Cost-effectiveness of HIV Prevention Interventions in Sub-Saharan Africa: A Systematic Review

Supriya Sarkar a,⁎, Phaedra Corso b, Shideh Ebrahim-Zadeh a, Patricia Kim c, Sana Charania d, Kristin Wall a

a Department of Epidemiology, Emory University, Atlanta, GA, USA

b Department of Health Policy and Management, Kennesaw State University, Kennesaw, GA, USA

c Department of Economics, Emory University, Atlanta, GA, USA

d Rollins School of Public Health, Emory University, Atlanta, GA, USA

ABSTRACT

Background: Sub-Saharan Africa carries the highest HIV burden globally. It is important to understand how interventions cost-effectively fit within guidelines and implementation plans, especially in low- and middle-income settings. We reviewed the evidence from economic evaluations of HIV prevention interventions in sub-Saharan Africa to help inform the allocation of limited resources.

Methods: We searched PubMed, Web of Science, Econ-Lit, Embase, and African Index Medicus. We included studies published between January 2009 and December 2018 reporting cost-effectiveness estimates of HIV prevention interventions. We extracted health outcomes and cost-effectiveness ratios (CERs) and evaluated study quality using the CHEERS checklist.

Findings: 60 studies met the full inclusion criteria. Prevention of mother-to-child transmission interventions had the lowest median CERs ($1144/HIV infection averted and $191/DALY averted), while pre-exposure prophylaxis interventions had the highest ($13,267/HIV and $799/DALY averted). Structural interventions (partner notification, cash transfer programs) have similar CERs ($3576/HIV and $392/DALY averted) to male circumcision ($2965/HIV) and were more favorable to treatment-as-prevention interventions ($7903/HIV and $890/DALY averted). Most interventions showed increased cost-effectiveness when prioritizing specific target groups based on age and risk.

Interpretation: The presented cost-effectiveness information can aid policy makers and other stakeholders as they develop guidelines and programming for HIV prevention plans in resource-constrained settings.

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1. Introduction

Sub-Saharan Africa (SSA) has experienced a large reduction in new HIV infections over the last decade, with the number of incident infections dropping over 30% since 2010 [1]. This decrease in burden reflects the accomplishment of a global effort focused on a region in which approximately 70% of all people living with HIV reside [2,3]. Despite this success, the decline in incidence is slowing, and gaps in the scale-up of HIV prevention services persist throughout SSA [3].

US$4.5 billion was allocated for HIV prevention investments in 2016 by the international community; however, a recent UNAIDS report stated that an additional annual investment of US$7 billion is urgently needed to meet the 2030 Sustainable Development Goals targets [4–6]. To improve the efficiency of programming for HIV prevention, optimizing limited financial resources is crucial to scale up high-quality, cost-effective interventions to maximize HIV prevention [7].

In addition to evidence-based prevention tools such as voluntary medical male circumcision (VMMC) and prevention of mother-to-child transmission (PMTCT) strategies, new prevention methods such as HIV pre-exposure prophylaxis (PrEP) have been heralded for their remarkable clinical results in the reduction of HIV transmission. However, it is important for policy- and decision-makers to identify where and how such costly interventions fit within regional and national HIV implementation plans and budgets, particularly in resource-limited countries [8].

Ascertaining the cost-effectiveness of prevention interventions is necessary for optimal resource allocation and for identifying inefficiencies within prevention programs [7].

A systematic review of HIV prevention intervention cost-effectiveness was published in 2009 by Galarraga et al., which concluded that the number and quality of cost-effectiveness studies were insufficient and too limited at that time to aid decision making and
Research in context

Evidence Before This Study

There is an increasing interest in cost-effectiveness of HIV programs among stakeholders. The last systematic review on the cost-effectiveness of all HIV prevention interventions was published nearly ten years ago. At that time, cost-effectiveness studies were limited and often unavailable for specific interventions. A 2013 systematic review presented evidence from studies specifically on pre-exposure prophylaxis and concluded that the intervention’s impact relied highly on contextual assumptions. In the past decade, an increasing number of cost-effectiveness studies in HIV prevention literature have become available, but there has not yet been a single review that synthesizes the evidence from all of these studies. We conducted a systematic review for cost-effectiveness studies on HIV prevention interventions. We searched PubMed/MEDLINE, Web of Science, Econ-Lit, Embase, and African Index Medicus, for studies published between January 1, 2009 and December 31, 2018. Search terms included “HIV”, “prevention” or “control”; “sub-Saharan Africa”; “cost” or “cost-effectiveness”.

Added Value of This Study

This is the first review that provides a comprehensive and up-to-date look at the cost-effectiveness of all HIV prevention interventions targeted towards HIV-individuals. Additionally, this review focuses solely on sub-Saharan Africa, the region that carries the vast majority of the global disease burden. We show that voluntary medical male circumcision (VMMC) and prevention of mother-to-child transmission (PMTCT) interventions are cost-effective in almost all contexts. We provide evidence of cost-effectiveness of other newer biomedical interventions, including pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP). We hope that the evidence from this review will aid various stakeholders, including Ministries of Health, program implementers, and international donors, in their decision-making regarding resource allocation policy for HIV prevention.

Implications of All the Available Evidence

The number of studies included in this review reflects the increasing importance of considering cost-effectiveness when designing or implementing HIV prevention programs in sub-Saharan Africa. Numerous studies focused on new biomedical interventions, and many of these studies used mathematical modeling to provide evidence of these interventions’ cost-effectiveness since they have not yet been scaled up in sub-Saharan Africa. However, this review shows that most interventions can be cost-effective in specific contexts. As such, we encourage others to use the results of this review with caution. Future economic and costing studies on HIV prevention should include more realistic scenarios so that these data are more accessible and relevant to policymakers and other stakeholders.

policy recommendations [9–10]. However, since 2009, many studies have been published on the cost-effectiveness of various prevention interventions, including newer PrEP technologies and treatment-as-prevention [8].

No systematic review to date has evaluated these newer prevention interventions with a focus on SSA. Such a review would provide important information on HIV prevention costs, outcomes, and effectiveness to support policies and decision-making [8,9]. The purpose of this review is to systematically review published analyses of the cost-effectiveness of HIV prevention interventions in SSA settings. We aim to 1) review evidence from studies published in the last decade that have evaluated cost and outcome metrics for HIV prevention interventions, 2) compare the costs and effects of specific prevention interventions, and 3) understand the assumptions driving cost-effectiveness in order to inform allocation of limited HIV prevention resources.

2. Methods

2.1. Search Strategy and Selection Criteria

We conducted this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. We searched PubMed/MEDLINE, Web of Science, Econ-Lit, Embase, and African Index Medicus. Additionally, we reviewed reference lists of retrieved articles as well as governmental and organizational reports to complement our search. We limited studies published between January 1, 2009 and December 31, 2018. The following keywords were used: “HIV”, “prevention” or “control”; “cost” or “cost-analysis” or “cost-effectiveness”; “sub-Saharan Africa”. The full search strategy, including keywords for each database, can be found in the supplemental material.

Inclusion criteria included full articles that were peer-reviewed and published in English, and reported cost and outcome measures or analysed cost-effectiveness of an HIV prevention intervention. Interventions included, but were not limited to: VMMC, PMTCT, TasP, PrEP, behavioural interventions, vaccinations, and microbicides. As a multi-pronged strategy, two types of PMTCT interventions were considered: Prong II, interventions to prevent unintended pregnancies of HIV-positive women, and Prong III, interventions providing services to reduce HIV transmission from HIV-positive women to their infants. Geography was limited to country settings within SSA, as defined by the United Nations [11]. A full list of eligible country settings can be found in the supplemental material. Studies that focused on HIV treatment with no prevention aspect, systematic reviews, meta-analyses, conference abstracts, and guideline reports were excluded. Studies assessing cost-effectiveness of an intervention’s combined impact for both HIV-positive and HIV-negative persons and studies that did not describe costing analyses and effectiveness measures were excluded. Two reviewers aggregated a list of articles produced by the database search and conducted independent screenings based on title and abstract. All discrepancies were resolved by a third reviewer.

