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Modeling and Cost-Effectiveness in HIV Prevention

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Abstract

With HIV funding plateauing and the number of people living with HIV increasing due to the roll-out of life-saving antiretroviral therapy, policy makers are faced with increasingly tighter budgets to manage the ongoing HIV epidemic. Cost-effectiveness and modeling analyses can help determine which HIV interventions may be of best value. Incidence remains remarkably high in certain populations and countries, making prevention key to controlling the spread of HIV. This paper briefly reviews concepts in modeling and cost-effectiveness methodology, then examines results of recently published cost-effectiveness analyses on the following HIV prevention strategies: condoms and circumcision, behavioral or community-based interventions, prevention of mother to child transmission, HIV testing, pre-exposure prophylaxis, and treatment as prevention. We find that the majority of published studies demonstrate cost-effectiveness; however, not all interventions are affordable. We urge continued research on combination strategies and methodologies that take into account willingness to pay and budgetary impact.

Keywords

HIV; prevention; cost-effectiveness; modeling

Introduction

UNAIDS estimates that in 2013, global funding toward the HIV/AIDS epidemic from all sources, including public spending as well as philanthropic aid, totaled over $19 billion [1]. This expenditure has had an enormous impact on the epidemic – curbing AIDS-related mortality and reducing new HIV infections – and yet HIV remains a major disease in the world. Despite this massive investment, UNAIDS also estimates that this funding falls well short of that required to treat all who meet treatment guidelines and to prevent infection in those at high risk [1].With inadequate funds and international contributions plateauing [1], policy makers must consider where and how to invest the limited available funds. Cost-effectiveness analysis is a useful method for comparing interventions to determine their clinical and economic value. In this paper, we focus on recently published cost-effectiveness analyses that examine various HIV prevention interventions.

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Cost-Effectiveness Analysis

Cost-effectiveness analysis is a method for evaluating costs and health outcomes of interventions that allows the relative value of different interventions to be compared [2]. **While** policy makers use cost-effectiveness analyses to assist in understanding what interventions might provide the best value for money [3], cost-effectiveness analyses – and their related sensitivity analyses – also provide important additional information such as clinical, epidemiologic, and/or economic benchmarks for interventions to achieve cost-effectiveness. If an intervention is not cost-effective under current conditions, analyses can project under what conditions it might become so. The Commission on Macroeconomics and Health of the World Health Organization asserts the international standard for determining whether an intervention is cost-effective is a country's Gross Domestic Product (GDP) *per capita*: a program that has an incremental cost-effectiveness ratio ([ICER] in $/ disability-adjusted life year [DALY] averted) of less than 3x the GDP *per capita* of a given country is considered cost-effective; and less than 1x the GDP per DALY averted is considered very cost-effective [4]. While this threshold takes into account the varied economies of different countries, it is a poor indicator of a country's willingness and ability to pay for healthcare. For example, South Africa's GDP *per capita* is approximately $6,500 and thus an intervention costing $19,500 or less for one DALY averted would be considered cost-effective according to international standards [5]. However, South Africa's healthcare budget can likely not accommodate that cost for a single averted DALY for its population of 53 million [6]. Country-specific GDPs also provide poor guidance in the case of outside partners – like the Global Fund to Fight AIDS, Tuberculosis and Malaria and the President's Emergency Plan for AIDS Relief (PEPfAR) – which pool support toward treatment and prevention efforts. As such, the international community is collectively moving towards defining new thresholds of cost-effectiveness that better account for a country's true ability to pay for health care [7].

Discounting

Discounting is a recommended component of cost-effectiveness analyses; convention in the United States is to employ an annual discount rate of or around 3% [2]. Discounting accounts for time preference of resources (and health); that is, we would prefer resources (and health) today over having them in the future. For consistency, both costs and health benefits need to be discounted simultaneously and at the same rate. The concept of discounting is critically important for prevention interventions which require upfront investments (and therefore are *not* subject to substantial discounting) to realize future gains in life expectancy. For example, an intervention that has a one-time cost of $10,000 today and averts 1 DALY 30 years from now might seem like a good investment with a cost-effectiveness ratio of $10,000/DALY averted. However, if we discount the DALY by an annual rate of 3%, we find that one DALY 30 years from now is only worth 0.41 DALYs, and the cost-effectiveness ratio becomes $24,400/DALY averted. It is recommended that analyses report results as discounted and undiscounted, with sensitivity analyses on the discount rate, to account for this important effect of discounting [2].

