Mail & Guardian, 29 August 2012.

85. Manual for early infant male circumcision under local anaesthesia. Geneva: World Health Organization; 2010.

86. Weiss HA et al. Complications of circumcision in male neonates, infants and children: a systematic review. BMC Urol. 2010;10:2.

87. Bode CO, Ikhisemojie S, Ademuyiwa AO. Penile injuries from proximal migration of the Plastibell circumcision ring. J Pediatr Urol. 2010;6(1):23 – 7.

88. Plank RM et al. A randomized trial of Mogen clamp versus Plastibell for neonatal male circumcision in Botswana. J Acquir Immune Defic Syndr. 2013;62(5):e131 – 7.

89. Plank RM et al. Single-arm evaluation of the AccuCirc device for early infant male circumcision in Botswana. J Acquir Immune Defic Syndr. 2014;66(1):1 – 6.

90. An action agenda to end AIDS. New York (NY): AVAC – AIDS Vaccine Advocacy Coalition /amfAR; 2012.

91. Framework for clinical evaluation of devices for male circumcision. Geneva: World Health Organization; 2012.

92. Overview of the prequalification of male circumcision devices assessment process. Prequalification of male circumcision devices. Geneva: World Health Organization; 2011.

93. Technical Advisory Group on Innovations in Male Circumcision: evaluation of two adult devices. Geneva: World Health Organization; 2013.

94. Acumen Fund invests in Circ MedTech, developer of breakthrough innovation in HIV prevention. New York (NY): Press release, 11 July 2011.

95. WHO list of prequalified male circumcision devices. Geneva: World Health Organization; 2013.

96. Orpaz N. A bloodless coup against AIDS. Haaretz (Israel), 2 August 2012.

97. Duffy K et al. Reach and cost-effectiveness of the PrePex device for safe male circumcision in Uganda. PLoS One. 2013:8(5):e63134.

98. Njeuhmeli E et al. Cost analysis of integrating the PrePex medical device into a voluntary medical male circumcision program in Zimbabwe. PLoS One. 2014;9(5):e82533.

99. Obiero W, Young MR, Bailey RC. The PrePex device is unlikely to achieve cost-savings compared to the forceps-guided method in male circumcision programs in sub-Saharan Africa. PLoS One. 2013;8(1):e53380.

100. Vandament LT et al. Estimating the cost efficiency of introducing the Prepex circumcision device in Zambia. 20th International AIDS Conference, Melbourne, 20 – 25 July 2014.

101. Bratt JH, Zyambo Z. Comparing direct costs of facility-based Shang Ring provision versus a standard surgical technique for voluntary medical male circumcision in Zambia. J Acquir Immune Defic Syndr. 2013;63(3):e109 – 12.

102. Edgil D et al. Voluntary medical male circumcision: logistics, commodities, and waste management requirements for scale-up of services. PLoS Med. 2011;8(11):e1001128.

103. Current and resolved drug shortages and discontinuations reported to FDA. Silver Spring (MD): Food and Drug Administration; Online database (http://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI = Lidocaine Hydrochloride (Xylocaine) Injection&st = c, accessed 28 June 2014).

104. Holmes KK, Levine R; Weaver M. Effectiveness of condoms in preventing sexually transmitted infections. Bull World Health Organ. 2004;82(6):454 – 61.

105. Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. Cochrane Database Syst Rev. 2002(1):CD003255.

106. AIDS at 30: nations at the crossroads. Geneva: Joint United Nations Programme on HIV/AIDS; 2011.

107. Collins K. Gates Foundation funds female condoms and Trojan cows. Wired, 3 June 2014 Available from: http://www.wired.co.uk/news/archive/2014-06/03/female-condoms-and-trojan-cows/viewgallery/335103, accessed 17 July 2014).

108. Donor support for contraceptives and condoms in family planning and STI/HIV prevention 2010. New York (NY): United Nations Population Fund; 2011.

109. Bryden D. Condom gap "quite disturbing" according to PEPFAR. Science Speaks: HIV & TB News (blog), 2 February 2011 (http://sciencespeaksblog.org/2011/02/02/condom-gap-quite-disturbing-according-to-pepfar/, accessed 14 August 2014).