2.2. Quality Assessment and Data Extraction

Two reviewers independently extracted data from each of the selected studies using a prepared data form, and an independent crosscheck by a third reviewer was conducted to identify and resolve any disagreements or uncertainties. We developed the data form using guidance from Emory colleagues and prior systematic reviews on similar topics. We assessed the quality of studies using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement, which contains a 24-point checklist to assess economic evaluation studies [12].

We extracted data on intervention type, study design or model type, geographic setting, HIV transmission method, population, intervention description, perspective, and time horizon. Additional extracted information included scenario descriptions, intervention effectiveness, cost-effectiveness metric results, and discounting rates for effects and costs. We categorized studies by prevention intervention type to compare intervention-specific results. The primary measures of interest were cost per HIV infection averted (HIA), cost per disability-adjusted life year (DALY) averted, cost per quality-adjusted life year (QALY) gained, and cost per life year gained (LYG). We converted study cost-effectiveness results to 2018 US$ using the Consumer Price Index.
(CPI) Inflation Calculator and compared them to the International Monetary Fund 2018 estimates of gross domestic product (GDP) per capita for each study setting [13,14].

For each intervention type, we calculated median CERs. Separate medians were calculated for studies reporting cost per HIA estimates and studies reporting cost per DALY averted, QALY gained, or LYG. For studies that explored more than one geographic setting, we considered results from the different settings as individual estimates if they were reported as such within a single study; these results were considered separately when we calculated median CERs.

3. Results

We identified and screened 1115 articles, of which 146 met criteria to be assessed for eligibility. The 969 articles that were initially excluded were deemed ineligible based on the article title and abstract and did not meet either the geographic setting or intervention criteria. Out of the 146 articles, 60 met the full inclusion criteria (Fig. 1). These 60 peer-reviewed studies provided cost-effectiveness results for the following HIV prevention interventions: 14 studies on VMMC, 13 studies on PrEP, five studies on PrS, 15 studies on PMTCT, nine studies on other biomedical interventions, one study on behaviour change, and three studies on structural interventions [15-74]. Among PMTCT studies, 14 considered Prong III strategies, while one focused on Prong II.

Table 1 describes characteristics of each study, including study design or model type, geographic setting, method of transmission, target population, time horizon, HIV prevalence of the target population, perspective, and description of the intervention assessed. Studies focused on heterosexual transmission among the general population except for studies exploring prevention of mother-to-child-transmission. Costs were predominately assessed through a healthcare payer perspective. Two studies included results from countries outside of SSA; non-SSA results were excluded from this review [56,62].

We extracted and converted each study's reported cost-effectiveness measure and converted them to 2018 US$. Table 2 describes these measures. Most studies provided discounted results, with discounting ranging from 0%-5% for the base case scenario, as is standard in cost-effectiveness literature [37]. Outcome measures were presented as number of HIV infections averted (HIA) for a specific scenario, with fewer studies reporting quality-adjusted life years (QALYs) gained or disability-adjusted life years (DALYs) averted. A number of studies did not provide numerical values for cost-effectiveness measures but rather stated whether an intervention was a dominant (cost-savings with better outcomes) or dominated (costlier with poorer outcomes) strategy [55,58,67]. The most cost-effective interventions included -$8356 per HIA for a microbicide intervention in South Africa, −$312 per HIA for a PMTCT intervention in Malawi, and $470 per HIA for a VMMC intervention in Uganda [18,49,62].

The median CERs for each intervention type were as follows: $2967 per HIA and $388/DALY averted for VMMC, $13,267 per HIA and $799 per QALY gained for PrEP, $7903 per HIA and $890 per DALY averted for PrS, $1421 per HIA and $191 per DALY averted or QALY gained for PMTCT, $1143 per HIA and $392/DALY averted for other biomedical interventions (microbicides, vaccination, praziquantel treatment, combination prevention, condom distribution), and $3575/HIA and $345/DALY averted for structural interventions (partner notification, cash transfer programs). For several of the intervention types, scenarios that prioritized specific sub-populations based on age and/or risk factors were more cost-effective than scenarios that targeted the general population (Figs. 2-7).

Table 3 and Fig. 8 provide the results of the quality assessment of each study using the CHEERS checklist.

4. Discussion

This review summarizes the evidence to date on recent studies of the cost-effectiveness of HIV prevention interventions and serves as an SSA-specific update to the 2009 review by Galarraga et al. [9] Results from this review illustrate that established interventions, such as VMMC and PMTCT, remain cost-effective, as previously found in the 2009
| Reference | Study design | Setting | Population | Time horizon | HIV prevalence | Perspective | Intervention description |
|-----------|--------------|---------|------------|--------------|---------------|-------------|--------------------------|
| Binagwaho et al. (2010) [15] | Deterministic compartmental simulation | Rwanda | 0-49 yo, male population | Lifetime | 2.7% | Health care payer | Scale-up of VMMC to infants, adolescents, and adults |
| Njeuhmeli et al. (2011) [16] | Deterministic compartmental simulation | Sub-Saharan Africa | 15-49 yo, general population | Lifetime | 4.8% | Health care payer | Scale-up of VMMC |
| Uthman et al. (2011) [17] | Probabilistic decision analysis | Sub-Saharan Africa | 15 + yo, general population | Lifetime | 5.5% | Health care payer | Scale-up of VMMC |
| Duffy et al. (2013) [18] | Cross-sectional descriptive cost-analysis | Uganda | 18 yo and older, male population | Lifetime | 5.9% | Health care payer | Scale-up of VMMC |
| Menon et al. (2014) [19] | Deterministic compartmental simulation | Tanzania | 10-49 yo, male population | Lifetime | 4.5% | Health care payer | Scale-up of VMMC |
| Awad et al. (2015) [20] | Deterministic compartmental simulation | Zimbabwe | 10-49 yo, male population | 15 years | 13.3% | Health care payer | Uptake of VMMC |
| Awad et al. (2015) [21] | Deterministic compartmental simulation | Zambia | 10-49 yo, male population | 15 years | 11.5% | Health care payer | Age prioritised VMMC scale up |
| Haacker et al. (2016) [22] | Deterministic compartmental simulation | South Africa | 15-59, male population | Lifetime | 18.8% | Health care payer | Age prioritised VMMC scale up |
| Kripke et al. (2016) [23] | Deterministic compartmental simulation | Malawi | 10 + yo, male population | 15 years | 9.6% | Health care payer | Age prioritised VMMC scale up |
| Kripke et al. (2016) [24] | Deterministic compartmental simulation | Zimbabwe | 20-29 yo; male population | 15 years | 13.3% | Health care payer | Age prioritised VMMC scale up |
| Kripke et al. (2016) [25] | Deterministic compartmental simulation | Sub-Saharan Africa | 10-49 yo, male population | 15 years | 4.8% | Health care payer | Age prioritised VMMC scale up |
| Kripke et al. (2016) [26] | Deterministic compartmental simulation | Eswatini | 10-49 yo; male population | 15 years | 27.4% | Health care payer | Age prioritised VMMC scale up |
| Kripke et al. (2016) [27] | Deterministic compartmental simulation | Malawi, South Africa, Eswatini, Tanzania, Uganda | 10-49 yo; male population | 15 years | 9.6% (Malawi) 18.8% (South Africa) 27.4% (Eswatini) 4.5% (Tanzania) 5.9% (Uganda) | Health care payer | Age prioritised VMMC scale up |
| Njeuhmeli et al. (2016) [28] | Deterministic compartmental simulation | Zimbabwe | Male infants | 36 years | 13.3% | Health care payer | Early infant male circumcision |
| Pretorius et al. (2010) [29] | Deterministic compartmental simulation | South Africa | 15-49 yo, general population | 10 years | 18.8% | Health care payer | PrEP is scaled up to recruit all uninfected individuals |
| Hallett et al. (2011) [30] | Microsimulation | South Africa | HIV serodiscordant couples | Lifetime | 18.8% | Health care payer | Combination prevention strategies of VMMC, early ART, and PrEP |
| Cremin et al. (2013) [31] | Deterministic compartmental simulation | KwaZulu-Natal, South Africa | 15-54 yo, general population | 10 years | 27.0% (KZN) Program | Health care payer | Combination prevention strategies of VMMC, early ART, and PrEP |
| Nichols et al. (2013) [32] | Deterministic compartmental simulation | Macha, Zambia | 12 + yo, general population | 10 years | 7.7% (Macha) | Health care payer | Program |
| Verguet et al. (2013) [33] | Deterministic compartmental simulation | Sub-Saharan Africa | 15-49 yo, general population | 5 years | 4.8% | Health care payer | Program |
| Alistar et al. (2014) [34] | Dynamic compartmental simulation | South Africa | 15-49 yo, general population | 20 years | 18.8% | Health care payer | Program |
| Nichols et al. (2014) [35] | Deterministic compartmental simulation | Macha, Zambia | 12 + yo, general population | 40 years | 7.7% (Macha) | Health care payer | Uptake of PrEP and TasP in combination |
| Cremin et al. (2015) [36] | Deterministic compartmental simulation | Nyanza province, Kenya | General population | 5 years | 13.9% (Nyanza) | Health care payer | Dynamic interaction between key determinants of PrEP impact and cost-effectiveness |
| Cremin et al. (2015) [37] | Deterministic compartmental simulation | Gaza province, Mozambique, Uganda | Adult male mine workers | 5 years | 30.0% (female) 17.0% (male) | Health care payer | Time-limited PrEP uptake among sexual partners of miners |
| Ying et al. (2015) [38] | Micro-costing analysis | HIV serodiscordant couples | 10 years | 7.1% | Program | Program |
| Glaubius et al. (2016) [39] | Deterministic compartmental simulation | South Africa | 15-49 yo, general population | 1) 10yrs 2) lifetime | 18.8% | Societal | Long-acting injective antiretrovirals used for PrEP |
| Walensky et al. (2016) [40] | Deterministic compartmental simulation | South Africa | 18-25 yo, high risk women | 5 years | Incidence: 5.0% | Program | Long-acting PrEP |