Modeling

A variety of model types are used in cost-effectiveness studies, including decision trees; deterministic and Markov models; dynamic and static models; and individual-based and population-based models. The models are used in different ways to appropriately answer different questions. Not all models are suited to address all questions so it is important to understand whether the best model has been chosen for the area of interest. Decision trees are the simplest form of decision-analytic models and are suited for scenarios that examine single events over a short period; time is not considered. Markov and deterministic models are better suited for projecting numerous events over a lifetime horizon; time – represented as model-cycle length – is an essential component. Decision trees and Markov models are commonly used in cost-effectiveness modeling studies because of their ability to track both specific clinical events and the resources associated with those events. Static and individual-based models excel at projecting clinical events over the lifetime of unique patients who retain their clinical trajectory history. Dynamic and population-based models are most often used to model transmission and to project population-level changes in incidence and prevalence over long horizons. The studies presented in this paper utilize many of these different model types.

HIV Prevention Interventions

We conducted a targeted review of recently published articles on HIV prevention, modeling, and cost-effectiveness analysis, limiting our search on PubMed from October 2013 to September 2015. We categorized studies into the six main areas of HIV prevention that follow. We note that while standards in cost-effectiveness suggest results should be denominated in $/DALY averted or $/quality-adjusted life year (QALY) gained, many HIV prevention studies report results in $/infection averted. While there is no “acceptable” threshold for what one should be willing to pay to avert an infection, we can use these ratios in comparison with one another to examine comparative value.

Circumcision & Condoms

Circumcision and condoms are effective, inexpensive interventions that do not require extensive resource allocation in the form of drugs, clinic visits, and health workers. Results consistently demonstrate that these interventions are some of the most cost-effective and affordable interventions available in HIV prevention.

Few studies have been published in the last two years on the cost-effectiveness of circumcision as HIV prevention techniques. A systematic review published in 2010 on the cost-effectiveness of circumcision in sub-Saharan Africa found the cost per infection averted ranged from $174-$2,808 [8]. Since that meta-analysis, a more recent study based in Tanzania estimated the cost per infection averted for voluntary medical male circumcision was reduced from $11,300 in the first 5 years of scale-up to $3,200 in subsequent years [9].

More studies have continued to demonstrate the value of condom promotion programs. A study on the cost-effectiveness of Vietnam’s HIV programs, found condom promotion to be very cost-effective for high-risk populations with costs ranging from $103-$302/DALY averted [10]. In a Nigerian study, condom promotion was estimated to be the most cost-

effective strategy for HIV prevention in serodiscordant couples (ICER $1,206/DALY averted), followed by the addition of treatment as prevention (ICER $1,607/DALY averted) and then the addition of pre-exposure prophylaxis (ICER $7,870/DALY averted) [11]. A study examining the benefits of the woman's condom in sub-Saharan Africa found costs ranging from $107-$303/DALY averted, depending on the volume of demand and the country context [12].

Behavioral or Community-Based Interventions

Female sex workers (FSW) and injecting drug users (IDUs), in addition to men who have sex with men (MSM), remain at particularly high risk of HIV infection around the globe [13]; behavioral interventions focus on harm reduction in these high-risk populations. In the United States, a comparison of increasingly intensive behavioral interventions for women IDUs reported that inclusion of well-woman exams was cost-saving compared to current standards in terms of QALYs gained [14]. Another study examining HIV-infected IDUs in the United States reported risk-reduction and health promotion programs had cost-effectiveness ratios ranging from $7,707 to $24,072/QALY gained [15]. In India, the comprehensive Avahan program for FSWs, which includes condom distribution, peer outreach, education, and treatment of sexually transmitted infections (STIs), had a mean ICER of $46/DALY averted at an incremental cost of $785/HIV infection averted when assessed at scale in 22 districts [16]. Adding community mobilization and empowerment to the program came at an incremental cost of approximately $14/DALY averted [17].

Prevention of Mother to Child Transmission

In 2013, the World Health Organization (WHO) released updated guidelines on the prevention of mother to child transmission (PMTCT) of HIV, recommending a shift from Option A (prophylaxis for mothers and infants) to Option B (antiretroviral therapy [ART] to women while pregnant or breastfeeding) or Option B+ (lifelong ART to pregnant women) [18]. Multiple studies have evaluated these recommendations in low-income countries and concluded that they are cost-effective, if not cost-saving [19-22]. The cost per infant infection averted reported in these studies for Option B+ ranged from $1,400 to $23,000, depending on the country [19 - 22] and the cost per QALY gained of B+ compared to B was estimated at $785 in Ghana [19]. Among recent studies published, there is variation in outcomes: estimates by Gopalappa et al. were substantially higher than values reported in other studies in the same country. For example, in Zambia, the cost per infant infection averted was reported to be $1,406 by Ishikawa [21] and $6,780 by Gopalappa [20], and in South Africa the cost per infant infection averted was reported at $2,060 by Yu [22] and $23,000 by Gopalappa [20]. These discrepancies are likely due to assumptions made in the models, including breastfeeding duration, rates of ART coverage, ART cost, and whether the analysis included the impact on sero-negative partners (rather than just on mother-to-child transmission).

