Chapter 7

Cost-Effectiveness of Interventions to Prevent HIV Acquisition

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INTRODUCTION

Because of the severe health consequences of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and the costs of lifelong treatment, inexpensive and effective HIV prevention is bound to be cost-effective. But what constitutes HIV prevention, and can it be affordable and effective? The use of condoms that cost a few cents and prevent a young adult from acquiring a chronic and fatal disease will, over time, be cost saving. Avoiding sex with someone who is infected with HIV/AIDS will be even more so. What can be done to get people to use condoms? What can be done to facilitate the avoidance of risky sexual encounters? Additional efficacious biomedical tools have become available, but similar questions persist: What can be done to get young women at risk to use oral truvada effectively as preexposure prophylaxis (PrEP) and to get young men at risk to be circumcised? The answers to these questions will determine what packages of prevention are essential, how much prevention programs should cost, and how cost-effective they can be. This chapter reviews current evidence about the efficacy, effectiveness, and costs of HIV/AIDS prevention products, programs, and approaches.

HISTORY OF THE HIV/AIDS PANDEMIC AND PREVENTION INITIATIVES

Clusters of fatal infectious and chronic diseases were first detected in 1981, leading to remarkably rapid identification of HIV; development of tests to identify persons infected; and mapping of the routes of transmission via sex, blood products, and sharing of injection equipment (Oppenheimer 1988). Unfortunately, it also became clear that over a long and variable period averaging about 12 years, everyone infected would develop AIDS and die (Brandt 1987). This awareness lent urgency to identifying ways of preventing and treating HIV. Restrictions on who could donate blood and HIV screening of blood products were found to close off transmission via blood products (Hoots 2001). The use of clean needles and syringes was found to stop transmission among people who injected drugs (Fuller, Ford, and Rudolph 2009). Consistent and correct use of condoms was found to stop sexual transmission of HIV (Steiner and others 2008). Lowering the number of sexual partners was found to reduce risks, with mutually monogamous couples protected from sexual transmission (May and Anderson 1987). Although too late for many, this new knowledge allowed many others to avoid

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acquiring HIV infection. However, it also required people to perceive the risk and to adopt and rigorously adhere to difficult and unappealing behaviors. HIV continued to spread (Anderson and others 1991).

Quantifying the impact of these interventions is difficult. It requires knowing what the incidence would be in their absence. Moreover, a concentrated epidemic with heterogeneous transmission and acquisition risks will become saturated (Anderson and May 1990). Thus, a drop in incidence and leveling off of prevalence are expected, even in the absence of prevention (Hallett and others 2006). Nonetheless, reported changes in risk behavior have reduced the spread of HIV in some populations, particularly among people who inject drugs (PWID) and men who have sex with men (MSM) in high-income countries (Fuller, Ford and Rudolph 2009), sex workers and their clients in Thailand (Nelson and others 1996), and the general population in Uganda and Zimbabwe (Gregson and others 2007; Stoneburner and Low-Beer 2004).

In 1996, combination antiretroviral treatment was reported to be efficacious in reducing viral replication and in reconstituting the immune system (Eron and Hirsch 2008). Effective treatment transformed the response to the epidemic, initially dramatically reducing AIDS deaths in high-income countries (Palella and others 1998). Major reductions in medication costs and increased investments from the U.S. President's Emergency Plan for AIDS Relief (PEPFAR); the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund); and others led to widespread treatment in low- and middle-income countries (LMICs) (Ford and others 2013). Initially, the impact of treatment on HIV transmission and spread was unclear, but evidence from randomized controlled trials (RCTs) demonstrated that antiretroviral treatment was extremely efficacious in preventing transmission (Cohen and others 2011). This finding and the clinical benefits of early treatment led the World Health Organization (WHO) to recommend that all people living with HIV should receive treatment (WHO 2015b; Holmes and others 2017).

However, the number of infected people on treatment remains far below the total number infected, and further prevention is required. By the end of 2014, an estimated 36.9 million people were living with HIV globally, and 2 million new infections were occurring each year (UNAIDS 2015), even with more than 15 million people globally receiving treatment. With the global response becoming difficult to sustain, there is an urgent need not only to scale up treatment, but also to make available other affordable and effective packages of prevention. Further expansion of treatment will reduce the infectiousness of infected persons; targets have been set for treatment expansion (including prevention among HIV-negative persons) (Piot and others 2015). However, logistical and social barriers mean that some delays will occur between infection and treatment, and many will fail HIV treatment. Even in populations in which coverage of treatment has hit the 90 percent targets for diagnosis, initiation of treatment, and suppression of viral load, the disease continues to spread (Gaolathe and others 2016).

CHALLENGES IN REVIEWING THE EFFICACY AND EFFECTIVENESS OF HIV PREVENTION

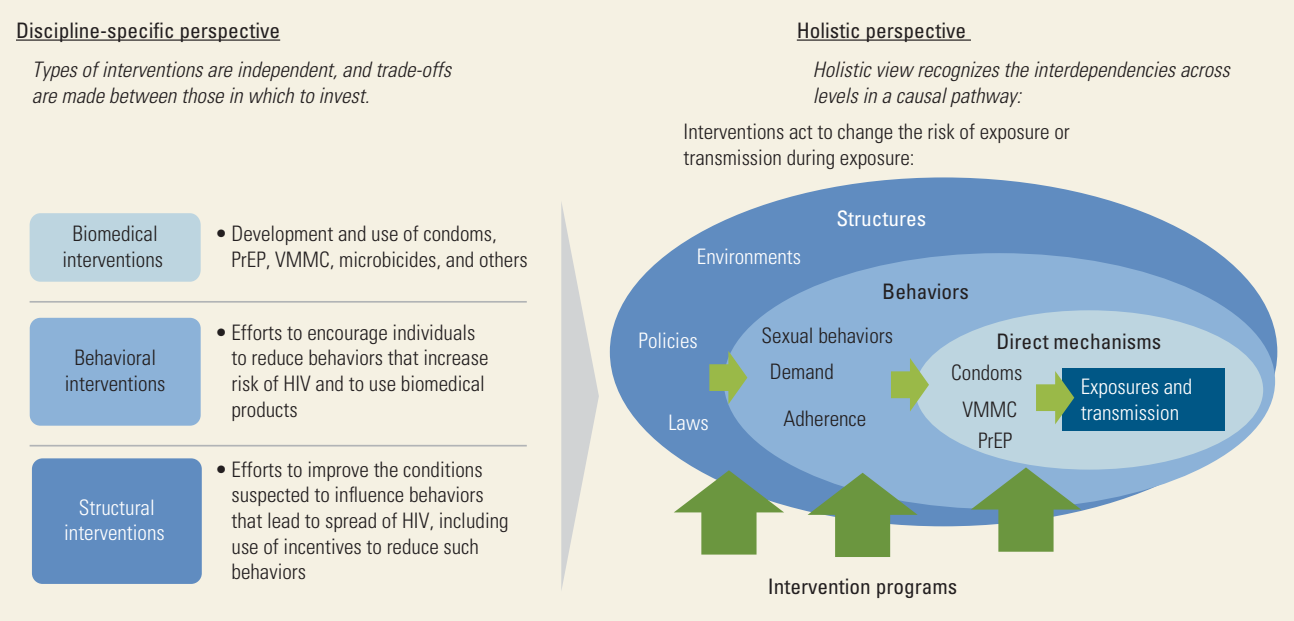
Determining the causal impact of prevention activities in affecting outcomes of interest (that is, reducing HIV infections and ultimately preserving health) has proved much more challenging than for many other kinds of health care intervention. We explore reasons for this challenge related to difficulties in categorizing and defining prevention interventions, defining and measuring intervention endpoints, and designing studies of impact.