(continued on next page)
| Reference                      | Study design                  | Setting                                      | Population                          | Time horizon | HIV prevalence<sup>a</sup> | Perspective<sup>b</sup> | Intervention description                                                                 |
|-------------------------------|------------------------------|----------------------------------------------|--------------------------------------|--------------|---------------------------|--------------------------|--------------------------------------------------------------------------------------------|
| Cremin et al. (2017) [41]    | Deterministic compartmental simulation | Nairobi, Kenya                              | Key populations                      | 10 years     | 4.8%                      | Health care payer          | PrEP provided to FSW                                                                |
| Barnighausen et al. (2012) [42] | Discrete time mathematical model | South Africa                                | 15 + yo, general population           | 10 years     | 18.8%                     | Health care payer          | Increased coverage of TasP, ART under the current WHO eligibility guidelines, and MMC |
| Granich et al. (2012) [43]   | Deterministic compartmental simulation | South Africa                                | 15 + yo, general population           | 1) 5 years   | 18.8%                     | Program                   | Enhanced combination prevention strategy                                               |
| Smith et al. (2015) [44]     | Individual-based simulation modelling study | KwaZulu-Natal, South Africa                  | 18 + yo, general population           | 10 years     | 27.0% (KZN)<sup>c</sup>  | Health care payer          | Home HIV counselling and testing                                                       |
| Bershnev et al. (2016) [45]  | Individual-based simulation modelling study | South Africa                                | General population                    | 20 years     | 18.8%                     | Health care payer          | Age-targeting outreach with HIV treatment and prevention                             |
| Ying et al. (2016) [46]      | Dynamic compartmental model   | KwaZulu-Natal, South Africa                  | General population                    | 10 years     | 27.0% (KZN)<sup>c</sup>  | Program                   | Home HIV testing and counselling                                                      |
| PMTCT                         |                              |                                              |                                      |              |                           |                          |                                                                              |
| Halperin et al. (2009) [47]  | Modelling analysis           | Sub-Saharan Africa                           | Pregnant, HIV-infected women          | 1 year       | 4.8%                      | Service delivery           | Antiretroviral prophylaxis programs and family planning programs                   |
| Nakakeeto et al. (2009) [48] | Forecasting model            | Core d’Ivoire, Malawi, Rwanda, South Africa  | HIV-infected women, HIV-exposed infants | 8 years      | 0.6% (Burkina Faso) 3.7% (Cameroun) 2.8% (Cote d’Ivoire) 2.7% (Rwanda) 4.5% (Tanzania) 11.5% (Zambia) | Health care payer          | PMTCT package including: family planning, HIV testing and counselling, and provision of antiretroviral and cotrimoxazole prophylaxis |
| Orlando et al. (2010) [49]   | Cost-effectiveness analysis  | Malawi, Tanzania                             | Pregnant, HIV-infected women          | 42 months    | 16.9% (ANC)               | Societal and Private       | HAART-based intervention                                                          |
| Robberstad et al. (2010) [50]| Decision analysis            | Tanzania                                     | Pregnant, HIV-infected women          | 18 months    | 6.6% (ANC)                | Health care payer          | HAART-based intervention                                                        |
| Shah et al. (2011) [51]      | Decision-based analytical model | Nigeria                                      | Pregnant, HIV-infected women          | 1 year       | 2.8%                      | Health care payer          | 2009 WHO PMTCT guidelines                                                        |
| Kuznik et al. (2012) [52]    | Cost-effectiveness analysis  | Uganda                                       | Pregnant, HIV-infected women          | 19.3 years   | 7.1%                      | Health care payer          | Combination ART                                                               |
| Binagwaho et al. (2013) [53] | Cost-effectiveness analysis  | Rwanda                                       | HIV-infected pregnant women and their infants | Lifetime     | 2.7%                      | Health care payer          | Dual ARV and short course HAART prophylaxis with breastfeeding or replacement feeding |
| Fasawe et al. (2013) [54]    | Decision analysis            | Malawi, South Africa                         | Pregnant, HIV-infected women          | 10 years     | 16.9% (ANC)               | Health care payer          | Implementation of Option B+                                                        |
| Maredza et al. (2013) [55]   | Cost-effectiveness analysis  | South Africa                                 | Pregnant, HIV-infected women          | 24 months    | 28.0% (ANC)               | Health care payer          | HAART-based intervention                                                        |
| Gopalappa et al. (2014) [56] | Deterministic compartmental simulation | Kenya, South Africa                         | 15-49 yo, female population           | Lifetime     | 18.8% (South Africa) 11.5% (Zambia) | Program                   | Implementation of Option B+                                                       |
| Ishikawa et al. (2014) [57]  | Decision analysis            | Zambia                                       | Pregnant, HIV-infected women          | 18 months    | 11.5%                     | Health care payer          | Comparison between Option A, Option B, and Option B+                                 |
| Yu et al. (2014) [58]        | Decision analysis            | South Africa                                 | Pregnant, HIV-infected women          | 18 months    | 28.0% (ANC)               | Health care payer          | 1) tested and treated promptly at any time during pregnancy (promptly treated cohort), 2) no testing or treatment until after delivery and appropriate standard treatments were offered (remedy treated cohort) |
| Zulliger et al. (2014) [59]  | Cost-effectiveness analysis  | South Africa                                 | Pregnant, HIV-infected women          | 1 year       | 28.0% (ANC)               | Health care payer          | Expedit expedition onto lifelong ART in pregnant women who met South African ART eligibility criteria |
| Price et al. (2016) [60]     | Decision analysis            | Zambia                                       | Pregnant women                        | Lifetime     | 11.5%                     | Health care payer          | Daily oral PrEP during pregnancy and breastfeeding                                |
| Twveya et al. (2016) [61]    | Individual-based simulation modelling study | Malawi                                       | Primigravida women                    | 50 years     | 16.9% (ANC)               | Health care payer          | Option B vs. Option B+                                                             |
| Other biomedical             |                              |                                              |                                      |              |                           |                          |                                                                              |
| Verguet et al. (2010) [62]   | Cost-effectiveness analysis  | South Africa                                 | 15-49 yo, female population           | 1 year       | 26.3% (Female)            | Health care payer          | Impact of microbicides distributed alongside condoms                               |
| Williams et al. (2011) [63]  | Dynamic compartmental model  | South Africa                                 | General population                    | 20 years     | 18.8%                     | Health care payer          | Tenofovir gel uptake by sexuality                                                  |
| Study                        | Methodology                        | Location/Region                              | Population Description                                      | Duration | HIV Prevalence | Healthcare Payer | Additional Details                                                                 |
|-----------------------------|------------------------------------|----------------------------------------------|-------------------------------------------------------------|----------|----------------|------------------|------------------------------------------------------------------------------------|
| Long et al. (2013) [64]     | Dynamic compartmental simulation   | South Africa                                 | 15-49 yo, general population                               | 10 years | 18.8%          | Health care payer            | HIV screening and counselling, ART, VMMC, microbicides                              |
| Mbah et al. (2013) [65]     | Dynamic compartmental simulation   | Zimbabwe                                     | 15-49 yo, female population                                 | 10 years | 13.3%          | Health care payer            | Praziquantel as a preventive antihelminthic chemotherapy                           |
| Terris-Prestholt et al. (2014) [66] | Deterministic compartmental simulation | Gauteng Province, South Africa Sub-Saharan Africa | 15-49 yo, general population + FSW and their partners     | 15 years | 17.6% (Gauteng) | Health care payer            | Uptake of tenofovir gel by women                                                 |
| Mvundura et al. (2015) [67] | Impact analysis                    | South Africa                                 | 15-49 yo, general population                               | 1 year   | 4.8%           | Health care payer            | Distribution of 100,000 female condoms                                             |
| Moodley et al. (2016) [68]  | Semi-Markov simulation             | South Africa                                 | Adolescents enrolled in school                              | Lifetime | 10.2% (females 15-24) 3.9% (males 15-24) | Health care payer            | Hypothetical HIV vaccination provided to adolescent students                        |
| Moodley et al. (2016) [69]  | Semi-Markov simulation             | South Africa                                 | Adolescents girls enrolled in school                       | Lifetime | 10.2% (females 15-24) 3.9% (males 15-24) | Health care payer            | National implementation of hypothetical HIV vaccination to adolescents            |
| Wall et al. (2018) [70]     | Cost-benefit analysis and cost-effectiveness analysis | Zambia                                      | HIV serodiscordant couples                                 | 5 years  | 11.5%          | Donor                  | Couples’ testing and counselling with TasP for seropositive partner               |
| Behavior change             |                                    |                                              |                                                             |          |                |                    |                                                                                    |
| Enns et al. (2011) [71]     | Stochastic network simulation      | Eswatini, Tanzania, Uganda, Zambia           | 15-49 yo, general population                               | 10 years | 27.4% (Eswatini) 4.7% (Tanzania) 7.1% (Uganda) 11.5% (Zambia) | Program                    | Concurrency reduction campaigns focused on behaviour change scenario: 1) increased monogamy, 2) high-risk partnership reduction, 3) untargeted partnership reduction |
| Structural                  |                                    |                                              |                                                             |          |                |                    |                                                                                    |
| Fieno et al. (2014) [72]    | Cost simulation                    | South Africa                                 | Women aged 15-20 yo, bottom quarter of income distribution | 6 years  | 18.8%          | Health care payer            | Cash transfers                                                                    |
| Remme et al. (2014) [73]    | Cost-benefit analysis and cost-effectiveness analysis | Malawi                                      | Adolescent girls attending school                          | 18 months | 9.0%           | Health care payer            | Cash transfers                                                                    |
| Ruststein et al. (2014) [74]| Decision-tree model                | Malawi                                       | 15-49 yo, partners of STI clinic indexes                   | 1 year   | 9.0%           | Health care payer            | Partner notification                                                            |