110. Safety of lubricants for rectal use: questions & answers for HIV educators and advocates. Chicago (IL): International Rectal Microbicide Advocates, 2010.

111. AccessRH product catalog: hundreds of reproductive health items. Copenhagen: United Nations Population Fund (http://www.myaccessrh.org/products, accessed 13 August 2014).

112. Peters AJ et al. Where does public funding for HIV prevention go to? The case of condoms versus microbicides and vaccines. Global Health, 2010;6:23.

113. Global condoms market to reach 27 billion units and $6.0 billion by 2015, according to new report by Global Industry Analysts, Inc. PRWeb press release, 12 August 2010.

114. Directory of condom manufacturers, condom exporters, medical & health. Export Bureau (website) (http://www.exportbureau.com/medical/condoms.html, accessed 29 June 2014).

115. UNFPA prequalified male condom manufacturing sites. New York (NY): United Nations Population Fund; 2014.

116. Vietnam's counterfeit condom crisis. IRIN humanitarian news and analysis. Bankok: Integrated Regional Information Networks; 2014.

117. Thurman AR, Clark MR, Doncel GF. Multipurpose prevention technologies: biomedical tools to prevent HIV-1, HSV-2, and unintended pregnancies. Infect Dis Obstet Gynecol. 2011;2011:1 – 10.

118. Feldblum PJ et al. Female condom introduction and sexually transmitted infection prevalence: results of a community intervention trial in Kenya. AIDS. 2001;15(8):1037 – 44.

119. Fontanet AL et al. Protection against sexually transmitted diseases by granting sex workers in Thailand the choice of using the male or female condom: results from a randomized controlled trial. AIDS. 1998;12(14):1851 – 9.

120. French PP et al. Use-effectiveness of the female versus male condom in preventing sexually transmitted disease in women. Sex Transm Dis. 2003;30(5):433 – 9.

121. Hoffman S et al. The future of the female condom. Int Fam Plan Perspect. 2004;30(3):139 – 45.

122. Hoke TH et al. Temporal trends in sexually transmitted infection prevalence and condom use following introduction of the female condom to Madagascar sex workers. Int J STD AIDS. 2007;18(7):461 – 6.

123. Liao S et al. Inclusion of the female condom in a male condom-only intervention in the sex industry in China: a cross-sectional analysis of pre- and post-intervention surveys in three study sites. Public Health. 2011;125(5): 283 – 92.

124. Macaluso M et al. Female condom use among women at high risk of sexually transmitted disease. Fam Plann Perspect. 2000;32(3):138 – 44.

125. Stein Z et al. Safer sex strategies for women: the hierarchical model in methadone treatment clinics. J Urban Health. 1999;76(1):62 – 72.

126. Wariki WM et al. Behavioral interventions to reduce the transmission of HIV infection among sex workers and their clients in low- and middle-income countries. Cochrane Database Syst Rev. 2012;2:CD005272.

127. Dowdy DW, Sweat MD, Holtgrave DR. Country-wide distribution of the nitrile female condom (FC2) in Brazil and South Africa: a cost-effectiveness analysis. AIDS. 2006;20(16):2091 – 8.

128. Marseille E et al. Cost-effectiveness of the female condom in preventing HIV and STDs in commercial sex workers in rural South Africa. Soc Sci Med. 2001;52(1):135 – 48.

129. Holtgrave DR et al. Cost-utility analysis of a female condom promotion program in Washington, DC. AIDS Behav. 2012;16(5):1115 – 20.

130. Francis-Chizororo M, Natshalaga NR. The female condom: acceptability and perception among rural women in Zimbabwe. Afr J Reprod Health. 2003;7(3):101 – 16.

131. Hatzell T et al. The female condom: is "just as good" good enough? Sex Transm Dis. 2003;30(5):440 – 2.

132. Stockman JK et al. Prevalence and correlates of female condom use and interest among injection drug-using female sex workers in two Mexico-US border cities. AIDS Behav. 2012;16(7):1877 – 86.