Categorizing and Defining HIV Prevention Interventions

HIV prevention interventions have been categorized as biomedical, behavioral, or structural. These categories are based on whether the intervention includes use of a biomedical product or procedure, involves people changing their risk behavior, or targets changes in the environment within which risk takes place (Merson and others 2008). Thinking of these approaches as separate and distinct ignores the requirements for interventions to be effective in the real world. HIV transmissibility needs to be reduced—either by a product used during exposure or by a reduction in exposure. We call these direct mechanisms. Getting these products to be used requires behavioral changes, for example using condoms, taking PrEP, or getting circumcised. Such changes are only possible when condoms are available; PrEP programs and circumcision are organized; and laws do not prevent people from accessing clean needles, condoms, circumcision, or oral PrEP. Holistic or combined approaches are required (Hankins and de Zalduondo 2010; Schwartländer and others 2011), and the trials to test interventions need to consider all three categories, each of which should be carefully described if they are to be replicated and scaled up (figure 7.1).

Such combination approaches have been promoted to prevent the spread of HIV (Hankins and de Zalduondo 2010; Schwärtlander and others 2011). However, combining the use of prevention products, each with evidence of biological efficacy, can also be thought of as

Figure 7.1 Elements of Discipline-Specific and Holistic Approaches to Intervention



Note: HIV = human immunodeficiency virus; PrEP = preexposure prophylaxis; VMMC = voluntary medical male circumcision.

combination prevention, with a narrower perspective of which products are needed (Cremin and others 2013; Vermund and others 2013). It is simpler to standardize a prevention product and experimentally test whether that product has biological efficacy than to standardize the design of interventions to change the environment and behaviors (Hallett, White, and Garnett 2007; Lagakos and Gable 2008). Accordingly, with interventions requiring structural and behavioral components, there are major challenges in measuring the effects and costs of prevention because the interventions are rarely standardized and units of intervention are often unclear.

Defining and Measuring Intervention Endpoints

In addition to defining the interventions, it is important to define the endpoints of interest, which in studies are often intermediate variables instead of HIV incidence. Ultimately, the goal of prevention is to reduce incidence, but measuring incidence is difficult and expensive, especially where incidence is low (Hallett, White, and Garnett 2007). If reducing the number of partners or increasing the use of condoms could be assumed to decrease HIV incidence, then these intermediate measures would be reasonable endpoints for trials (Laga and others 2012). Alternatively, if correlated measures such as other acute sexually transmitted infections (STIs) or pregnancy share risks with HIV, they can be used to indicate a change in HIV risks. Unfortunately, the causal pathways are often not clear and intermediate risks are not reliable measures of HIV risk, so the findings of studies using other endpoints—the majority of studies—have to be treated with caution (Garnett and others 2006).

Designing Studies of Impact

A third challenge pertains to the design of studies measuring the efficacy and effectiveness of HIV prevention interventions. For biomedical products intended to protect the individual, RCTs provide rigorous, causal evidence of efficacy (Lagakos and Gable 2008), but they do not guarantee impact at scale (Hallett, White, and Garnett 2007). Furthermore, some structural and behavioral elements of interventions need to be delivered to communities, not individuals—for example, education and communication campaigns or changes in policies. To have an impact, interventions often need to reach key individuals and to scale up what protects individuals so that the interventions protect communities. Such interventions can be evaluated in cluster or community randomized trials, but conducting such trials can be expensive and logistically challenging (Hallett, White, and Garnett 2007). When these trials find no impact, it is not clear whether the intervention was ineffective or the implementation in the trial was ineffective (Hallett, White, and Garnett 2007). RCTs are desirable if causality is to be established, the trials need to have a valid counterfactual with which to compare the effect of the

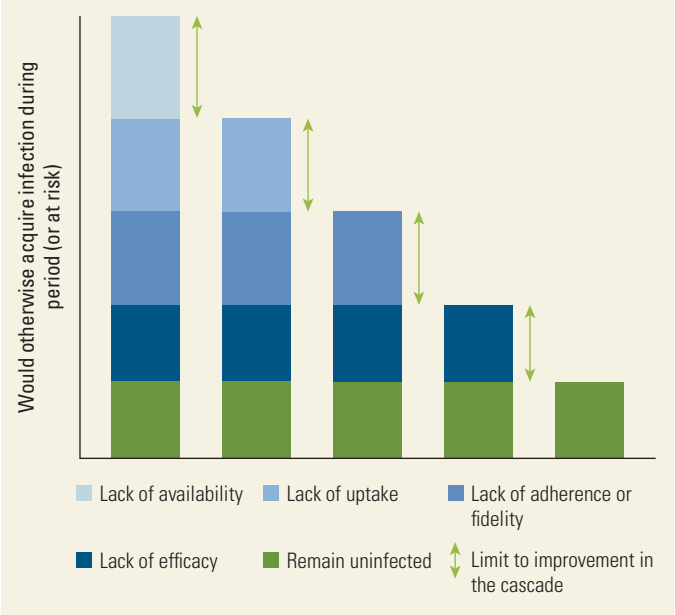
intervention and should be randomized to distribute unmeasured confounding variables (Gertler and others 2011). Evaluation using methods other than RCTs can examine the delivery of programs at scale, trends in the incidence of infection and disease, qualitative data on risks and responses to interventions, and logical pathways by which interventions could have an impact. Analyses from such studies create a better understanding of the results of RCTs and yield plausibility arguments useful for improving implementation (Hargreaves and others 2016).

HIV PREVENTION CASCADES

Prevention cascades could be a powerful tool for analyzing how a prevention product should be delivered and identifying the steps required for it to have an impact. To date, in studying HIV interventions, cascades for treatment and prevention of mother-to-child transmission (PMTCT) have predominated (Gardner and others 2011; Mahendra and others 2007). The WHO has promoted a comprehensive approach to HIV, including prevention for those who are negative (WHO 2015a). A single, all-encompassing cascade is attractive. However, whether it can be populated with data and used successfully remains to be seen.

An alternative approach is to consider the different ways of preventing HIV and develop multiple cascades (Garnett and others 2016). This approach has the disadvantage of thinking in programmatic siloes, but it is useful for illuminating the steps needed to reduce the risk of acquisition (figure 7.2). A hypothetical cascade starts with the number of individuals who would acquire infection or who are at risk over a period of time and calculates who will remain uninfected (or become infected) because of the intervention. Steps in the cascade represent the potential reasons for failure of a prevention intervention.

Figure 7.2 HIV Prevention Cascade for a Single Intervention



Source: Garnett and others 2016.
Note: HIV = human immunodeficiency virus.

From the perspective of a policy maker or implementer, delivering a successful intervention requires targeting the population at risk, creating demand for prevention in that population, having a system in place to supply prevention, promoting adherence, and providing a direct and biologically efficacious prevention mechanism.

HIV prevention trials that focus on these aspects can be categorized. In a description of the literature, Krishnaratne and others (2016) classified reviews and primary studies under one of the following:

- **Demand interventions,** in which the principal aim is to influence behavior by targeting risk perception or strengthening awareness of, and positive attitudes toward, HIV prevention behaviors and technologies. These interventions could include providing information, education, and communication and aim to influence perceived norms through peer-based approaches.
- **Supply interventions,** in which the principal aim is to influence the supply of HIV prevention products and messages. These interventions include mass condom distribution, needle exchange initiatives, attempts to mainstream prevention within other services, and STI treatment strategies.
- **Use of or adherence to interventions,** in which the principal aim is to support adoption or maintenance of prevention behaviors, including the use of prevention technologies. They include interventions that provide risk counseling and target social determinants of behavior hypothesized to encourage or discourage access and adherence, such as conditional cash transfers or livelihood interventions.
- **Direct mechanisms for HIV prevention,** in which the principal aim is to stop transmission. These interventions include biomedical products or procedures, for example, microbicides or medical male circumcision (MMC).

SYSTEMATIC REVIEWS OF HIV PREVENTION

To understand the evidence available on prevention and address some of these challenges, Krishnaratne and others (2016) undertook three systematic reviews of prevention interventions. They then reviewed the original

studies, reclassifying the interventions into a cascade framework, dissecting different endpoints, and grading the quality of evidence. The initial search identified 666 reviews of which 88 were eligible for inclusion. From these 88 reviews, 1,964 primary studies were identified, of which 292 were eligible for inclusion.