HIV Testing

Recent cost-effectiveness analyses are varied in scope for HIV testing interventions. In high-income countries such as the United Kingdom, annual targeted testing to MSM, IDUs, and people from HIV-endemic countries has been reported to prevent 4%-15% of infections and

require testing 2,500 people per HIV diagnosis, with an ICER of £17,500/QALY gained (~ $26,700, 2012 USD) [23]. Testing MSM more frequently (at 3 or 6 month intervals) is reported to be cost-effective and even cost-saving in some scenarios over a one-year period in the United States [24]. A study based in Zimbabwe quantified the potential savings in health care costs with HIV self-testing: while only 7,000 DALYs are averted over 20 years in a population of 7.5 million, the authors suggest the $75 million saved by self-testing might be used to avert further DALYs by investing this money in other highly cost-effective prevention or treatment interventions [25]. A study on home-based HIV testing and counseling (HTC) in South Africa estimated that home-testing yields a higher clinical impact than facility-based testing, with ICERs for home-testing ranging from $1,090-1,360/DALY averted, depending on the ART initiation criteria [26]. Another South African study found that adding a mobile testing unit to existing facility-based testing would result in a very cost-effective ICER of $2,400/year of life saved [27].

HIV screening during pregnancy is yet another cost-effective option: a study in China reported a cost of $5,636/DALY averted [28]. Enhanced partner notification after a positive HIV test can also be a cost-effective means of preventing new HIV infections. A study in Malawi compared provider and contract notification with passive referral; contract notification had an ICER of $3,560/transmission averted compared to passive referral and provider notification had an ICER of $51,421 compared to contract notification [29]. HIV testing, whether it is routine, self-testing, home-based, or via a mobile unit consistently proves throughout literature to be a cost-effective prevention method in a variety of settings.

Pre-Exposure Prophylaxis (PrEP)

Oral PrEP was approved by the Food and Drug Administration (FDA) for use in the United States in 2012 [30]. Since then, research teams have conducted several **open-label** trials around the world to determine the real-world effectiveness of PrEP, with very mixed results. With **randomized and open-label** trials reporting PrEP **efficacy and effectiveness values** ranging from 0% to 92% [31-37], cost-effectiveness studies are examining in what settings and in what populations PrEP is a worthy investment.

In developed countries, several studies have previously been published supporting the cost-effectiveness of PrEP as a prevention strategy, especially among MSM and other high-risk populations [38-41]. The focus of recent modeling studies is largely on prioritizing and targeting PrEP to achieve the greatest value for the investment. In New York, a modeling study examined 12 different strategies of PrEP prioritization to MSM, IDUs, and/or heterosexuals. This study found that PrEP can confer nearly 80% of clinical benefits at 15% of the cost if prioritized only to high-risk MSM, who constitute 3% of the model population [42]. Another US-based study estimated that if PrEP is provided to all MSM in the country, the cost per QALY gained is $160,000, a value that can be reduced to $3,000/QALY gained if used with high adherence in high prevalence settings [43].

An Australian-based study found that PrEP targeted to MSM in serodiscordant relationships was cost-effective (ICER $8,400-11,575 Australian dollars [~$7,790-10,740 USD, 2013]), whereas PrEP to all MSM or targeted to high-risk MSM was not cost-effective in the Australian context [44]. A study on IDUs in Ukraine compared PrEP with methadone

maintenance programs and with ART. Strategies with PrEP alone were dominated by strategies containing methadone maintenance with or without ART. Compared with a methadone maintenance and ART program, the addition of a PrEP strategy had a cost-effectiveness ratio of $1,700/QALY gained (at 25% PrEP coverage) [45]. A French analysis assessing reproduction strategies for serodiscordant couples determined that PrEP targeted to fertile days is more effective compared to treatment as prevention and unprotected sex during fertile days, but has an unfavorable ICER of €1,130,000 (~$1,492,000 in 2013 USD) [46].