Abbreviations: ANC = antenatal care clinic; ARV = antiretrovirals; ART = antiretroviral therapy; FSW = female sex worker; HAART = highly active antiretroviral therapy; KZN = KwaZulu-Natal, South Africa; MC = male circumcision; MMC = medical male circumcision; PMTCT = prevention of mother-to-child transmission; PrEP = pre-exposure prophylaxis; TasP = treatment as prevention; VMMC = voluntary medical male circumcision; WHO = World Health Organization; yo = years old.
| Reference | Scenario | Outcome measure | Cost-effectiveness measure reported in publication (US$) | Cost-effectiveness measure (US$ 2018) | Discount rate | Country GDP per capita (current US$), 2018** [76] |
|-----------|----------|-----------------|---------------------------------------------------------|---------------------------------------|--------------|-----------------------------------------------|
| Binagwaho et al. (2010) [15] | Infants Adults | VMMC coverage in 13 countries | 1288 HIA 1283 HIA 859 HIA 9 VMMCs/1 HIA | Cost-saving CER = $3,932/HIA CER = $4,949/HIA $809/HIA $927/HIA | 3% | Rwanda: $800–21 |
| Njeuhmi et al. (2011) [16] | All adult males | PrePex circumcision method | NR | $325-DALY averted (cost savings) | NR | SSA: $1,620–00 |
| Uthman et al. (2011) [17] | Surgical circumcision method | Scale-up and maintenance of 80% VMMC coverage | NR | $420/HIA $580/HIA $3,200/HIA $3,668/HIA | 3% | Tanzania: $1,090–00 |
| Duffy et al. (2013) [18] | VMMC program with subpopulation prioritization | Current VMMC scale-up program | 326,000 HIA 11 VMMCs/1 HIA (2010–2025) 10-53 VMMCs/1 HIA | $1,010/HIA $1,072/HIA | 3% | Malawi: $1,270–00 |
| Menon et al. (2014) [19] | VMMC program with subpopulation prioritization | Current VMMC scale-up program | 306,000 HIA 23 VMMCs/1 HIA (2010–2017) 12 VMMCs/1 HIA (2017–2025) 11-36 VMMCs/1 HIA | $1,089/HIA $1,156/HIA | 3% | Zambia: $1,145–00 |
| Awad et al. (2015) [20] | VMMC program with subpopulation prioritization | VMMC program with subpopulation prioritization | 4-2 VMMCs/HIA | $859/HIA $919/HIA $705/HIA $24,157/HIA $25,846/HIA | 3% | South Africa: $6,560–00 |
| Adata et al. (2015) [21] | VMMC program with subpopulation prioritization | VMMC program with subpopulation prioritization | 4-4 VMMCs/HIA | $699/HIA | 3% | Malawi: $349–13 |
| Haacker et al. (2016) [22] | VMMC at 20 yo VMMC at 55 yo | VMMC at 0 yo | 79 HIA 92 HIA 106 HIA 104 HIA 148 HIA 87,000 HIA | $5,100/HIA $4,600/HIA $6,800/HIA $7,346/HIA $3,642/HIA | 3% | Tanzania: $1,090–00 |
| Kripke et al. (2016) [23] | 50% EIMC coverage/80% coverage among 10–29 yo | 50% EIMC coverage/80% coverage among 10–29 yo 50% EIMC coverage/80% coverage among 15–49 yo | 80% Scenario: Scale up to 80% among 10–29 yo | $4,800/HIA $4,994/HIA $4,994/HIA | 3% | South Africa: $6,560–00 |
| Kripke et al. (2016) [24] | VMMC program with subpopulation prioritization | VMMC program with subpopulation prioritization | 63,000 HIA | $6,000/HIA | 3% | South Africa: $6,560–00 |
| Kripke et al. (2016) [25] | 80% coverage among 15–49 yo | Actual VMMC performance through 2014 | 2400,000 HIA (229,000, 572,000) 1,082,000 HIA (744,000, 1,839,000) | $4,400/HIA (median over 14 countries) | 3% (costs only) | SSA: $1,620–00 |
| Kripke et al. (2016) [26] | 50% EIMC coverage/80% coverage among 10–24 yo | 50% EIMC coverage/80% coverage among 10–24 yo | 20,000 HIA (14,000, 24,000) 27,000 HIA (19,000, 34,000) 29,000 HIA (21,000, 38,000) | $1,500/HIA ($1,100, $1,900) $1,300/HIA ($900, $1,600) $1,200/HIA ($900, $1,600) | 3% | Malawi: $349–13 |
| Kripke et al. (2016) [27] | 80% coverage among 10–49 yo Malawi: 149,000 HIA South Africa: 375,000 HIA Eswatini: 31,500 HIA | 80% coverage among 15–49 yo Malawi: 149,000 HIA South Africa: 375,000 HIA Eswatini: 31,500 HIA | 50% EIMC coverage/80% coverage among 10–34 yo | $4,600/HIA $4,600/HIA $4,600/HIA $4,600/HIA $4,600/HIA $4,600/HIA | 3% | South Africa: $6,560–00 |
| Kripke et al. (2016) [28] | 80% coverage among 15–49 yo Malawi: 149,000 HIA South Africa: 375,000 HIA Eswatini: 31,500 HIA | 80% coverage among 15–49 yo Malawi: 149,000 HIA South Africa: 375,000 HIA Eswatini: 31,500 HIA | South Africa: 372,000 HIA Eswatini: 32,200 HIA Tanzania: 50,500 HIA Uganda: 486,000 HIA Malawi: 148,000 HIA | $4,100/HIA $4,266/HIA $4,000/HIA | 3% | Malawi: $349–13 |
| Kripke et al. (2016) [29] | 80% coverage among 15–24 yo Malawi: 82,200 HIA South Africa: 182,000 HIA Eswatini: 18,900 HIA | 80% coverage among 15–24 yo Malawi: 82,200 HIA South Africa: 182,000 HIA Eswatini: 18,900 HIA | Tanzania: 28,300 HIA Uganda: 486,000 HIA Malawi: 148,000 HIA | $4,300/HIA $4,720/HIA | 3% | South Africa: $6,560–00 |
| Kripke et al. (2016) [30] | 80% coverage among 15–29 yo Malawi: 109,000 HIA South Africa: 246,000 HIA Eswatini: 25,700 HIA | 80% coverage among 15–29 yo Malawi: 109,000 HIA South Africa: 246,000 HIA Eswatini: 25,700 HIA | Tanzania: 36,200 HIA Uganda: 324,000 HIA Malawi: 128,000 HIA | $4,300/HIA $4,720/HIA | 3% | Eswatini: $4,090–00 |
| Kripke et al. (2016) [31] | 80% coverage among 15–34 yo Malawi: 128,000 HIA South Africa: 303,000 HIA | 80% coverage among 15–34 yo Malawi: 128,000 HIA South Africa: 303,000 HIA | Tanzania: 36,200 HIA Uganda: 324,000 HIA Malawi: 128,000 HIA | $4,300/HIA $4,720/HIA | 3% | Tanzania: $1,090–00 |
| Kripke et al. (2016) [32] | 80% coverage among 15–34 yo Malawi: 128,000 HIA South Africa: 303,000 HIA | 80% coverage among 15–34 yo Malawi: 128,000 HIA South Africa: 303,000 HIA | Tanzania: 36,200 HIA Uganda: 324,000 HIA Malawi: 128,000 HIA | $4,300/HIA $4,720/HIA | 3% | Uganda: $717–50 |
| Reference | Scenario | Outcome measure | Cost-effectiveness measure reported in publication (US$) | Cost-effectiveness measure (US$ 2018) | Discount rate | Country GDP per capita (current US$), 2018a [76] |
|-----------|----------|-----------------|----------------------------------------------------------|--------------------------------------|---------------|-----------------------------------------------|
| Pretorius et al. (2010) [29] | Targeted PrEP for 25-35 yo women | NR | $12,500 - $20,000/HIA | $14,328 - $22,924/HIA | NR | South Africa: $6,560 - 00 |
| Halliet et al. (2011) [30] | PrEP always used after HIV diagnosis in serodiscordant couple | 15% - 52% HIA | $0 - $26,000/HIA | $0 - $28,944/HIA | 3% | South Africa: $6,560 - 00 |
| Cremin et al. (2013) [31] | PrEP used up through ART initiation for HIV infected partner | 11% - 36% HIA | $-2,200 - $21,000/HIA | $-2,449 - $26,025/HIA | |
| Nichols et al. (2013) [32] | PrEP used only during periods of trying to conceive a pregnancy and during pregnancy | 1% - 2% HIA | $-6,000 - $8,000/HIA | $-6,679 - $8,906/HIA | |
| Verguet et al. (2013) [33] | PrEP intervention | 3 - 2% HIA | $10,540/HIA | $11,362/HIA | 3% | South Africa: $6,560 - 00 |
| Alistar et al. (2014) [34] | Prioritized PrEP | 3 - 6% HIA | $9,390/HIA | $10,122/HIA | |
| Nichols et al. (2014) [35] | PrEP provided to 7.3% of uninfected 15-24 yo | 3 - 2% HIA | $1,843/QALY gained | $2,051/QALY gained | 3% | Zambia: $1,145 - 00 |
| | PrEP provided to 4.4% of uninfected 15-54 yo | 3 - 6% HIA | $325/QALY gained | $359/QALY gained | |
| | Non-prioritized PrEP | 2,333 HIA; 23,571 QALYs gained | $1,843/QALY gained | $2,051/QALY gained | 3% | Zambia: $1,145 - 00 |
| | 3,200 HIA; 36,216 QALYs gained | $325/QALY gained | $359/QALY gained | |
| | Prioritized PrEP | 2,333 HIA; 23,571 QALYs gained | $325/QALY gained | $359/QALY gained | |
| | 3,200 HIA; 36,216 QALYs gained | $325/QALY gained | $359/QALY gained | |
| | 200 - 94,100 HIA; 3,300 - 1,266,000 DALYs averted | $550 - $44,600/DALY gained | $612 - $49,651/DALY gained | |
| | 3,381,214 HIA | $1,158/QALY gained | $1,239/QALY gained | 3% | South Africa: $6,560 - 00 |
| | 3,084,508 HIA | $1,873,744 HIA | CER = cost saving | CER = cost saving | 3% | South Africa: $6,560 - 00 |
| | 3,642,543 HIA | 1,837,744 HIA | CER = cost saving | CER = cost saving | 3% | South Africa: $6,560 - 00 |
| | 3,840,111 HIA | 3,084,508 HIA | CER = cost saving | CER = cost saving | 3% | South Africa: $6,560 - 00 |
| | 4,468,827 HIA | 3,642,543 HIA | CER = cost saving | CER = cost saving | 3% | South Africa: $6,560 - 00 |
| | 4,663,411 HIA | 3,840,111 HIA | CER = cost saving | CER = cost saving | 3% | South Africa: $6,560 - 00 |
| | 2,998,344 HIA | 4,468,827 HIA | CER = cost saving | CER = cost saving | 3% | South Africa: $6,560 - 00 |
| | 3,381,214 HIA | 4,663,411 HIA | CER = cost saving | CER = cost saving | 3% | South Africa: $6,560 - 00 |
| | 3,084,508 HIA | 2,998,344 HIA | CER = cost saving | CER = cost saving | 3% | South Africa: $6,560 - 00 |
| | 3,642,543 HIA | 3,381,214 HIA | CER = cost saving | CER = cost saving | 3% | South Africa: $6,560 - 00 |
| | 3,840,111 HIA | 3,642,543 HIA | CER = cost saving | CER = cost saving | 3% | South Africa: $6,560 - 00 |
| | 4,468,827 HIA | 3,840,111 HIA | CER = cost saving | CER = cost saving | 3% | South Africa: $6,560 - 00 |
| | 4,663,411 HIA | 4,468,827 HIA | CER = cost saving | CER = cost saving | 3% | South Africa: $6,560 - 00 |
| | 2,998,344 HIA | 4,663,411 HIA | CER = cost saving | CER = cost saving | 3% | South Africa: $6,560 - 00 |
| | 3,381,214 HIA | 2,998,344 HIA | CER = cost saving | CER = cost saving | 3% | South Africa: $6,560 - 00 |