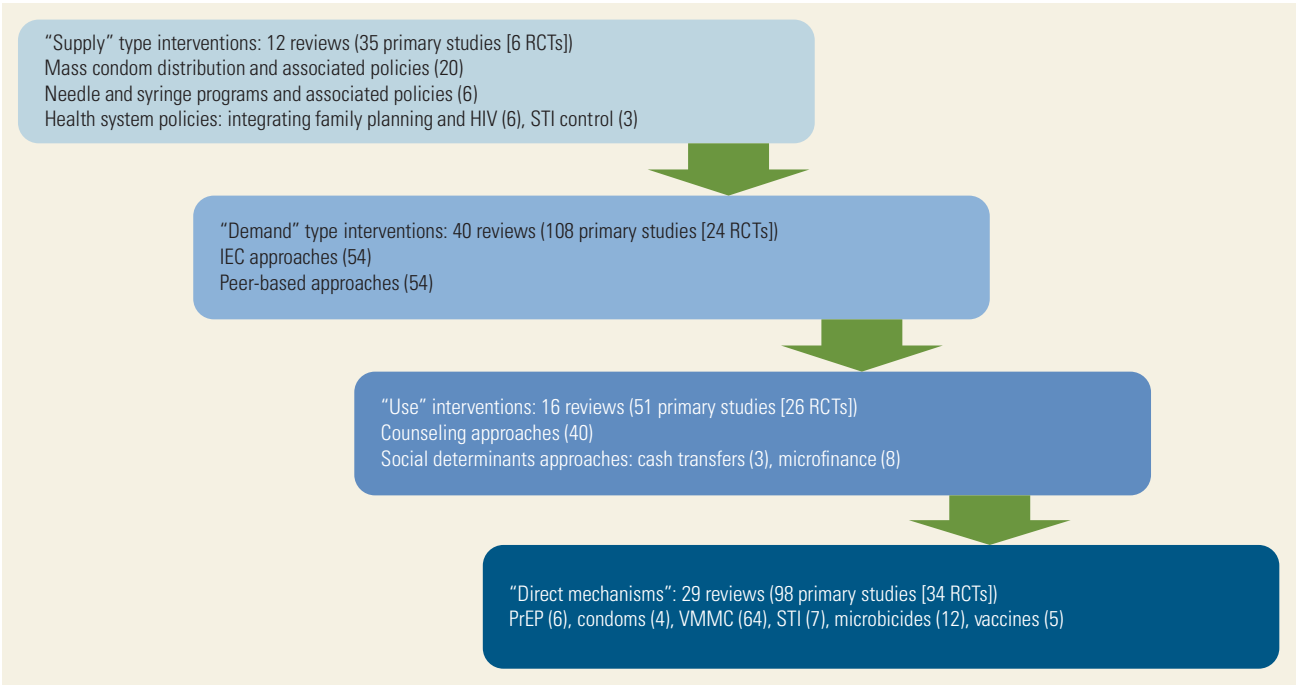
The division of studies within the cascade framework is notable for several reasons (figure 7.3). First, there were many more studies of demand interventions and direct mechanisms than studies of supply and use interventions. Most supply interventions were mass distribution of condoms and clean needles and syringes. The overwhelming majority of use interventions entailed counseling. With regard to study design, use and direct interventions were highly likely to be RCTs.

Two dimensions were used to summarize the evidence, following the scheme that Mavedzenge, Luecke, and Ross (2014) used to review HIV prevention interventions aimed at adolescents. The first dimension classifies the level of internal validity and replication, emphasizing proof of causation and generalizability. It does not include evidence of scalability, impact, or cost-effectiveness. The second dimension describes the direction of the effect.

Results from demand, supply, and use interventions could include intermediate variables, and Krishnaratne and others (2016) included condom use and HIV testing as endpoints. In addition, HIV prevalence could be compared between arms in a trial as a marker of past incidence, rather than directly assessing incidence by following up trial participants. For this reason, HIV prevalence was included as an endpoint. Table 7.1 summarizes the evidence from the review; the number of studies by type of intervention is shown with the number of RCTs in parentheses.

Of note, HIV incidence was most often an endpoint in trials of direct mechanisms, and some of these interventions were consistently found to be efficacious. Where the endpoint was HIV incidence, the evidence for demand, supply, and use interventions was either mixed or consistently ineffective; the single exception was a non-RCT of couples counseling. Demand interventions were ineffective in reducing HIV prevalence, whereas supplying condoms and clean needles and syringes was consistently associated with a decline in HIV prevalence but only in non-RCT studies. The majority of studies measured condom use and HIV testing rather than HIV incidence and prevalence. Across populations, there is good evidence of effectiveness in increasing condom use

Figure 7.3 Mapping HIV Prevention Studies to the HIV Prevention Cascade



Source: Based on a systematic review of HIV prevention studies in low- and middle-income countries by Krishnaratne and others 2016.
Note: HIV = human immunodeficiency virus; IEC = information, education, and communication; PrEP = preexposure prophylaxis; RCT = randomized controlled trial; STI = sexually transmitted infection; VMMC = voluntary medical male circumcision.

Table 7.1 Trials Assessing HIV Incidence and Prevalence, with Condom Use and Testing as Endpoints

	Outcome							
Type of intervention	Incidence; number of studies (number of RCTs)	Incidence: QA rating	Prevalence; number of studies (number of RCTs)	Prevalence; QA rating	Condom use; number of studies (number of RCTs)	Condom use: QA rating	Testing; number of studies (number of RCTs)	Testing: QA rating
Demand-side interventions								
Impact of IEC interventions focused on youth	3 (1)	B4	1 (1)	B4	28 (7)	A3		
Impact of IEC interventions focused on men					9 (3)	A2	1 (0)	C1
Impact of IEC interventions focused on women					2 (2)	B3		
Impact of IEC interventions using mass media	1 (1)	B3			9 (1)	B4		
Impact of IEC interventions focused on PWUD					4 (3)	A1		
Impact of peer-based interventions focused on youth	1 (1)	B4			11 (0)	C2	2 (0)	C1
Impact of peer-based interventions focused on MSM					3 (1)	B1	1 (0)	C1
Impact of peer-based interventions focused on FSW	3 (1)	B4	4 (0)	C4	22 (3)	A2	3 (0)	C1
Impact of peer-based interventions focused on PWUD/alcohol	2 (2)	B4	1 (1)	B4	5 (2)	B3		
Impact of peer-based interventions with no population focus					10 (2)	B1	1 (0)	C1
Supply-side interventions								
Impact of interventions that integrate HIV services into routine care					1 (0)	C1	5 (0)	C1
Impact of clean needle and syringe programs	2 (0)	C3	6 (0)	C1				
Impact of condom distribution interventions			3 (0)	C1	20 (5)	A1		
Impact of community-level STI interventions	3 (3)	A4			1 (1)	B4		
Adherence interventions								
Impact of couples-based counseling	1 (0)	C1			9 (3)	A1	4 (3)	A3
Impact of HIV testing and counseling	1 (1)	B4			8 (1)	B2	3 (2)	B1
Impact of individual-level counseling	1 (1)	B3			12 (7)	A1	2 (1)	B3
Impact of HIV prevention counseling					7 (4)	A3		
Impact of microfinance interventions	1 (1)	B4			8 (4)	A3	1 (1)	B1
Impact of cash transfer interventions	2 (2)	B4	2 (2)	B1	1 (1)	B4		

table continues next page

Table 7.1 Trials Assessing HIV Incidence and Prevalence, with Condom Use and Testing as Endpoints (continued)

	Outcome							
Type of intervention	Incidence; number of studies (number of RCTs)	Incidence: QA rating	Prevalence; number of studies (number of RCTs)	Prevalence; QA rating	Condom use; number of studies (number of RCTs)	Condom use: QA rating	Testing; number of studies (number of RCTs)	Testing: QA rating
Direct mechanisms								
MMC heterosexual risk (female to male)	38 (3)	A1						
MMC heterosexual risk (male to female)	7 (1)	B3						
Male circumcision, MSM individual level	19 (0)	C3						
Condoms (heterosexual), individual level	4 (0)	C1						
Oral PrEP (overall), individual level	6 (6)	A2						
Microbicide prophylaxis, individual-level studies	12 (12)	A3						
STI treatment, individual-level studies	7 (7)	A4						
HIV vaccine, individual-level studies	5 (5)	A3						

Source: Krishnaratne and others 2016.
Note: Level of internal validity and replication available is defined as A (3 or more RCTs), B (1–2 RCTs), and C (no RCT). The direction of effectiveness is defined as 1 (consistently effective), 2 (mainly effective), 3 (mixed results), and 4 (consistently ineffective). FSW = female sex workers; HIV = human immunodeficiency virus; IEC = information, education, and communication; MMC = medical male circumcision; MSM = men who have sex with men; STI = sexually transmitted infection; PrEP = preexposure prophylaxis; PWUD = people who use drugs; QA = quality assessment; RCT = randomized controlled trial. Blank cells = not available.

and testing. Unfortunately, the impact of condom use depends on who is using the condoms and when, that is, in sexual acts where they would be exposed to the virus. The impact of HIV testing depends on changes in subsequent behavior, and there is scant evidence that this is a focus or product of HIV testing.