Analyses in resource-limited settings are concentrated in sub-Saharan Africa and examine PrEP use in larger portions of the population: serodiscordant couples, heterosexual women, and migrant workers. Given the range of settings and assumptions made in model parameters, estimates for ICERs range from cost-saving to approximately $10,000/DALY averted, to $71,400 per infection averted [47-52]. Microbicide gels used by women on a per sex-act basis have one of the lowest reported ICERs with $297/DALY averted in South Africa, assuming 54% efficacy in HIV prevention and use in 72% of sex acts [47]. Another study examined both PrEP and ART scale-up; it suggests universal ART is the most cost-effective strategy and that oral PrEP with 60% efficacy provided to all HIV-uninfected adults in South Africa would provide few benefits beyond ART scale-up, but that PrEP focused to the highest risk individuals could be cost-saving compared to the status quo [48]. In serodiscordant couples, an estimated ICER for PrEP plus increased ART coverage in Uganda is $5,354/DALY averted [49], and in South Africa a similar intervention – with inclusion of ART initiation among eligible serodiscordant partners – has an ICER of $10,383/DALY averted [50]. A Mozambique-based study examined PrEP for partners of migrant miners; the cost per infection averted was $71,374 for year-long PrEP and was reduced to $9,538 if limited to a six-week high-risk period when the miners return home [51].

Model input parameters in cost-effectiveness studies on PrEP are widely varied across countries and target populations, making it difficult to accurately compare studies. Yet most studies have concluded that PrEP is cost-effective in their targeted population if properly administered with high adherence. While PrEP may be cost-effective, it is also important to consider the budget feasibility of the modeled programs. PrEP would require enormous upfront costs, especially if scaled-up to reach substantial proportions of the high-risk individuals in need. A study comparing ART expansion and PrEP in Zambia estimated that over the next 40 years $20 million would be needed to treat HIV at ART initiation thresholds of CD4≤350 cells/μl; PrEP, they found, should only be considered if the budget exceeds $180 million for that period, an unlikely occurrence [53]. Given the state of current HIV funding, while most studies demonstrate cost-effectiveness, few resource-limited settings are likely able to afford large-scale PrEP programs.

Treatment as Prevention (TasP)

TasP has emerged in recent years as a leading ideal in HIV prevention due to its combined public health (HIV prevention) and individual health (HIV treatment) benefits. The HPTN052 clinical trial published in 2011 proved that ART provision for an HIV-infected

individual could successfully prevent infection in the individual's seronegative partner [54]. More recently, in both the TEMPRANO and START Trials, the individual health benefits of early ART have also been definitively demonstrated [55, 56]. A cost-effectiveness analysis based on the HPTN052 trial results found TasP to be a very cost-effective method of HIV prevention if provided to all serodiscordant couples [57]. In South Africa, the ICER over a lifetime horizon was only $590 per year of life saved and in India it was $530 per year of life saved. Importantly, these results excluded the costs of case identification and the frequent testing required to identify participants with high CD4 counts. Results of a different study implementing TasP for all HIV-infected adults in South Africa were also very cost-effective with an ICER between $160-$220/QALY gained and more favorable than providing PrEP to the HIV-negative population (also noted above) [48]. A study based in Uganda found expanding ART to 55% of serodiscordant couples resulted in an incremental cost per infection averted of $1,452 [49]. A Zambian study comparing TasP (ART at CD4 <500 cells/μl) to scenarios of PrEP use in general-risk HIV-uninfected individuals found that expanding ART was the only cost-effective option (ICER $62/QALY gained) [53].

Conclusions

In our targeted review of the literature on the cost-effectiveness of HIV prevention interventions over the last two years, we find that few HIV preventions analyses are reported to be not cost-effective. When examined in isolation, condoms and circumcision, behavioral interventions, prevention of mother to child transmission, PrEP, HIV testing, and TasP are all likely to be considered cost-effective by current international standards (reliant on 3x and 1x a country's GDP *per capita*). These standard thresholds for cost-effectiveness may soon change, making it more difficult to "meet" the threshold.

When interpreting the results of cost-effectiveness analyses, it is important to keep in mind the heterogeneity between models. Model inputs, structure, assumptions, and methodologies can vary greatly among studies. For example, a model of PrEP in sub-Saharan Africa could consider PrEP use for 25% or 100% of a population; it could also assume a high-risk or a general target population. These assumptions made by the modeler can have large effects on the results. A critical reader of these models needs to keep these types of assumptions in mind and pay special attention to input values and methodologies before comparing across studies.