133. Thomsen SC et al. A prospective study assessing the effects of introducing the female condom in a sex worker population in Mombasa, Kenya. Sex Transm Infect. 2006;82(5):397 – 402.

134. Mantell JE et al. The acceptability of the female condom: perspectives of family planning providers in New York City, South Africa, and Nigeria. J Urban Health. 2001;78(4):658 – 68.

135. Gollub E, Stein Z. Living with uncertainty: acting in the best interests of women. AIDS Res Treat. 2012;2012:524936.

136. Zhang H et al. Predictors of consistent condom use based on the information-motivation-behavioral skills (IMB) model among female sex workers in Jinan, China. BMC Public Health. 2011;11:113.

137. Mack N et al. Central American sex workers' introduction of the female condom to different types of sexual partners. AIDS Educ Prev. 2010;22(5):466 – 81.

138. Choi KH et al. Social network characteristics and HIV risk among African American, Asian/Pacific Islander, and Latino men who have sex with men. J Acquir Immune Defic Syndr. 2013;64(5):496 – 501.

139. Guerra FM, Simbayi LC. Prevalence of knowledge and use of the female condom in South Africa. AIDS Behav. 2014;18(1):146 – 58.

140. Liao S et al. Female condom use in the rural sex industry in China: analysis of users and non-users at post-intervention surveys. AIDS Care. 2011;23(Suppl 1):66 – 74.

141. Technical issue brief. The female condom is safe and effective. United States Agency for International Development; 2012.

142. Acceptability of the female condom after a social marketing campaign in Campinas, Brazil. New York (NY): Population Council; 2002.

143. Frank M. Case in point: marketing the female condom. Washington Post, 1 December 2012.

144. Witte SS et al. Promoting female condom use to heterosexual couples: findings from a randomized clinical trial. Perspect Sex Reprod Health. 2006;38(3):148 – 54.

145. Artz L et al. Effectiveness of an intervention promoting the female condom to patients at sexually transmitted disease clinics. Am J Public Health. 2000;90(2):237 – 44.

146. Marseille E, Kahn JG. Smarter programming of the female condom: Increasing its impact on HIV prevention in the developing world. Boston (MA): FSG Social Impact Advisors; 2008.

147. Contraceptive commodities for women's health. New York (NY): United Nations Population Fund; 2012.

148. Traeger H, United Nations Population Fund. Personal commmunication, June 2014.

149. HIV prevention gains momentum. Successes in female condom programming. New York (NY): United Nations Population Fund; 2011.

150. Pebody R. Female condom choices are expanding—new models have low failure rates and are acceptable to users. London: nam AIDSmap, 9 October 2013.

151. FCMI + . Female condom market intellignce (http://www.fcmi.org/resources/publications.html, accessed 17 July 2014).

152. United States Securities and Exchange Commission form 10-Q. Chicago (IL): Female Health Company; 2012 (http://femalehealth.investorroom.com/index.php?s = 116&cat = 7).

153. Female Condom Product Brief. Reproductive Health Supplies Coalition; 2012 (http://www.path.org/publications/files/RHSC_fem_condom_br.pdf, accessed 5 November, 2014).

154. Female condom (website). Global Campaign for Microbicides (http://www.global-campaign.org/female-condom.htm, accessed 13 August 2014).

155. Nelson AL. New frontiers in female contraception (and male condoms): 2012. Expert Opin Investig Drugs. 2012;21(5):677 – 93.

156. Technology solutions for global health: woman's condom. Seattle (WA): PATH; 2012.

157. A unique kind of condom. Seattle (WA): PATH; 2014 (http://www.path.org/projects/womans_condom.php, accessed 7 July 2014).

158. Coffey PS et al. Short-term acceptability of the PATH Woman's Condom among couples at three sites. Contraception. 2006;73(6):588 – 93.

159. Schwartz JL et al. Comparative crossover study of the PATH Woman's Condom and the FC Female Condom. Contraception. 2008;78(6):465 – 73.

160. A unique kind of condom. Seattle (WA): PATH; 2014 (http://www.path.org/projects/womans_condom.php, accessed 7 July 2014).

161. Chinese condoms too small for South Africans. Agence France-Presse; 2011 (http://www.capitalfm.co.ke/news/2011/09/chinese-condoms-too-small-for-south-africans/).