Cash transfers are an area of interest. An RCT found that cash transfers were associated with reduced HIV prevalence in young women in Malawi (Baird and others 2012). However, the effect was reversed when the transfers were withdrawn. Another study found no impact of cash transfers in a less resource constrained setting, where many girls stayed in school regardless of the intervention (HPTN 2015).

EFFICACY, EFFECTIVENESS, AND DURATION OF PROTECTION

The distinction between efficacy and effectiveness is crucial and somewhat opaque. By definition, trials measure the effect of an intervention in an artificial setting because the subjects have been recruited, have consented to take part, and are observed. Accordingly, there is a well-acknowledged distinction between effectiveness in a trial and in the real world, with real-world effectiveness expected to be lower than trial effectiveness. To partly address this discrepancy, trials distinguish between participants that do and do not follow the intervention and trial protocol closely. Analysis of the effects according to protocol attempts to approximate the underlying biological effect of the product, while intention-to-treat analysis attempts to approximate its potential effectiveness in the real world. Unfortunately, the situation is much more complicated because there is very likely a difference between the efficacy observed in the according-to-protocol analysis of a trial and the biological effect of a product in reducing transmission. A trial compares the cumulative incidence of HIV among participants who potentially have multiple exposures. Biological efficacy is the reduction in risk for one exposure and is the parameter that would logically be used in models of HIV transmission (Jewell and others 2015).

To add to the confusion, a product could protect a fraction of individuals from all challenges (take-type efficacy) or all individuals from a fraction of challenges (degree-type efficacy) and have the same efficacy (Garnett 2005). Cumulatively as the number of challenges increases, take-type efficacy will fare better than degree-type efficacy because, in the former, the number of breakthrough infections will plateau as all those still at risk acquire infection. RCTs are not capable of distinguishing between these types of efficacy.

Likewise, effectiveness in the real world will depend on similarities in adherence and exposure in different settings with those found during the trial.

A further challenge is in estimating how long protection lasts. A trial will uncover whether protection is short lived, but if protection wanes over the medium or long term, assessing the duration of protection will be harder. The results of studies of the effectiveness of direct mechanisms of HIV prevention need to be considered, keeping these problems of interpretation in mind.

EVIDENCE OF EFFICACY OF DIRECT MECHANISMS OF HIV/AIDS PREVENTION

Barrier Methods

Male and female condoms that prevent HIV from crossing the barrier in vitro may prevent the acquisition of HIV (Steiner and others 2008). However, there is a problem in ethically and practically testing the effectiveness of condoms in RCTs. Observational studies need to consider whether condom use is consistent and correct and whether self-reported use is valid. Observed effectiveness will likely underestimate biological efficacy.

Good-quality studies on the effectiveness of condoms against HIV are lacking. Estimates of effectiveness in the past have been low. Weller (1993) concluded that condoms were only 69 percent effective in preventing acquisition of HIV. However, that study misaggregated some groups on condom use and did not compare "always" users with "never" users. Other researchers attempted to address this issue by exploring the direction of transmission. Pinkerton and Abramson (1997) concluded that condoms were 90 percent to 95 percent effective when used consistently. However, Davis and Weller (1999) criticized their paper for incorrectly categorizing "sometimes" users with never users and estimated effectiveness at 87 percent (as low as 60 percent or as high as 96 percent).

A meta-analysis by Weller and Davis (2002) concluded that condoms reduced HIV seroconversion approximately 80 percent, comparing always users with never users; their analysis used the difference between the two pooled rates to estimate effectiveness.

None of the reviews identified HIV effectiveness data for female condoms. However, one systematic review of the effectiveness of female-controlled barrier methods in preventing STI and HIV transmission concluded that RCTs provide evidence that female condoms confer as much protection from STIs as male condoms (Minnis and Padian 2005). However, this finding was based on results for chlamydia, gonorrhea, syphilis, and trichomoniasis rather than for HIV.

No trials found that the use of diaphragms affords significant protection. Marrazzo and Cates (2011) compared protection using a diaphragm and condom versus using a condom alone and found that using both provided no additional protection. They concluded that diaphragms should not be relied on for protection against STIs or HIV.

Medical Male Circumcision

Early in the study of heterosexually transmitted HIV infection in Sub-Saharan Africa, an association was observed at both the national (Bongaarts and others 1989) and individual (Cameron and others 1989) levels between circumcision status and HIV risk. Subsequent data collection repeatedly showed a protective effect of circumcision, with a systematic review and meta-analysis of 27 studies showing a 48 percent lower risk without controlling for other variables, and a meta-analysis of 15 studies showing a reduced risk of 58 percent that did account for confounding (Weiss, Quigley, and Hayes 2000).

Despite this observational evidence, two major questions remained:

- Could uncontrolled confounding related to the characteristics and behaviors of men from cultural groups that circumcise explain the observed protective effect?
- Would an intervention providing adult male circumcision provide the same protection as infant circumcision?

These questions required clinical trials using randomization to avoid uncontrolled confounding. The first trial in South Africa was stopped early because circumcision was found to be protective, with 20 HIV infections in circumcised men and 49 in uncircumcised men. Calculated rates of 0.85 per 100 person years in circumcised men and 2.1 per 100 person years in uncircumcised men meant that this was a 60 percent reduction in risk (Auvert and others 2005). In Kenya, 22 circumcised men and 47 uncircumcised men acquired HIV, representing a 53 percent reduction in risk (Bailey and others 2007). In Uganda, 0.66 cases of HIV per 100 person years in circumcised men and 1.3 cases per 100 person years in uncircumcised men represented a 55 percent reduction in risk (Gray and others 2007). These three rigorous trials provided definitive evidence of the protective effect of adult MMC in protecting men from heterosexual acquisition of HIV infection over time.

There is little evidence that MMC directly reduces the risk of HIV in women through vaginal intercourse: the one RCT that included this outcome measure was

stopped early with some infections acquired by women whose partners acquired infection before the wound from the circumcision had healed (Wawer and others 2009). However, the fact that male circumcision reduces the incidence of HIV in men will indirectly benefit women by lessening their exposure to HIV. Male circumcision has also been shown to reduce rates of genital ulcers in men, as well as bacterial vaginosis and trichomoniasis in female partners of circumcised men (Tobian, Kacker, and Quinn 2014).

For MSM, the evidence of protection via circumcision is weak. A meta-analysis of observational studies concluded that there was insufficient evidence that circumcision provided protection for MSM (Millett and others 2008). In a subgroup analysis by sexual role in the relationship, 7 of 21 studies indicated that male circumcision is more protective among MSM who have a mainly insertive role (Wiysonge and others 2011).

Oral Preexposure Prophylaxis

The effectiveness of oral PrEP using either truvada (tenofovir plus emtricitabine) or tenofovir alone has been studied in trials of MSM and of men and women in HIV-discordant couples (figure 7.4).

Analyses accounting for adherence have shown greater effectiveness with high adherence and no significant effectiveness with poor adherence (Marrazzo and others 2015; Van Damme and others 2012).