Cost-effectiveness analysis determines if an intervention is of good value, however, it does not determine if it is affordable. HIV prevention is clearly an admirable aspiration; such interventions promote long-term health benefits and the opportunity to avert downstream HIV care costs. However, this objective is stymied by the limited HIV budgets governments and agencies are facing around the world. Prevention requires upfront costs with benefits that do not payout for many years, making it difficult for policy makers to commit to or obtain the upfront investment required. Further, most policy makers are motivated by and committed to meeting short-term budget constraints. A prevention intervention can be simultaneously cost-saving over a lifetime horizon and yet entirely economically infeasible today.

Cost-effectiveness analyses on HIV prevention are helpful for prioritization, but they would be even more valuable if they also assessed affordability **of and feasible resource allocation for** interventions examined. Two models were recently developed specifically to aid policy-makers with optimization of resource allocation and investment in different strategies given certain budget restrictions. Juusola and Brandeau designed a model to help decision makers determine the most advantageous investment in HIV treatment versus prevention for a population [41]. Kerr et al. developed a model (Optima) that allows the user to specify certain program or spending objectives and then to determine the best resource allocation to meet those objectives [58]. For example, a user can define the program objective as “minimize HIV incidence by 2020” or “minimize resources needed to achieve a 15% reduction in HIV incidence.” These models are important steps towards helping policy makers allocate available funding effectively and economically.

The WHO recently raised recommended ART initiation thresholds to ART for all persons with HIV [59] and as governments continue to build ART programs, TasP is slowly becoming a reality. However, the success of a TasP program depends on early identification through comprehensive testing programs to identify undiagnosed HIV-infected people, patient retention and adherence on ART, and available finances for full scale-up of ART coverage. All these areas will need substantial investments to accomplish the dual HIV prevention/treatment benefits of “treatment as prevention” at the level of cost-effectiveness predicted by modeling studies. Given limited budgets, policy makers will need to strategically prioritize resource allocation for all facets of TasP and the care cascade to achieve maximum impact [60]. This will involve deliberate investments in the most economically efficient components of outreach, routine testing, and comprehensive ART programs.

As countries work towards establishing these comprehensive TasP programs, prevention interventions will continue to merit funding. Cost-effectiveness analyses should continue to look at prioritization of resource allocation for current prevention, testing, treatment, and retention strategies, while also examining the potential cost-effectiveness of novel interventions. Research on combination strategies and methodologies that take into account willingness to pay and budgetary impact will be key as we move towards universal treatment of HIV-infected individuals.

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Table 1

Cost-effectiveness analyses on circumcision, condom and behavioral/community-based HIV prevention strategies

Title	Model Type	Strategy	Results		
			$/Infection averted	**$/QALY gained or $/DALY averted[1]**	**Other**
Circumcision & Condoms					
Costs and impacts of scaling-up voluntary medical male circumcision in **Tanzania** [9]	Decision-Makers' Program Planning Tool	Circumcision scale-up to 88% coverage	$3,200-11,300 depending on time horizon	Not reported (2010 USD)	Avert 190,500 infections over 15 yrs
Estimating the cost-effectiveness of HIV prevention programs in **Vietnam**, 2006-2010: a modeling study [10]	Optima [58] dynamic, population based	Determine cost-effectiveness of condom promotion	$360 for MSM $1,061 for FSW	$103/DALY averted for MSM $302/DALY averted for FSW (2015 USD*)	ART cost $3,186/infected averted and $164/DALY averted
Modelling the impact and cost-effectiveness of combination prevention amongst HIV serodiscordant couples in **Nigeria** [11]	Deterministic, compartmental, cohort	Compare condom promotion, PrEP, and TasP in serodiscordant couples	Not reported	ICER $1,206/DALY (2012 USD)	ICER of adding TasP ($1,607/DALY), and short-term PrEP ($7,870/DALY)
Estimating the hypothetical dual health impact and cost-effectiveness of the Woman's Condom in selected **sub-Saharan African** countries [12]	Impact 2 (Marie Stopes Intl) PSI DALY calculator	Distribute 100,000 woman's condoms to each country during a 1-year period	Not reported	$107-303/DALY averted depending on country and condom cost (2012 USD)	Prevent on average 21 HIV infections and 194 pregnancies per country
Behavioral or Community-Based					
Cost-effectiveness of interventions to prevent HIV and STDs among women: a randomized controlled trial (**United States**) [14]	Bernoullian mathematical	Comparison of three increasingly intensive behavioral interventions for IDU women	$50,774-208,316 depending on intervention	Well-woman exam is cost-saving and dominates other strategies (2014 USD*)	Well-woman exam also most cost-effective for preventing STDs
Cost-effectiveness analysis of brief and expanded evidence-based risk reduction interventions for HIV-infected people who inject drugs in the **United States** [15]	Dynamic compartmental transmission	Compare two behavioral interventions for HIV-infected IDUs to the status quo	Not reported	$7,707-24,072/QALY gained depending on strategy (2015 USD*)	Avert 19,000-74,000 infections depending on strategy and coverage
Cost-effectiveness of HIV prevention for high-risk groups at scale: an economic evaluation of the Avahan programme in south **India** [16]	Population-level dynamic compartmental	Estimate impact and cost of scale-up of a combination behavioral intervention for MSM and FSW	$785	$46/DALY averted (2011 USD)	ART savings as a result of the program would be $77 million