(continued on next page)
| Reference | Scenario | Outcome measure | Cost-effectiveness measure reported in publication (US$) | Cost-effectiveness measure (US$ 2018) | Discount rate | Country GDP per capita (current US$), 2018a [76] |
|-----------|----------|-----------------|--------------------------------------------------------|--------------------------------------|--------------|---------------------------------------------|
| Cremin et al. (2015) [36] | Standard PrEP intervention ($20 million budget) | All uninfected women eligible to receive PrEP | ICR = dominated $2,060 - $36,360/HIA | $2,293 - $40,478/HIA | 3% | South Africa: $6,560-00 |
| Cremin et al. (2015) [37] | Providing PrEP only to partners of miners | Providing PrEP only to partners of miners only during the last six weeks of the year | NR | $71,374/HIA | $79,458/HIA | Mozambique: $481-25 |
| Ying et al. (2015) [38] | 40% overall ART coverage; 10% coverage for persons with CD4 < 350-500 cells/μL | Increase ART Coverage [50% coverage for persons with CD4 < 350-500 cells/μL] | 94,000 HIA | Ref. | -- | Uganda: $717-50 |
| Glaubius et al. (2016) [39] | Targeted PrEP and ART to 90% serodiscordant couples | Targeted PrEP and ART to 90% serodiscordant couples | 120,000 HIA | $1,340/HIA | $1,466/HIA | |
| Walensky et al. (2016) [40] | Long-acting PrEP | Standard PrEP | 127 HIA | $10,100/HIA | $11,094/HIA | South Africa: $6,560-00 |
| Cremin et al. (2017) [41] | 50% PrEP coverage to all FSW | 50% PrEP coverage to all FSW | NR | $65,160/HIA (95% CI: $43,520 - $95,250) | $66,404/HIA (95% CI: $44,351 - $97,069) | Kenya: $1,870-00 |
| TasP Barnighausen et al. (2012) [42] | Coverage: 70% ART, 20% TasP, 45% MMC | Coverage: 70% ART, 20% TasP, 45% MMC | 650,000 HIA (compared to 50% ART and 45% MMC) | $7,157/HIA | $7,813/HIA | South Africa: $6,560-00 |
| Granich et al. (2012) [43] | ART initiation at CD4 count ≤ 350 cells/μL vs. ≥ 350 cells/μL | ART initiation at CD4 count ≤ 350 cells/μL vs. ≥ 350 cells/μL | 200,000-1,400,000 HIA | $182/DALY averted | $199/DALY averted | |
| Smith et al. (2015) [44] | ART initiation at ≤ 200 cells/μL vs. ≥ 200 cells/μL | ART initiation at ≤ 200 cells/μL vs. ≥ 200 cells/μL | 2,000 DALYs averted | High ART cost | $22,300/HIA | South Africa: $6,560-00 |
| | ART initiation at ≥ 350 cells/μL vs. ≤ 350 cells/μL | ART initiation at ≥ 350 cells/μL vs. ≤ 350 cells/μL | 3,100 DALYs averted | Low ART cost | $1,960/HIA | |
| | ART initiation at ≤ 500 cells/μL vs. ≥ 500 cells/μL | ART initiation at ≤ 500 cells/μL vs. ≥ 500 cells/μL | 3,300 DALYs averted | $1,300/DALY averted | $1,790/DALY averted | |
| | Universal ART | Universal ART | 3,300 DALYs averted | $8,961/HIA | $8,961/HIA | |