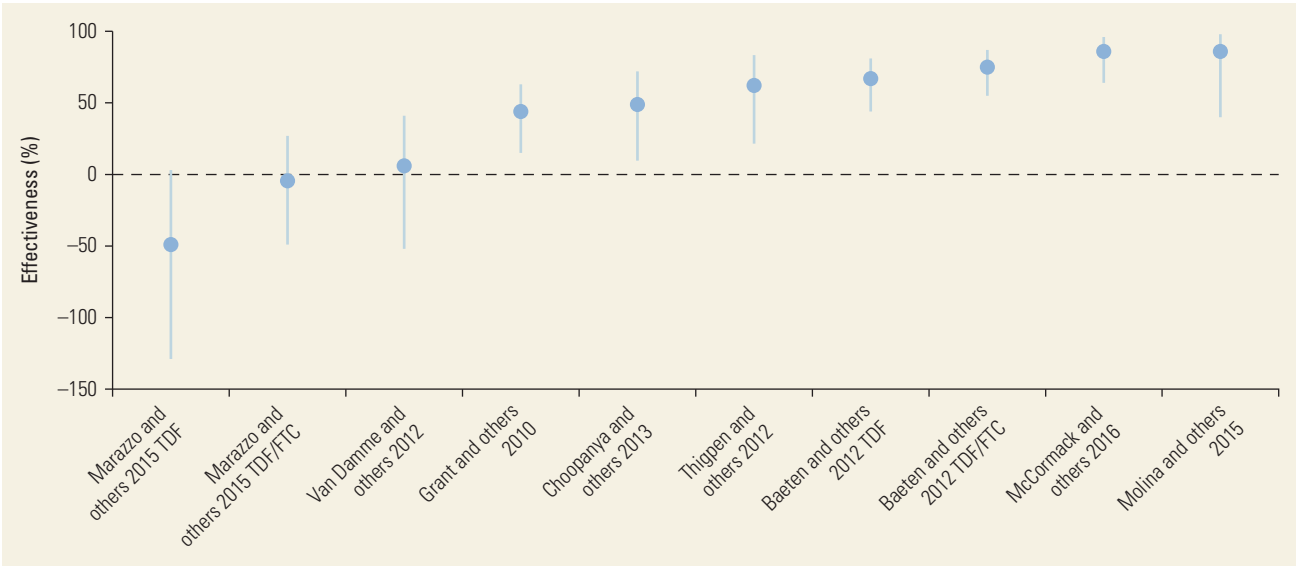
A study of on-demand PrEP in MSM found 86 percent effectiveness (Molina and others 2015); a trial comparing immediate PrEP to PrEP deferred for one year found a similar 86 percent relative effectiveness (McCormack and others 2016). In both cases, infections occurred among those who ceased taking the drug. Subsequent WHO guidelines, based on a meta-analysis showing 51 percent effectiveness across reviewed trials, included a strong recommendation for offering oral PrEP to persons with a high risk of acquiring HIV (WHO 2015b).

Vaginal or Rectal Microbicides

A wide range of topical products to prevent HIV acquisition has been studied. A review by Obiero and others (2012) of 13 trials for vaginal microbicides conducted between 1996 and 2011 found no evidence of a significant reduction in risk of HIV in a pooled analysis, but one proof-of-concept trial of tenofovir gel and a placebo gel conducted in South Africa found a significant reduction in the risk of acquisition (Abdool Karim and others 2010). Two further phase 3 studies of tenofovir gel showed no significant effectiveness: one found only a 14.5 percent lower incidence of HIV infection in the tenofovir arm (Marrazzo and others 2015) and one found no difference (Rees and others 2015).

Work on longer-acting topical delivery of an antiviral agent through a vaginal ring was tested in women in two trials. One found 27 percent effectiveness (Baeten and others 2016), and one found 31 percent effectiveness (IPM 2016). In both cases, effectiveness was higher in women older than age 21 years, with continuous

Figure 7.4 Effectiveness of Oral PrEP in Randomized Controlled Trials, by Order of Increasing Effectiveness



Sources: Baeten and others 2012; Marazzo and others 2015.
Note: FTC = emtricitabine; PrEP = preexposure prophylaxis; TDF = tenofovir.

use of the ring needed to prevent HIV acquisition. Whether this effectiveness is sufficient to warrant launch of a product remains to be seen.

Vaccines

Systematic reviews of vaccines were included in broader reviews of HIV prevention measures (Marrazzo and Cates 2011; Padian and others 2010). Of four trials, only one (a double-blind, placebo-controlled trial conducted in more than 16,000 adults in Thailand) found a protective effect. In a modified intention-to-treat analysis, the combination of a vaccine plus a booster was 31 percent effective (Rerks-Ngarm and others 2009).

SEXUALLY TRANSMITTED INFECTION TREATMENT AS HIV PREVENTION

HIV acquisition is correlated with the presence of other STIs, and it has been hypothesized that the presence of these other infections could increase the transmissibility of HIV. Genital ulceration associated with chancroid; syphilis; herpes simplex virus (HSV) type 1 or 2; or inflammation associated with chlamydia, gonorrhea, trichomoniasis, or human papillomavirus may increase risks of HIV (Røttingen, Cameron, and Garnett 2001). Unfortunately, because of the common routes of transmission and the impossibility of measuring the complete sexual network, observational studies will always have unmeasured confounding.

To determine the effect of controlling STIs on HIV incidence, community randomized trials provided enhanced STI control in intervention communities. The first of these trials, conducted in Mwanza, Tanzania, using syndromic management of STIs found a 40 percent reduction in HIV incidence (Grosskurth and others 1995). This finding was not replicated in further trials of syndromic management or mass treatment of the population (Gregson and others 2007; Kamali and others 2003; Wawer and others 1999). This discrepancy was explained by the importance of symptoms to HIV risk and stage of the HIV epidemic. Padian and others (2010) reviewed nine STI treatment trials, only one of which was effective in preventing HIV acquisition. Three RCTs assessed the impact on HIV acquisition of suppressing HSV-2 with acyclovir. None of the trials found a protective effect. Adherence was reportedly mixed between the trials, and good prevention services were available to the control group, which may have affected behavior in all arms. The strength of the HSV-2 regimen also might have influenced susceptibility to HIV.

MEASURING THE HIV PREVENTION CASCADE TO EXPLORE IMPACT

From a population-based study in rural Zimbabwe, HIV prevention cascades were constructed to determine the effectiveness of HIV prevention and gaps in preventing infection (Garnett and others 2016). Figure 7.5 shows two cascades. The cascade in panel a is for male circumcision in 2009–11, where the cascade is applied to a population of men at risk of HIV. The initial step depends on whether there is a provider of voluntary medical male circumcision within 20 kilometers. Where there is, the next step includes persons who report having been circumcised; because adherence does not apply to circumcision, there is no drop-off at this step. The next drop-off is where circumcision is not efficacious. Finally, persons on the right were protected by circumcision.