Title	Model Type	Strategy	Results		
			$/Infection averted	$/QALY gained or $/DALY averted[1]	Other
Community mobilisation and empowerment as part of HIV prevention for female sex works in southern **India**: a cost-effectiveness analysis [17]	Population-level dynamic compartmental	Add community mobilization and empowerment to core HIV prevention services	$230	$14/DALY averted (2011 USD)	Cost-saving if include ART costs

QALY: quality-adjusted life year; DALY: disability-adjusted life year; USD: United States dollars; yr: year; MSM: men who have sex with men; FSW: female sex workers; ART: antiretroviral therapy; PrEP: pre-exposure prophylaxis; TasP: treatment as prevention; ICER: incremental cost-effectiveness ratio; PSI: Population Services International; STD: sexually transmitted disease; IDU: injecting drug user.

[1] The asterisk (*) next to YEAR USD indicates year of article publication when year of USD is not reported in the article.

Table 2

Prevention of Mother to Child Transmission and HIV Testing Strategies

Title	Model Type	Strategy	Results		
			$/Infection Averted	$/QALY gained or $/DALY averted[1]	Other
Prevention of Mother to Child Transmission (PMTCT)					
Cost-effectiveness of option B plus for PMTCT of HIV in resource-limited countries: evidence from Kumasi, **Ghana** [19]	State transition	Compare Option B+ to Option B in HIV-infected pregnant women	Not reported	$785/QALY gained (2015 USD*)	Option B+ gains additional 0.1 maternal and 3.2 child QALYs
The costs and benefits of Option B+ for the PMTCT of HIV (**Kenya, Zambia, South Africa, Vietnam**) [20]	Deterministic	Compare Option A, Option B, and Option B+ in pregnant women	$6,000-$23,000 (B+) depending on country	Not reported (2014 USD*)	Option B+ prevents the most number of transmissions
Health outcomes and cost impact of the new WHO 2013 guidelines on PMTCT of HIV in **Zambia** [21]	Decision tree	Compare Option A, Option B, and Option B+ in pregnant women	$1,034 (A), $1,140 (B), $1,406 (B+)	$75-132/QALY gained (2012 USD)	33% risk reduction for infant transmission
The cost-effectiveness of different feeding patterns combined with prompt treatments for PMTCT in **South Africa**: estimates from simulation modeling [22]	Decision analytic model with Monte Carlo simulation	Compare promptly treating pregnant women with ART or testing and treating with ART after delivery	$2060 for promptly treated	$70/YLS saved for promptly treated $120/YLS for treated after delivery (2012 USD)	Replacement feeding is more cost-effective ($135/YLS) than breastfeeding ($195/YLS)
HIV Testing					
Expanded HIV testing in low-prevalence, high-income countries: a cost-effectiveness analysis for the **United Kingdom** [23]	Dynamic compartmental	Compare universal and targeted HIV testing at various repeat intervals (once and every 1 yr, 2 yr, or 3 yr)	Not reported	1-yr targeted testing: £17,500/QALY gained (~$26,700) (2012 USD)	Universal: £67,000-106,000/QALY gained ($102,100-161,600)
Cost-effectiveness of frequent HIV testing of high risk populations in the **United States** [24]	Transmission model (no further details provided)	Compare 3 and 6 mo vs. annual testing in MSM and IDUs	$259,000-$4,468,900	ICER is cost-saving to $910,600/QALY gained (2012 USD)	Costs and ICERs depend on risk group, testing frequency and test type
Assessment of the potential impact and cost-effectiveness of self-testing for HIV in low-income countries (**Zimbabwe**) [25]	Individual-based stochastic transmission	Compare introduction of HIV self-testing over 20 year time frame to provider delivered HTC	Not reported	Cost-saving (2015 USD*)	Self-testing saves $75 million and averts 7000 DALYs over 20 years