162. Kelvin EA et al. Off-label use of the female condom for anal intercourse among men in New York City. Am J Public Health. 2011;101(12):2241 – 4.

163. Sharma P. Few takers for female condoms, cost a factor. DNA (India): Daily News & Analysis, 1 November 2010.

164. PEPFAR blueprint. Creating an AIDS-free generation. Washington (DC): US President's Emergency Plan for AIDS Relief; 2012.

165. Beksinska MP et al. Performance and safety of the secnd-generation female condom (FC2) versus the Woman's, the VA worn-of-women and Cupid female condoms: a randommised controlled non-inferiority crossover trial. Lancet Glob Health. 2013;1:e146 – 52.

166. The Female Health Company reports fourth quarter and FY2013 operating results. Chicago (IL): Female Health Company; 2013.

167. Female Health Company receives FDA approval for FC2 female condom. Chicago (IL): Female Health Company; 2009.

168. Cupid Limited: manufacturers and suppliers of male and female condoms (website). (http://www.cupidltd.com, accessed 14 August 2014).

169. Potter W. Personal communication, February 2013.

170. Product brief. Female condom. Seattle (WA): Caucus on New and Underused Reproductive Health Technologies; 2012.

171. Female condoms and US foreign assistance: an unfinished imperative for women's health. Washington (DC): Center for Health and Gender Equity (CHANGE); 2011.

172. Haddock SH et al. Comprehensive HIV prevention: condoms and contraceptives count. Washington (DC): Population Action International; 2008.

173. Kelly CG, Shattock RJ. Specific microbicides in the prevention of HIV infection. J Intern Med. 2011;270(6):509 – 19.

174. Skoler-Karpoff S et al. Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial. Lancet, 2008;372(9654):1977 – 87.

175. Van Damme L et al. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. N Engl J Med. 2008;359(5):463 – 72.

176. Abdool Karim Q et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329(5996):1168 – 74.

177. Tan D. Potential role of tenofovir vaginal gel for reduction of risk of herpes simplex virus in females. Int J Womens Health. 2012;4:341 – 50.

178. ARV-based prevention research and development product pipeline: a research timeline. New York (NY): AVAC – AIDS Vaccine Advocacy Coalition; 2013 (http://www.avac.org/infographic/arv-based-prevention-research-and-development-product-pipeline-research-timeline, accessed 7 July 2014).

179. MTN statement on decision to discontinue use of tenofovir gel in VOICE, a major HIV prevention study in women. Pittsburgh (PA): Microbicide Trials Network; 2011.

180. Marrazzo J et al. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine, or vaginal tenofovir gel in the VOICE Study (MTN 003). Atlanta (GA): 20th Conference on Retroviruses and Opportunistic Infections, 3 – 6 March 2013.

181. Next steps 1% tenofovir gel. Geneva: World Health Organization; 2010.

182. Mertenskoetter T, Kaptur PE. Update on microbicide research and development - seeking new HIV prevention tools for women. Eur J Med Res. 2011;16(1):1 – 6.

183. Camut C, International Partnership for Microbicides. Personal communication, February 2013.

184. Devlin B et al. Development of dapivirine vaginal ring for HIV prevention. Antiviral Res. 2013;100(Suppl):S3 – 8.

185. Backgrounder: ASPIRE—a study to prevent infection with a ring for extended use. Pittsburgh (PA): Microbicide Trials Network. 2013 http://www.mtnstopshiv.org/news/studies/mtn020/backgrounder, accessed 29 June 2014).

186. ASPIRE Phase III trial of a vaginal ring for HIV prevention completes enrollment of 2,629 women. Pittsburgh (PA): Microbicide Trials Network; 2014.

187. First combination ARV vaginal ring for HIV prevention being tested in Phase I safety trial. Pittsburgh (PA): Microbicide Trials Network; 2011.

188. Chen B et al. Safety and pharmacokinetics/pharmacodynamics of dapivirine and maraviroc vaginal rings. 21st Conference on Retroviruses and Opportunistic Infections, Boston (MA), 3 – 6 March 2014.