Note: HIA = health impact analysis, DALY = disability-adjusted life year, ART = antiretroviral therapy, PrEP = pre-exposure prophylaxis, TasP = treatment as prevention, MMC = multimedication combination, US$ = United States dollars.
Table 2 (continued)

| Reference             | Scenario | Outcome measure | Cost-effectiveness measure reported in publication (US$) | Cost-effectiveness measure (US$ 2018) | Discount rate | Country GDP per capita (current US$), 2018a [76] |
|-----------------------|----------|-----------------|----------------------------------------------------------|--------------------------------------|---------------|-----------------------------------------------|
| Bershteyn et al. (2016) [45] | Targeting 10-30 yo | NR | $310/DALY averted | $6,238/HIA | $6,491/HIA | 3% South Africa: $6,560-00 |
| Ying et al. (2016) [46] | Base case (36% of HIV-infected people achieving viral suppression) | Home HTC (48% of HIV-infected people achieving viral suppression) | 152,000 HIA | $3,290/HIA | $3,546/HIA | 3% South Africa: $6,560-00 |
| Ackerman et al. (2016) [47] | Perinatal HIV transmission prevention program | Services to prevent unintended pregnancies | 241,596 HIA | $543/HIA | $631/HIA by perinatal infection | NR SSA: $1,620-00 |
| Nakakeeto et al. (2009) [48] | PMTCT | Meeting UNCASS targets for PMTCT by 2010 | 72,000 HIA | $359/HIA | $417/HIA by unintended pregnancy | 3% Malawi: $349-13 |
| Orlando et al. (2010) [49] | PMTCT program with VCT, HAART, treatment of malnutrition, TB, malaria, STDs (private perspective) | 370 HIA | $988/HIA | $35-36/DALY averted | $310/DALY averted | 3% Nigeria: $2,050-00 |
| Robberstad et al. (2010) [50] | Single-dose NVP | 0 00051 HIA (per pregnancy) | $26,826/HIA | $2,741/HIA | 3% Burkina Faso: $734-03 |
| Shah et al. (2011) [51] | Current PMTCT Coverage (10% of all HIV-infected women) | 1400 HIA | $3,620/HIA | $20,749/HIA | $2,741/HIA | 3% Uganda: $717-50 |
| Kuznik et al. (2012) [52] | 18 months ART vs. sdNVP | 5-21 DALYs averted | $46/DALY averted | $310/DALY averted | 3% Malawi: $349-13 |
| Binagwaho et al. (2013) [53] | Dual ARV + breastfeeding | 9,837 HIV uninfected children still alive | $12,882/HIA | $12,882/HIA | 3% Rwanda: $800-21 |
| Fasawe et al. (2013) [54] | Current Practice | 4,503 HIA | $816/HIA | $935/HIA | 3% Malawi: $349-13 | |