Title	Model Type	Strategy	Results		
			$/Infection Averted	$/QALY gained or $/DALY averted[1]	Other
Cost-effectiveness of community-based strategies to strengthen the continuum of HIV care in rural **South Africa**: a health economic modelling analysis [26]	Individual-based microsimulation transmission	Implement home HTC package at different ART initiation thresholds	Not reported	$1,090-$1,360 depending on ART initiation threshold (2012 USD)	Decrease HIV morbidity by 10-22% and averted 9-47% of infections
Mobile HIV screening in Cape Town, **South Africa**: clinical impact, cost and cost-effectiveness [27]	Deterministic, individual-based Markov	Compare addition of mobile testing to clinic testing to clinic testing only	Not reported	$2,400/year of life saved (2012 USD)	Addition of mobile testing increases life expectancy by 8 years
Cost-effectiveness of integrated routine offering of prenatal HIV and syphilis screening in **China** [28]	Markov cohort state transition	Compare HIV, syphilis, and HIV+syphilis screening vs. no screening	Not reported	$5,636/DALY averted for HIV only (2010 USD)	$359/DALY averted for HIV+syphilis screening
Cost-effectiveness of provider-based HIV partner notification in urban **Malawi** [29]	Decision tree	Compare three notification strategies: passive referral, contract and provider notification	ICER $3,560 (contract vs. passive) $51,421 (provider vs. contract)	(2010 USD)	27.9 transmissions averted (provider) and 27.5 (contract) compared to passive

QALY: quality-adjusted life year; DALY: disability-adjusted life year; ART: antiretroviral therapy; Option A: HIV prophylaxis for mothers and infants; Option B: ART to women while pregnant or breastfeeding; Option B+: lifelong ART to pregnant women; WHO: World Health Organization; ICER: incremental cost-effectiveness ratio; yr: year; mo: month; MSM: men who have sex with men; IDU: injecting drug user; HTC: HIV testing and counseling.

[1]The asterisk (*) next to YEAR USD indicates year of article publication when year of USD is not reported in the article.

Table 3

Pre-Exposure Prophylaxis and Treatment as Prevention Strategies

Citation	Model Type	Strategy	Results		
			$/Infection Averted	**$/QALY gained or $/DALY averted[1]**	**Other**
Pre-Exposure Prophylaxis					
Evaluating the impact of prioritization of antiretroviral pre-exposure prophylaxis in New York (**United States**) [42]	Monte Carlo with deterministic compartmental transmission	Compare prioritization of PrEP between high risk heterosexuals, high risk MSM, all MSM, IDUs, and all high risk	Ranges from $1.6 million to $54 million	Not reported (2012 USD)	Diminishing returns when PrEP is expanded beyond high risk MSM
Clinical effectiveness and cost-effectiveness of HIV PrEP in MSM: risk calculators for real-world decision-making (**United States)** [43]	Decision-analytic based on decision tree framework	Estimate the number needed to treat for MSM in various risk, adherence, and behavioral scenarios	Not reported	$160,000/QALY for PrEP to all MSM in the US (2012 USD)	Number needed to treat is 64
A cost-effectiveness analysis of HIV PrEP for MSM in **Australia** [44]	Stochastic agent-based	Compare PrEP to all MSM, high risk MSM, and serodiscordant MSM to no PrEP	Not reported	$8,400-11,575 (AUD) /QALY gained to serodiscordant MSM ($7,790-10,740 USD, 2013)	>$400,000 (AUD)/QALY gained to all MSM (>$371,000 USD)
Effectiveness and cost-effectiveness of oral PrEP in a portfolio of prevention programs for IDUs in mixed HIV epidemics (**Ukraine**) [45]	Dynamic compartmental	Compare PrEP, ART and/or methadone maintenance therapy (MMT) to no intervention in IDUs	Not reported	MMT: $520/QALY gained Adding PrEP: $1,700 (2008 USD)	PrEP becomes as cost-effective as MMT if priced less than $650 and cost-saving is priced less than $370
HIV-serodiscordant couples desiring a child: “treatment as prevention,” preexposure prophylaxis, or medically assisted procreation? (**France**) [46]	Markov decision tree	Compare conception strategies: PrEP, TasP, medically assisted procreation	Not reported	PrEP limited to fertile days: €1.13M (~$1.5M) per life year saved compared to TasP and intercourse limited to fertile days (2013 Euro or USD)	Medically assisted procreation is €3.6M (~$4M) per life year saved compared to limited PrEP
Cost-effectiveness of tenofovir gel in urban **South Africa**: model projections of HIV impact and threshold product prices [47]	Population-level deterministic compartmental transmission	Linear scale-up of tenofovir gel to 30% uptake over 10 years; gel used in 72% of sex acts	Not reported	ICER $297/DALY averted (2012 USD)	Reduce HIV incidence by 12.5%
Comparative effectiveness and cost-effectiveness of ART and PrEP for HIV prevention in	Dynamic compartmental	Compare ART scale-up at different initiation thresholds	Not reported	Adding targeted PrEP ranges from $160-220/QALY	