189. Kenney J et al. A single dose of a MIV-150/Zinc acetate gel provides 24 h of protection against vaginal simian human immunodeficiency virus reverse transcriptase infection, with more limited protection rectally 8 – 24 h after gel use. AIDS Res Hum Retroviruses. 2012;28(11):1476 – 84.

190. HIV prevention research & development database. New York (NY): AVAC – AIDS Vaccine Advocacy Coalition; 2014.

191. Lasry A et al. HIV sexual transmission risk among serodiscordant couples: assessing the effects of combining prevention strategies. AIDS. 2014;28(10):1521 – 9.

192. Arora S. Rectal microbicide research gives hope for HIV protection. Citizens News Service, July 2014 (http://www.citizen-news.org/2012/07/rectal-microbicides-one-of-tools-for.html, accessed 14 August 2014).

193. Beyrer C et al. Global epidemiology of HIV infection in men who have sex with men. Lancet. 2012;380(9839):367 – 77.

194. McGowan I. Rectal microbicides: can we make them and will people use them? AIDS Behav. 2011;15(Suppl 1):S66 – 71.

195. Carballo-Dieguez A et al. Preference for gel over suppository as delivery vehicle for a rectal microbicide: results of a randomised, crossover acceptability trial among men who have sex with men. Sex Transm Infect. 2008;84(6):483 – 7.

196. Pines HA et al. Acceptability of potential rectal microbicide delivery systems for HIV prevention: a randomized crossover trial. AIDS Behav. 2013;17(3):1002 – 15.

197. Ventuneac A et al. Acceptability of UC781 gel as a rectal microbicide among HIV-uninfected women and men. AIDS Behav. 2010;14(3):618 – 28.

198. Heffron R et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. Lancet Infect Dis. 2012;12(1):19 – 26.

199. McMahon JM et al. Potential impact of vaginal microbicides on HIV risk among women with primary heterosexual partners. J Assoc Nurses AIDS Care. 2011;22(1):9 – 16.

200. Bentley ME et al. Acceptability of a microbicide among women and their partners in a 4-country phase I trial. Am J Public Health. 2004;94(7):1159 – 64.

201. Woodsong C, Alleman P. Sexual pleasure, gender power and microbicide acceptability in Zimbabwe and Malawi. AIDS Educ Prev. 2008;20(2):171 – 87.

202. Schwartz JL et al. A multi-compartment, single and multiple dose pharmacokinetic study of the vaginal candidate microbicide 1% tenofovir gel. PLoS One. 2011;6(10):e25974.

203. Williams BG et al. Epidemiological impact of tenofovir gel on the HIV epidemic in South Africa. J Acquir Immune Defic Syndr. 2011;58(2):207 – 10.

204. Verguet S, Walsh JA. Vaginal microbicides save money: a model of cost-effectiveness in South Africa and the USA. Sex Transm Infect. 2010;86(3):212 – 6.

205. Walensky RP et al. The cost-effectiveness of pre-exposure prophylaxis for HIV infection in South African women. Clin Infect Dis. 2012;54(10):1504 – 13.

206. Preparing for microbicide access: Tanzania country profile. Bath: Constella Futures Ltd; 2006.

207. Preparing for access to PRO 2000 microbicide. Geneva: World Health Organization, 2009.

208. Next steps for tenofovir gel: CONRAD and TIA sign license agreement. Arlington (VA): CONRAD, 2011.

209. HIV Vaccines and Microbicides Resource Tracking Working Group. From research to reality: investing in HIV prevention and research in a challenging landscape. New York (NY): AVAC – AIDS Vaccine Advocacy Coalition; 2013.

210. Preparing for access to microbicides and the dapivirine ring for HIV prevention: preliminary strategy. Silver Spring (MD): International Partnership for Microbicides; 2011.

211. Rice VM et al. Cultural differences in acceptability of a vaginal microbicide: a comparison between potential users from Nashville, Tennessee, USA, and Kafue and Mumbwa, Zambia. HIV AIDS (Auckl). 2012;4:73 – 80.