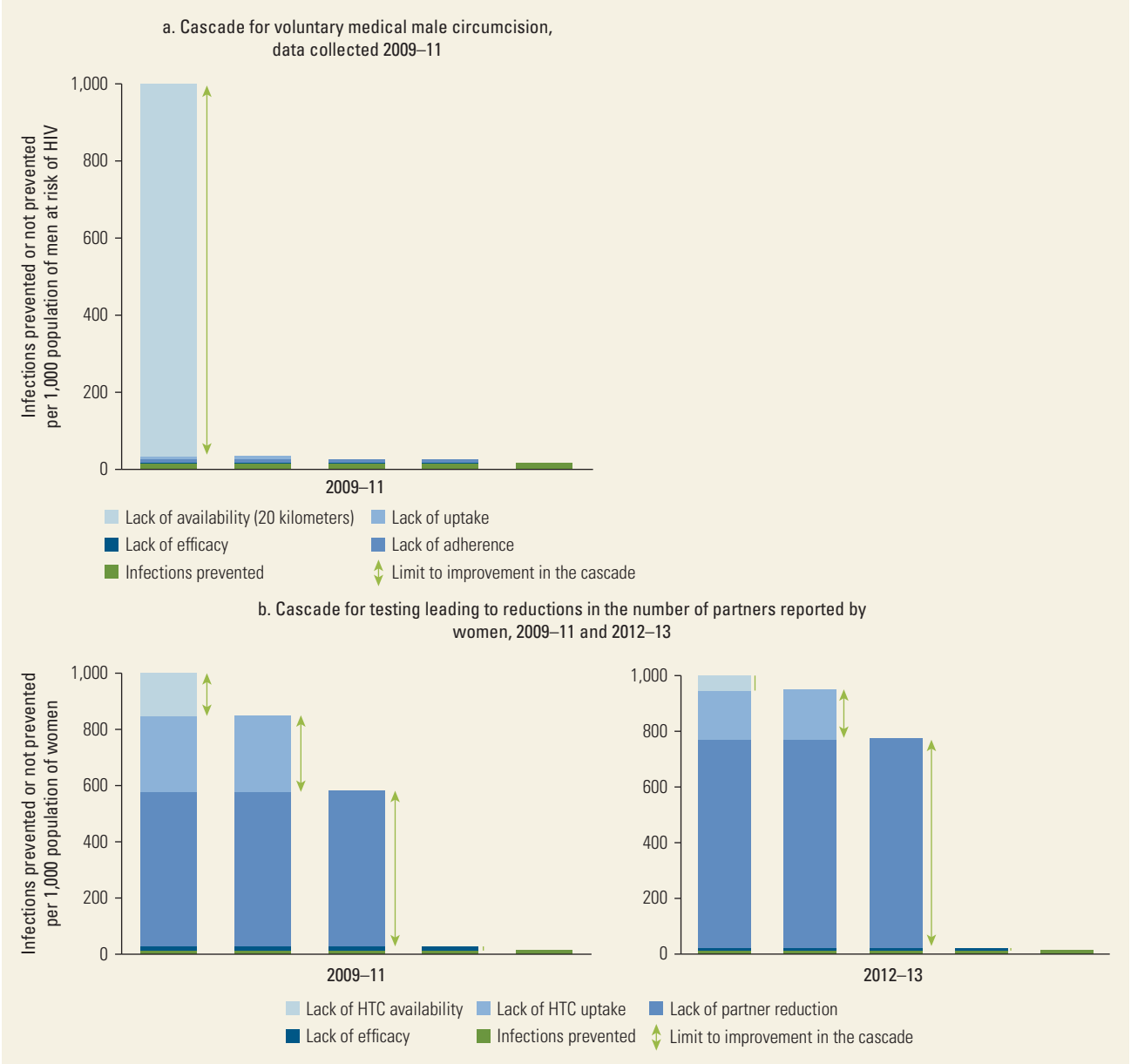
The cascade in panel b is for HIV testing and counseling (HTC), with a reduction in the number of partners as the direct mechanism for protecting women from infection. The cascade is shown for women in two periods, 2009–11 and 2012–13. The first step is small because most women have access to testing services, but many do not use them; this situation improves over time. The greatest fall-off in protection occurs because the vast majority of women tested do not reduce the number of sexual partners, which suggests that HTC services will have little impact on HIV acquisition through this mechanism.

COSTS OF HIV PREVENTION

To understand the cost-effectiveness of HIV prevention interventions and how to budget for them, the costs of delivering the interventions have to be known. A literature search yielded 2,151 references, of which 66 were relevant. These papers varied in the interventions costed, the types of costing undertaken, the analyses performed, and the ability to link cost to effectiveness. Finding comparable, well-documented costing of interventions linked to outcomes is challenging. Walker (2003) found that many interventions were not covered, costs were inadequately described, and impact was rarely measured. In another systematic review, Galárraga and others (2009) found that HIV prevention was extremely cost-effective compared with treatment, but effectiveness was rarely measured, there was a gap in examining bundles of prevention interventions, and synergies were not included.

Avenir Health maintains a database of HIV intervention costs from 1993 to the present (Avenir Health 2016). UNAIDS (Joint United Nations Programme on HIV/AIDS) uses this database to estimate resource needs

Figure 7.5 Prevention Cascades from Rural Zimbabwe



Source: Garnett and others 2016.
Note: HTC = HIV (human immunodeficiency virus) testing and counseling.

(Hecht and others 2010). A large fraction of the costs in the database was gathered from regional experts in a series of workshops. The interventions reporting costs tend to be delivered in health facilities—PMTCT, VMMC, and HTC. This last intervention, HTC, is mostly geared toward diagnosing HIV-infected individuals; however, if testing and counseling attempt to reduce risky behaviors, the intervention could be considered preventive. The evidence suggests that persons who are HIV-positive do alter their behaviors, while those who are HIV-negative do not (Hallett and others 2009). Other findings are that India has the most data on costs of HIV prevention, costs are often given per person reached, costs are generally for specific programs rather than the whole system, and costs decline over time (Avenir Health 2016).

Two international studies costing HIV prevention nearly a decade apart had similar findings: extreme heterogeneity in unit costs across sites and possibility of economies of scale in delivery (Bautista-Arrendondo and others 2015; Marseille and others 2007). One study examined the costs of voluntary counseling and testing;

male circumcision; PMTCT; risk reduction for people who inject drugs; risk reduction for sex workers; treatment of STIs; information, education, and communication; condom social marketing; and school curricula in India, Mexico, the Russian Federation, South Africa, and Uganda in 2003 and 2004 (Marseille and others 2004). The majority of costs measured were for "people reached," except for voluntary counseling and testing and for circumcision. Costs for the former varied 40-fold in Uganda and 2.5-fold in South Africa without adequate explanation. Programs showed efficiencies of scale, but the proportion of variation differed greatly between countries.

The other study examined the costs of HTC, PMTCT, and VMMC in Kenya, Rwanda, South Africa, and Zambia between 2011 and 2013 (Bautista-Arrendondo and others 2015; Sosa-Rubí and others 2015). For facilities carrying out HTC, a 10 percent increase in scale was associated with a 5.8 percent reduction in costs. For facilities carrying out VMMC, a 10 percent increase in procedures was associated with a 41 percent reduction in costs, and an increase in procedures was positively correlated with quality as measured in exit interviews. The main focus of both studies was efficiency. However, measuring the quality and impact of services is difficult, but necessary to determine efficiency, since lower costs could otherwise be offset by reduced effectiveness.

Extensive costing of HIV prevention service delivery was carried out between 2004 and 2008 as part of the Bill & Melinda Gates Foundation's Avahan Program in India. In this program, costs of prevention services depended on the scale of support provided to nongovernmental organizations, extent of community involvement, and organization of clinical services (Lépine and others 2016). A model-derived estimate of impact found a mean incremental cost of US$785 per HIV infection averted and US$46 per disability adjusted life-year (DALY) averted (Vassall and others 2014).

Based on RCT results for adult male circumcision, the WHO promoted the scale-up of circumcision programs in 14 Sub-Saharan African countries, leading to more than 9 million circumcisions (WHO 2015c). The circumcision programs allowed costs to be estimated across countries and across models of circumcision, including shifting tasks from doctors to nurses, using models to improve client flow, and using circumcision devices. In six countries, Bollinger and others (2014) found that the cost per circumcision varied between US$22 and US$70 (table 7.2). This finding is in line with estimated cost per circumcision used in exploring the cost-effectiveness of VMMC.

Cost-Effectiveness Analysis

In the Avahan program, the number of HIV infections averted was derived by comparing observed prevalence with a modeled counterfactual representing HIV spread without the intervention and self-reported increase in condom use among sex workers (Vassall and others 2014). Often the modeled effectiveness of interventions compares modeled incidence with and without the intervention; this is especially true of interventions using products in development and before scale-up. For prevention interventions, effectiveness is best established for VMMC and PrEP, the direct mechanisms with the most meaningful cost-effectiveness analyses.

Models were used to demonstrate that circumcision would be a cost-saving intervention where circumcision rates are low and HIV incidence is high. In a systematic review of circumcision cost-effectiveness, costs per HIV infection averted varied from US$174 to US$2,808 (Uthman and others 2010). In a subsequent analysis, Njeuhmeli and others (2011) found that circumcision would generate net savings, with predicted costs per

Table 7.2 Costs of Adult Male Circumcision in Six Sub-Saharan African Countries

Country	Period	Number of facilities	Number of circumcisions per facility	Average costs, 2012 US$ PPP
All		99	750 (average)	$49
Kenya	March 2010	29	743	$38
Namibia	April–May 2006	8	35	$31
South Africa	April 2008–March 2009	9	3,828	$22
Tanzania	2010–11	18	1,914	$70
Uganda	June–July 2009	26	286	$30
Zambia	2010	9	308	$61

Source: Bollinger and others 2014.
Note: PPP = purchasing power parity.

infection averted over the period 2011–25 varying from US$442 in Lesotho to US$4,096 in Rwanda.