Citation	Model Type	Strategy	Results		
			$/Infection Averted	**$/QALY gained or $/DALY averted[1]**	**Other**
South Africa [48]		and scale-up; determine additional cost of adding PrEP		gained (2014 USD*)	
Cost-effectiveness of PrEP targeted to high-risk serodiscordant couples as a bridge to sustained ART use in Kampala, **Uganda** [49]	Dynamic transmission	Current ART coverage vs. ART scale-up for CD4<500 vs. PrEP+ART scale-up	ICER $1,340 (PrEP+ART)	ICER $5,354 (PrEP+ART) per DALY averted (2012 USD)	PrEP+ART averts 43% of infections
Estimating the cost-effectiveness of PrEP to reduce HIV-1 and HSV-2 incidence in HIV-serodiscordant couples in **South Africa** [50]	Microsimulation	PrEP to uninfected partner prior to and during 1st year of ART initiation in infected partner	Not reported	$9,757-10,383/DALY averted (2015 USD*)	HSV-2 prevention has little impact on cost-effectiveness
Seasonal PrEP for partners of migrant miners in southern **Mozambique**: a highly focused PrEP intervention [51]	Population-level deterministic transmission	6 weeks of targeted PrEP each year for partners of miners timed when miners return home from South Africa	$71,374 for year-long PrEP $9,540 for 6 week period	Not reported (2012 USD)	For cost/infection averted to be <$3,000, cost of PrEP would need to decrease and users would need good adherence
Cost-effectiveness of PrEP in HIV/AIDS control in **Zambia**: a stochastic league approach [53]	Deterministic, Monte Carlo	Compare ART scale-up, prioritized PrEP, and general PrEP	Not reported	ICER PrEP+ART: $5,861/QALY gained (2012 USD)	PrEP would require a 10-fold increase in budget
Treatment as Prevention					
Cost-effectiveness of HIV treatment as prevention in serodiscordant couples (**South Africa, India**) [57]	Deterministic, individual-based Markov	Compare early ART initiation with guideline-concordant ART initiation	Not reported	South Africa ICER $590/LYS India ICER $530/LYS (2011 USD)	Results exclude costs of case identification and testing required to indentify participants with high CD4 counts
Comparative effectiveness and cost-effectiveness of ART and PrEP for HIV prevention in **South Africa** [48]	Dynamic compartmental	Compare ART scale-up at different initiation thresholds and scale-up; determine additional cost of adding PrEP	Not reported	ICER for ART scale-up ranges from $310-990/QALY gained (2014 USD*)	
Cost-effectiveness of PrEP targeted to high-risk serodiscordant couples as a bridge to sustained ART use in Kampala, **Uganda** [49]	Dynamic transmission	Current ART coverage vs. ART scale-up for CD4<500 vs. PrEP+ART scale-up	ICER $1,452 (ART alone)	ICER $1,075 (ART scale-up) per DALY averted (2012 USD)	ART scale-up averts 37% of infections
Cost-effectiveness of PrEP in HIV/AIDS control in **Zambia**: a stochastic league approach [53]	Deterministic, Monte Carlo	Compare ART scale-up, prioritized PrEP, and general PrEP	Not reported	ICER ART scale-up: $62/QALY gained (2012 USD)	

QALY: quality-adjusted life year; DALY: disability-adjusted life year; PrEP: pre-exposure prophylaxis; CAD: Canadian dollars; USD: United States dollars; AUD: Australian dollars; ART: antiretroviral therapy; MSM: men who have sex with men; IDU: injecting drug user; TasP: treatment as prevention; ICER: incremental cost-effectiveness ratio; YLS: year of life saved.

[1]The asterisk (*) next to YEAR USD indicates year of article publication when year of USD is not reported in the article.