212. Mantell JE et al. Microbicide acceptability research: current approaches and future directions. Soc Sci Med. 2005;60(2):319 – 30.

213. Nel AM et al. Acceptability of vaginal film, soft-gel capsule, and tablet as potential microbicide delivery methods among African women. J Womens Health (Larchmt). 2011;20(8):1207 – 14.

214. van der Straten A et al. Women's experiences with oral and vaginal pre-exposure prophylaxis: the VOICE-C qualitative study in Johannesburg, South Africa. PLoS One. 2014;9(2):e89118.

215. Corneli A et al. for the FEM-PrEP study team. FEM-PrEP: participant explanations for non-adherence. 21st Conference on Retroviruses and Opportunistic Infections, Boston (MA), 3 – 6 March 2014.

216. Microbicide stakeholders meeting. Washington (DC): United States Agency for International Development; 2010.

217. Foss A et al. When would the distribution of tenofovir gel be cost saving? In Model projections of HIV impact and break-even product prices in urban South Africa. XIX International AIDS Conference, 22 – 27 July 2012, Washington (DC).

218. Paper microbicide applicators: a low-cost solution to increase access to HIV prevention methods. Seattle (WA): PATH; 2012.

219. The strategic use of antiretrovirals to help end the HIV epidemic. Geneva: World Health Organization; 2012.

220. Fauci AS. AIDS: let science inform policy. Science. 2011;333(6038):13.

221. Guidance on pre-exposure oral prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: recommendations for use in the context of demonstration projects. Geneva: World Health Organization; 2012.

222. Grant RM et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363(27):2587 – 99.

223. Choopanya K et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2013;381(9883):2083 – 90.

224. Preexposure prophylaxis for the prevention of HIV infection in the United States—2014. Atlanta (GA): Centers for Disease Control and Prevention; 2014.

225. Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. Geneva: World Health Organization; 2014.

226. Van Damme L et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012;367(5):411 – 22.

227. Celum C, Baeten JM. Tenofovir-based pre-exposure prophylaxis for HIV prevention: evolving evidence. Curr Opin Infect Dis. 2012;25(1):51 – 7.

228. Understanding the results of VOICE. MicrobicideTrials Network; 2013 (http://www.mtnstopshiv.org/node/2003, accessed 29 June 2014).

229. Cogan M, UNFPA. Personal communication, October 2014.

230. Abraham BK, Gulick R. Next-generation oral preexposure prophylaxis: beyond tenofovir. Curr Opin HIV AIDS. 2012;7(6):600 – 6.

231. Paltiel AD et al. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. Clin Infect Dis. 2009;48(6):806 – 15.

232. Schackman BR, Eggman AA. Cost-effectiveness of pre-exposure prophylaxis for HIV: a review. Curr Opin HIV AIDS. 2012;7(6):587 – 92.

233. Untangling the web of antiretroviral price reductions, 17th edition. Geneva: Médecins Sans Frontières; 2014.

234. Post-exposure prophylaxis to prevent HIV infection. Joint WHO/ILO guidelines on postexposure prophylaxis (PEP) to prevent HIV infection. Geneva: World Health Organization; 2007.

235. Ford NS et al. Adherence to PEP along the cascade of care: a systematic review and meta-analysis. 20th International AIDS Conference, Melbourne, 20 – 25 July 2014.

236. Recommendations for prevention of HIV infection in health-care settings. MMWR Morb Mortal Wkly Rep. 1987;36(Supp. 2S).

237. Smith D et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States. MMWR Morb Mortal Wkly Rep: 2005;54(RR02):1 – 2.

238. Programmatic update: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. Geneva: World Health Organization; 2012.

239. HIV/AIDS. WHO fact sheet, No. 360. Geneva: World Health Organization; 2013 (http://www.who.int/mediacentre/factsheets/fs360/en/, accessed 29 June 2014).

240. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Recommendations for a public health approach. Geneva: World Health Organization; 2010.

241. Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. Geneva: Joint United Nations Programme on HIV/AIDS; 2011.

242. Global HIV/AIDS response: epidemic update and health sector progress towards universal access. Geneva: World Health Organization, Joint United Nations Programme on HIV/AIDS, United Nations Children's Fund; 2011.