(continued on next page)
| Reference | Scenario | Outcome measure | Cost-effectiveness measure reported in publication (US$) | Cost-effectiveness measure (US$ 2018) | Discount rate | Country GDP per capita (current US$), 2018* [76] |
|-----------|----------|-----------------|--------------------------------------------------------|---------------------------------------|--------------|-----------------------------------------------|
| (2013) [55] | NVP to infants (rural) Promote formula feeding (rural) | 420 DALYs averted | $1,300/DALY averted | $1,490/DALY averted | Dominant | Kenya: $1,870/00 South Africa: $25,590/00 |
| | | | 160 DALYs averted | | $1,490/DALY averted | Dominant | Zambia: $1,145/00 |
| Ishikawa et al. (2014) [57] | Option B | 7,176 HIA | $1,023/HIA | $1,094/HIA | 3% | Zambia: $1,145-00 |
| Yu et al. (2014) [58] | Option B | 110 infant HIA | $1,254/HIA | $1,341/HIA | 3% | Zambia: $1,145-00 |
| | | 421 infant HIA | | | | |
| Zulliger et al. (2014) [59] | | 11 infant HIA | | | | |
| Price et al. (2016) [60] | Option B | 608 infant HIA | | | | |
| | | 360 infant HIA | | | | |
| Gopalappa et al. (2014) [56] | Option B vs. Option A | NR<sup>a</sup> | Kenya: $6,763/HIA | | 3% | Kenya: $1,870-00 South Africa: $6,560-00 |
| | | | South Africa: $22,987/HIA | | | South Africa: $6,560-00 |
| | | | Zambia: $7,545/HIA | | | Zambia: $1,145-00 |
| Zulliger et al. (2014) [59] | | 883 infant HIA | | | | |
| Price et al. (2016) [60] | | 16.88 QALYs saved | $1,160/QALY gained | $1,291/QALY gained | 3% | South Africa: $6,560-00 |
| | | 381 HIA | $965/DALY averted | $1,025/DALY averted | 3% | Zambia: $1,145-00 |
| Tewya et al. (2016) [61] | Option B vs. Option B | 133 DALYs averted | $841/DALY averted | $875/DALY averted | 3% | Malawi: $349-13 |
| Other biomedical | Access to condoms and microbicide effective at 55% | 1,908 HIA | $-6,712/HIA | $-8,356/HIA | NR | South Africa: $6,560-00 |
| Verguet et al. (2010) [62] | Tenoforv 25% Coverage | 250,000 HIA (20,000 – 380,000) | $2,392/HIA | $2,662/HIA | 3% | South Africa: $6,560-00 |
| Williams et al. (2011) [63] | Tenoforv 90% Coverage | 1,100,000 HIA (60,000 – 2,040,000) | $1,701/HIA | $1,893/HIA | 3% | South Africa: $6,560-00 |
| | Tenoforv 90% Coverage | 12-1% HIA | $420-2,992/HIA | $467-3,319/HIA | | |
| Long et al. (2013) [64] | Scale-up of VMMC to 75% of all men | 14-1% HIA | $525/QALY gained | $602/QALY gained | | |
| | Tenoforv gel used by 50% of women | 28-43% HIA | $9,009/QALY gained | $10,326/QALY gained | | |
| | Use of PrEP by 50% of all uninfected persons | 43-5% HIA | $5,739/QALY gained | $6,578/QALY gained | 3% | Zimbabwe: $1,270-00 |
| Mbab et al. (2013) [65] | VMMC, microbicide, and PrEP | 21,120 HIA | $259/HIA | $314/HIA | | |
| | Praziquantel treatment received during childhood | 41,500 HIA | $132/HIA | $174/HIA | | |
| | Praziquantel treatment received during childhood and FGS prevalence is reduced relative to those who did not receive treatment | 72% microbicide gel use consistency and 54% HIV efficacy | 55,366 HIA | $297/DALY averted | $392/DALY averted | 3% | South Africa: $6,560-00 |
| | Distribution of 100,000 female condoms | 273 HIA | $588/DALY averted | | | |
| | | | | | | |
| | | | | | | |
| Moodley et al. (2016) [68] | HIV vaccine intervention for school-based adolescents 60% coverage at $12 per vaccine dose | 4-36 QALYs gained in lifetime | $48,981.60 (95% CI: $27-77,511.60) | $54,651.60 (95% CI: $33-12,70) | 3% | South Africa: $6,560-00 |
| Moodley et al. (2016) [69] | Nationwide CVCT | | $394/HIA | $394/HIA | | |
| Wall et al. (2018) [70] | Tasp for serodiscordant couples identified by CVCT | 166,153 HIA | $7,930/HIA | $7,930/HIA | 0% | Zambia: $1,145-00 |
The assumption of 100% PrEP coverage considered in many studies was unrealistic. This scenario implies that every eligible individual would receive PrEP, which may not be realistic in settings where universal treatment has not even been realized. Many other factors, such as PrEP’s cost-effectiveness, sustainability, and acceptability, also need to be considered.

The VMMC studies included in this review agreed that the intervention was cost-effective. Seven different studies developed models that estimated cost effectiveness of VMMC at 80% coverage, which is a common target for many HIV prevention programs; however, achieving this level of coverage is often not feasible in many settings [16,19,23–27]. Additional studies exploring cost effectiveness at various levels of VMMC coverage may help inform decision makers in areas where 80% coverage would be difficult to attain. Multiple studies explored scenarios targeting VMMC at different age groups, with a consensus that prioritizing younger males is more favourable and cost-saving compared to targeting the general male adult population [15,22,24].

Similarly, a common conclusion was that PrEP strategies targeting specific risk groups were more cost-effective than general PrEP strategies [29,32,34,35,39]. Four studies found that PrEP was most cost-effective when using a prioritization strategy aimed at young individuals who are most at-risk, including having more than four partners and reporting low condom use [32,34,39,41]. The majority of included PrEP studies were set in South Africa, a country that could perhaps better absorb the higher costs of PrEP implementation compared with others in the region. However, three studies in Zambia and Mozambique agreed that prioritizing high-risk individuals would create the most effective scenario for PrEP implementation, adding to the evidence that a targeted PrEP strategy could be feasible across country settings [32,35,36].

The assumption of 100% PrEP coverage considered in many studies may be difficult to implement [11,14]. This scenario implies that every eligible individual would receive PrEP, which may not be realistic in settings where universal treatment has not even been realized. Many

Table 2 (continued)

| Reference | Scenario | Outcome measure | Cost-effectiveness measure reported in publication (US$) | Cost-effectiveness measure (US$ 2018) | Discount rate | Country GDP per capita (current US$), 2018* [76] |
|-----------|----------|-----------------|----------------------------------------------------------|----------------------------------------|--------------|-------------------------------------------|
| Enns et al. (2011) [71] | Increased monogamy | 77 (8.7%) HIA | NR | -- | 3% | Eswatini: $4,990 - 00 |
| | High-risk partnership reduction | 115 (11.7%) HIA | NR | -- | Tanzania: $1,090 - 00 |
| | Untargeted partnership reduction | 76 (8.9%) HIA | NR | -- | Uganda: $717 - 50 |
| | | | | | Zambia: $1,145 - 00 |
| Structural | Fieno et al. (2014) [72] | Cash transfer at $5 monthly benefit | 3,400 HIA | $1,650/HIA | $1,919/HIA | NR | South Africa: $6,560 - 00 |
| | | Cash transfer at $10 monthly benefit | 4,250 HIA | $2,640/HIA | $3,071/HIA | | |
| | | Cash transfer at $20 monthly benefit | 5,100 HIA | $4,400/HIA | $5,118/HIA | | |
| | Remme et al. (2014) [73] | Long-term benefits of 18-month cash transfer trial | 93,600 HIV DALYs averted | $297/HIV DALY averted | $345/HIV DALY averted | NR | Malawi: $349 - 13 |
| | Rutstein et al. (2014) [74] | Passive Referral | Ref. | ICER = $3,560/HIA | $4,080/HIA | NR | Malawi: $349 - 13 |
| | | Provider Notification | 27.5 HIA | -- | -- | -- | |
| | | Contract Notification | 0.4 HIA | ICER = $51,421/HIA | $58,941/HIA | | |

* Country GDP estimates retrieved from International Monetary Fund, World Economic Outlook.