The cost-effectiveness of oral PrEP in models is much less clear because it depends on assumptions made about HIV incidence, costs of the program, and coverage of the PrEP. In a systematic review of models of oral PrEP, the cost per infection averted in a generalized HIV epidemic varied from cost saving to US$39,900 (Gomez and others 2013).

Other cost-effectiveness analyses are of dubious validity because they depend upon assumed effectiveness. Topical PrEP (since found ineffective) was estimated to cost between US$18 and US$181 per DALY averted and between US$1,800 and US$2,700 per life year saved, with the major differences being due to assumptions about costs. Subsequent analyses for tenofovir gel estimated a cost of less than US$300 per DALY averted (Terris-Prestholt and others 2014), assuming effectiveness. Similarly, the incremental cost-effectiveness for an HIV vaccine, also assuming effectiveness, was US$43 per DALY averted (Moodley, Gray, and Bertram 2016). A study of female condom program modeling found a low of US$107 per DALY averted in Zimbabwe and a high of US$303 per DALY averted in Mozambique, assuming that condoms would be used and would be effective (Mvundura and others 2015).

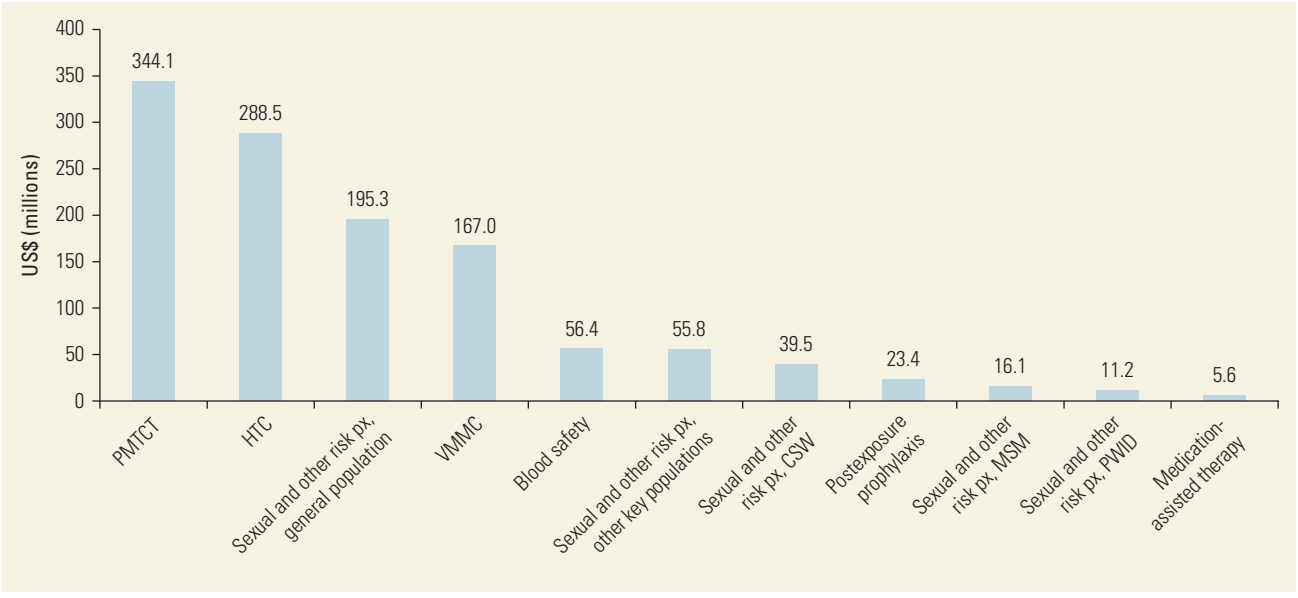
Expenditure Analyses

The unit costs assumed in models and estimated from programs are substantially different from the resources expended on programs.

Analyses of expenditure indicate what programs are costing and what interventions are being prioritized by policy makers. PEPFAR has made expenditures available online, but expenditure by one donor does not describe the full expenditure on a program in a country. An estimated US$4.5 billion was spent on HIV prevention in low- and middle-income countries in 2012, with PEPFAR providing US$1.6 billion of this from its total expenditure of US$4.5 billion (UNAIDS 2015). Figure 7.6 shows the distribution of PEPFAR expenditures for HIV prevention in fiscal year 2013, excluding treatment as prevention. The largest fraction of spending was on PMTCT and HTC.

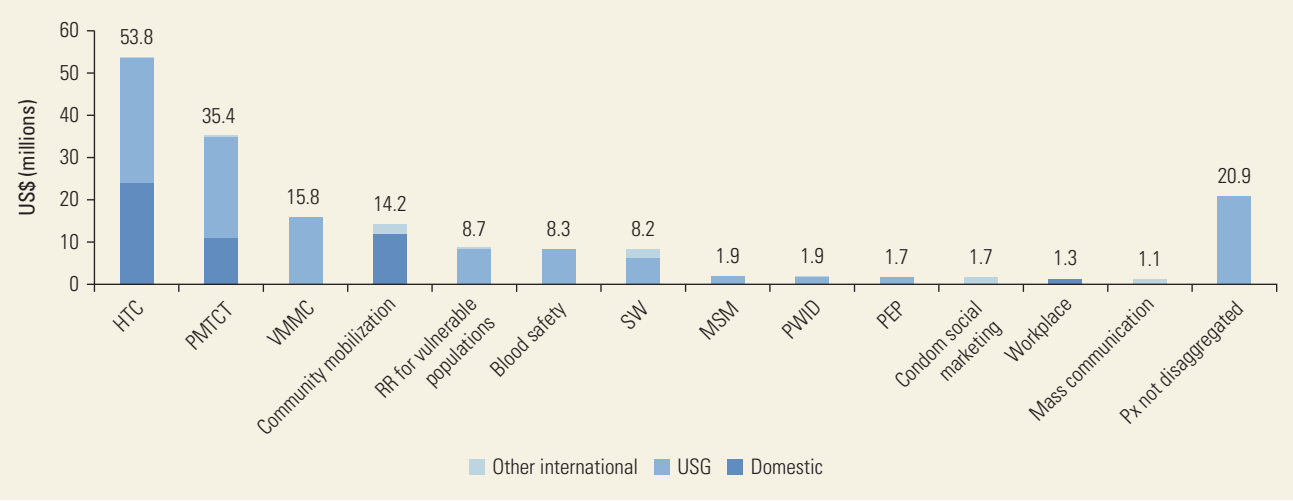
With the addition of country spending, we can focus on one country with complete expenditure data. Such data are rarely available, but have been compiled in Kenya (figure 7.7) and show that the majority of domestic HIV prevention resources (which excludes treatment as prevention) are deployed for HTC and PMTCT, and the proportion allocated to HTC and PMTCT was even greater than the proportion of all PEPFAR prevention expenditures in 19 countries on PMTCT and HTC.

Figure 7.6 PEPFAR Expenditure on HIV Prevention across Selected Countries, by Category of Prevention, 2014



Source: PEPFAR (President's Emergency Plan for AIDS Relief) 2014, Data Dashboard, http://www.pepfar.gov/funding/c63793.htm, accessed March 31, 2015.
Note: CSW = commercial sex workers; HIV = human immunodeficiency virus; HTC = HIV testing and counseling; MSM = men who have sex with men; PEPFAR = President's Emergency Plan for AIDS Relief; PMTCT = prevention of mother-to-child transmission; PWID = persons who inject drugs; px = prevention; VMMC = voluntary medical male circumcision. Includes 17 countries in Sub-Saharan Africa, Haiti, and Vietnam.

Figure 7.7 Expenditure on HIV Prevention for Kenya, by Category of Prevention, 2012



Sources: PEPFAR (President's Emergency Plan for AIDS Relief) 2014, Data Dashboard, http://www.pepfar.gov/funding/c63793.htm, accessed March 31, 2015; Kenya National AIDS Spending Assessment 2014, http://files.unaids.org/en/media/unaids/contentassets/documents/data-and-analysis/tools/nasa/20141017/kenya_2011_en.pdf, last accessed October 19, 2016.
Note: HIV = human immunodeficiency virus; HTC = HIV testing and counseling; MSM = men who have sex with men; PEP = postexposure prophylaxis; PMTCT = prevention of mother-to-child transmission; PWID = persons who inject drugs; Px = prevention; RR = risk reduction; SW = sex workers; USG = United States government; VMMC = voluntary medical male circumcision.