243. Programmatic update antiretroviral treatment as prevention (TASP) of HIV and TB. Geneva: World Health Organization; 2012.

244. Jia Z et al. Antiretroviral therapy to prevent HIV transmission in serodiscordant couples in China (2003 – 11): a national observational cohort study. Lancet. 2013:382(9899):1195 – 203.

245. Tanser F et al. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science. 2013;339(6122):966 – 71.

246. Eaton JW et al. HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. PLoS Med. 2012;9(7):e1001245.

247. Cohen MS, McCauley M, Gamble TR. HIV treatment as prevention and HPTN 052. Curr Opin HIV AIDS. 2012;7(2):99 – 105.

248. Granich R. Personal communication, July 2014.

249. Degenhardt L et al. Prevention of HIV infection for people who inject drugs: why individual, structural, and combination approaches are needed. Lancet. 2010;376(9737):285 – 301.

250. Burris S, Chiu JV. Punitive drug law and the risk environment for injecting drug users: understanding the connections. Working paper prepared for the Third Meeting of the Technical Advisory Group of the Global Commission on HIV and the Law, 7 – 9 July 2011.

251. World Health Organization, United Nations. Office on Drugs and Crime, Joint United Nations Programme on HIV/AIDS. Technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users. Geneva: World Health Organization; 2009.

252. Harm Reduction Coalition policy statement on auto-disable syringes. New York (NY): Harm Reduction Coalition; 2012.

253. Guidelines for the psychologically assisted pharmacological treatment of opioid dependence. Geneva: World Health Organization; 2009.

254. Overview of market prices of opioid agonist treatment drugs. Central and Eastern European Harm Reduction Network; 2003.

255. Wolfe D. Personal communcation, February 2013.

256. Opioid substitution therapy and morphine database. Geneva: World Health Organization; 2013.

257. Schwartlander B et al. Towards an improved investment approach for an effective response to HIV/AIDS. Lancet. 2011;377(9782):2031 – 41.

258. The twin epidemics of HIV and drug use: innovative strategies for healthy communities. New York (NY)/Geneva: amfAR/International AIDS Society;2012.

259. The funding crisis for harm reduction. Brighton: International HIV/AIDS Alliance; 2014.

260. Shilts R. And the band played on. New York (NY): Viking Penguin Inc.; 1987.

261. Girard MP, Plotkin SA. HIV vaccine development at the turn of the 21st century. Curr Opin HIV AIDS. 2012;7(1):4 – 9.

262. Kahn P, editor. AIDS vaccine handbook, second 2nd edition: Global perspectives. New York (NY): AVAC – AIDS Vaccine Advocacy Coalition; 2005.

263. HIV vaccine trial ends in failure. BBC News, 12 November 2003 (http://news.bbc.co.uk/2/hi/health/3265089.stm, accessed 14 August 2014).

264. Song KM, Ostrom CM. Failure of AIDS vaccine punctures soaring hopes. SeattleTimes, 8 November 2007.

265. Rerks-Ngarm S et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009;361(23):2209 – 20.

266. Bennett S. Shark oil for HIV shot takes cue from Hemingway's old man. Bloomberg News, 27 June 2012,

267. Grant D. Inching toward a vaccine. The Body, 2012 (http://www.thebody.com/content/71286/inching-toward-a-vaccine.html, accessed 28 June 2012).

268. Progress on the path toward an AIDS vaccine. New York (NY): International AIDS Vaccine Initiative; 2012.

269. NIH discontinues immunizations in HIV vaccine study. Bethesda (MD): National Institutes of Health; 2013.

270. Barnabas RV, Celum C. Infectious co-factors in HIV-1 transmission herpes simplex virus type-2 and HIV-1: new insights and interventions. Curr HIV Res. 2012;10(3):228 – 37.

271. Watson-Jones D et al. Effect of herpes simplex suppression on incidence of HIV among women in Tanzania. N Engl J Med. 2008;358(15):1560 – 71.

272. Celum C et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. Lancet. 2008;371(9630):2109 – 19.

273. Celum C et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. N Engl J Med. 2010;362(5):427 – 39.