Because of the limited data on effectiveness for interventions other than PMTCT, VMMC, and oral PrEP (which has only recently been recommended), this expenditure may be appropriate. It does illustrate that few funds are being spent on the prevention interventions with a weak evidence base or even on those that are likely efficacious in preventing transmission and that the largest proportion of prevention funding is spent on HTC as an entry to treatment.

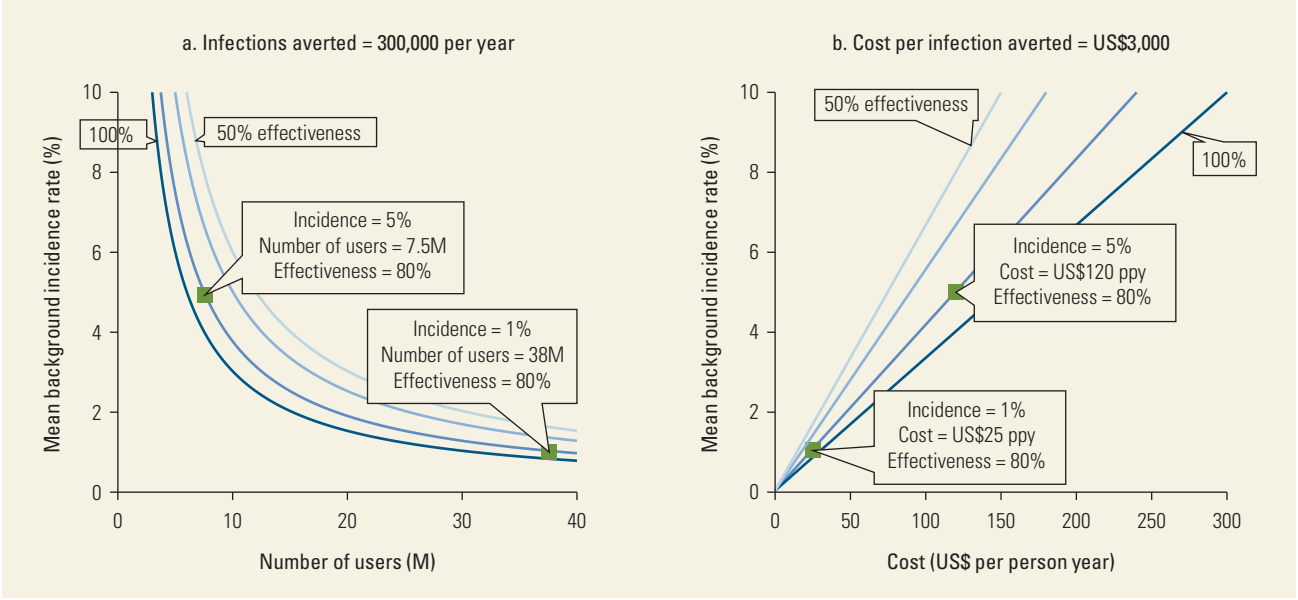
TARGETING HIV PREVENTION

The relationship between expenditure and health benefit is straightforward for treatment interventions. In comparison, the cost-effectiveness of interventions for prevention depends on the risk of acquiring infection and disease. This risk can vary across individuals and populations and over time, making a single measure of cost-effectiveness nonsensical. Simply viewed, prevention interventions will be more cost-effective the higher incidence would otherwise be. However, changes in individual- and population-level risk as a function of coverage and intensity greatly complicate the relationship between costs and benefits, especially with the cost-effectiveness of one intervention depending on the success of other interventions. This relationship has been challenging in modeling the impact of prevention, where if coverage of treatment as prevention is assumed to be high and effective, other prevention interventions have a smaller role to play (Stover and others 2014).

The more that prevention interventions can focus on persons who would otherwise acquire or spread infection, the more cost-effective they can be: targeting should increase cost-effectiveness. However, effectiveness is not the same as impact. As interventions target progressively fewer, higher-risk individuals, they may become more cost-effective but have less impact. Taking into account the full cost of developing and implementing programs, this lack of impact could lower the attractiveness of investments in programs to develop and use new prevention products.

This sequence can be illustrated by exploring what would be required to avert 20 percent of HIV infections using approximately 20 percent of the HIV prevention budget (figure 7.8). Assuming that there are 1.5 million new infections each year, US$4.5 billion is spent on prevention (UNAIDS 2015), the goal explored is to reduce new infections by 300,000, and the budget is US$0.9 billion, it is possible to explore, for different effectiveness, the relationship between incidence in the target population and the number of people who would have to be covered. To achieve a given impact goal with a budget, there is a trade-off between how well the intervention can be focused and the resources available per person reached; the higher the incidence, the more could be spent per person in the program. Figure 7.8a shows how many people at a given HIV incidence would need to be reached to avert 300,000 infections; figure 7.8b shows the cost per person reached with prevention allowable, if the cost per infection averted is to be US$3,000.

Figure 7.8 Isoclines Showing the Values Required to Achieve Target Reductions in HIV Infections and Costs of Infection Averted



Note: HIV = human immunodeficiency virus; M = millions; ppy = per person year. In panel a, to avert 300,000 infections, the lines show effectiveness of 50, 60, 80, and 100 percent for direct mechanisms of prevention; the number of users in millions; and a given incidence of infection. In panel b, to achieve a cost per infection averted of US$3,000, the lines show effectiveness of 50, 60, 80, and 100 percent for direct mechanisms of prevention; the required cost per person year; and a given incidence of infection.

Better targeting of HIV prevention to persons with a high incidence of acquisition or transmission makes the intervention more cost-effective, but this invites the questions of how to target and what impact is possible.

CONCLUSIONS

Prevention has probably averted many millions of HIV infections, but it is impossible to be sure how many, given the difficulties of knowing what the scale of spread would have been in the absence of behavior changes among those at risk. Despite the scale-up of effective treatment, which can contribute to HIV prevention, other prevention interventions are needed, but which ones? HIV prevention should be a cost-effective intervention, but 35 years into the global HIV pandemic, large questions remain about which prevention programs are effective, how best to implement them, and how much should be spent on them. A fundamental problem is identifying those who are at risk and then ensuring that they adopt preventive behavior.

Large gaps are evident in the supply of prevention interventions. Furthermore, data on effectiveness are available for only a few direct mechanisms. Evidence of effectiveness exists for VMMC and oral PrEP, and it is logical that using condoms and having fewer partners will reduce risk. Costing data for HIV prevention, except for VMMC, are also unavailable. When appropriately targeted, HIV prevention will, at most thresholds, be cost-effective, but that cost-effectiveness will depend on the other interventions in use and the ability to target interventions appropriately.

What resources should be used for HIV prevention and what should they be used for? Two prevention products—VMMC and oral PrEP—conservatively should reduce HIV incidence by 50 percent; using condoms and having fewer partners could have similar effectiveness. However, products are not interventions. Interventions need to get people to use the products, and resources need to be directed to this effort.

An HIV infection costs either decades of lost life or decades of expense on treatment. If an infection causes 20 DALYs and averting 1 DALY is "worth" US$500, then an infection prevented is worth US$10,000. Alternatively, if treating someone for 20 years would cost US$500 per year, then treating an infection would cost US$10,000. So if it is possible to prevent half of the infections with current products and HIV incidence is 10 percent, we should be spending US$500 per person per year on prevention. If HIV incidence is 1 percent, we should be spending US$50 per person per year. If HIV incidence is 0.1 percent, we should be spending US$5 per person per year. Alternatively, if there are 2 million HIV infections per year, we should be spending at least US$5 billion per year. By any account, the world is falling well short of providing what is needed for HIV prevention.

NOTE

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  (a) lower-middle-income = US$1,046 to US$4,125
  (b) upper-middle-income (UMICs) = US$4,126 to US$12,745
- High-income countries (HICs) = US$12,746 or more.

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