Abbreviations: DT = dual therapy (zidovudine and lamivudine); ANC = antenatal care clinic; ARV = antiretrovirals; ART = antiretroviral therapy; CI = confidence intervals; DALY = disability-adjusted life year; EIMC = early infant male circumcision; FGS = female genital schistosomiasis; FSW = female sex worker; HAART = highly-active antiretroviral therapy; HIA = HIV infections averted; LGV = life years gained; NVP = nevirapine; PMTCT = prevention of mother-to-child transmission; PrEP = pre-exposure prophylaxis; QALY = quality-adjusted life year. *HIV infections averted; LYG = life years gained; NVP = nevirapine; PMTCT = prevention of mother-to-child transmission; PrEP = pre-exposure prophylaxis; QALY = quality-adjusted life year; Sc-HAART = short-course highly-active antiretroviral therapy; sdNVP = single dose nevirapine; SSA = sub-Saharan Africa; STD = sexually transmitted disease; TB = tuberculosis; UGASS = UN General Assembly Special Session on AIDS; VCT = voluntary counselling and testing; VMMC = voluntary medical male circumcision; yo = years old. A number of studies have since provided evidence supporting the WHO guidelines of transitioning from Option A and of recommending PMTCT Option B and Option B+. When WHO began the policy transition from Option B to Option B+ in 2013, the agency conducted a preliminary cost analysis to estimate the incremental cost of switching to the new policy [75]. The authors argued that researchers should develop additional cost-effectiveness models to appropriately evaluate the cost of the policy with programmatic data. A number of studies have since provided evidence supporting the policy decisions around Option B+ [56,57]. However, stakeholders should be mindful that implementation of strategies like Option B+ raises concerns since many of these studies do not take into account initial costs and upfront investment required to scale up PMTCT programs to a level that can be considered cost-effective over an extended time period [61,75]. Additionally, while the majority of PMTCT studies included in this review focused on Prong III, only one study addressed PMTCT Prong II by studying the expansion of family planning services as a cost-effective method to avert HIV infections through the prevention of unintended pregnancies [47]. This focus may reflect recent programmatic shifts towards PMTCT Prong III and treatment of HIV infected women, even though family planning is effective in reducing MTCT.

The review found that PMTCT and VMMC interventions were the most cost-effective. Studies on PMTCT interventions, including HAART, infant feeding methods, expedited ART, and Option B+ suggest that these strategies are very cost-effective [47,49,50,54,56,57,59]. These studies provide evidence supporting WHO guidelines of transitioning from Option A and of recommending PMTCT Option B and Option B+. When WHO began the policy transition from Option B to Option B+ in 2013, the agency conducted a preliminary cost analysis to estimate the incremental cost of switching to the new policy [75]. The authors argued that researchers should develop additional cost-effectiveness models to appropriately evaluate the cost of the policy with programmatic data. A number of studies have since provided evidence supporting the policy decisions around Option B+ [56,57]. However, stakeholders should be mindful that implementation of strategies like Option B+ raises concerns since many of these studies do not take into account initial costs and upfront investment required to scale up PMTCT programs to a level that can be considered cost-effective over an extended time period [61,75]. Additionally, while the majority of PMTCT studies included in this review focused on Prong III, only one study addressed PMTCT Prong II by studying the expansion of family planning services as a cost-effective method to avert HIV infections through the prevention of unintended pregnancies [47]. This focus may reflect recent programmatic shifts towards PMTCT Prong III and treatment of HIV infected women, even though family planning is effective in reducing MTCT.

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studies point out that achieving such a high level of PrEP coverage would be less cost-effective than simply increasing ART coverage. Accordingly, WHO issued recommendations in 2015 to provide PrEP as a prevention option to individuals at substantial risk of acquiring HIV in settings with high HIV incidence [76]. Although studies have shown that PrEP can be cost-effective when targeted towards high-risk groups and when assuming high adherence, it remains a challenging intervention due to high costs, ethical issues, and inequitable distribution [8].

The five studies included in this review were not in agreement with regard to the cost-effectiveness or the feasibility of TasP strategy; one
study concluded that TasP was less cost-effective than a combination of VMMC and ART, which is already the standard practice in many sub-Saharan African settings [42]. From this review, it is unclear whether or not TasP would be more cost-effective in certain settings over others. Despite this uncertainty, many countries have already developed and implemented guidelines for TasP and universal test-and-treat (UTT)

Fig. 3. Cost-effectiveness measures of PrEP interventions. Data points reflect the measures from PrEP studies reporting cost per HIV infection averted (above) and cost per DALY averted or QALY gained (below). Points represent study-specific cost-effectiveness estimates; error bars represent estimate ranges, if provided in study results.
Healthcare investment to provide UTT services successfully is substantial, especially in extensive resource-constrained settings [78]. This review also included studies that explored cost-effectiveness of methods that are still in development and not currently available on the market, including long-acting PrEP injections, HIV vaccines, and microbicide gels. The findings from these studies suggest that these interventions would be cost-effective once accessible [62–64,66,68,69]. Only one study included in this review considered the reduction of HIV incidence by estimating the intervention effect of schistosomiasis treatment. Mbah et al. showed that mass praziquantel administration

Fig. 4. Cost-effectiveness measures of TasP interventions. Data points reflect the measures from TasP studies reporting cost per HIV infection averted (above) and cost per DALY averted (below). Points represent study-specific cost-effectiveness estimates; error bars represent estimate ranges, if provided in study results.
would be a cost-effective approach to reduce HIV transmission. In addition to its affordability, praziquantel treatment is very safe, well tolerated, and easily administered, but it has not been explicitly considered as a HIV prevention intervention, as the link between HIV acquisition and schistosomiasis remains unclear [65].

The vast majority of the included studies determined cost-effectiveness based on the WHO-CHOICE guidance that considers interventions to cost-effective if the cost per DALY averted is between one and three times the study country’s GDP per capita [79]. This threshold is becoming increasingly contested, as many experts believe that it does not consider governments’ ability to generate the appropriate resources or willingness to pay [80,81]. Some studies have translated HIA to DALYs; we did not find a standard conversion that would be applicable to the various country settings [17]. Moreover, the usefulness of this type of threshold is especially important when discussing high cost interventions, such as PrEP and TasP. Although these prevention strategies may be considered cost-effective under certain assumptions, this may not always translate into feasible implementation. The GDP-based threshold is unrelated to national and donor HIV budgets, both of which are needed to understand an intervention’s affordability. Thus, more information is need on whether many SSA countries would be able to implement a large-scale PrEP program, although its use as a main prevention strategy has been heavily emphasized in policy discussion [8]. Many countries are already struggling to provide universal ART, and adding a high-cost strategy may apply further pressure on resource limited prevention programs.

In the 2009 review, Galarraga et al. concluded that not enough information regarding cost-effectiveness of many prevention strategies existed for decision-making or policy change [9]. Their review included many cost-effectiveness studies on interventions for behaviour change, intravenous drug use (IDU) harm reduction, and information, education, and communication. The present review found only two studies

**Fig. 5.** Cost-effectiveness measures of PMTCT interventions. Data points reflect the measures from PMTCT studies reporting cost per HIV infection averted (above) and cost per DALY averted or QALY gained (below). Points represent study-specific cost-effectiveness estimates.

**Fig. 6.** Cost-effectiveness measures of biomedical interventions. Data points reflect the measures from miscellaneous biomedical studies reporting cost per HIV infection averted (above) and cost per DALY averted or QALY gained (below). Points represent study-specific cost-effectiveness estimates; error bars represent estimate ranges, if provided in study results.
on behaviour change and structural interventions, with most recently published studies focusing on biomedical interventions. This shift represents a reflection of changing priorities of the international donor community and emerging technology available from pharmaceutical companies. The authors mentioned the lack of cost-effectiveness studies on vulnerable groups, such as men who have sex with men (MSM) and female sex workers (FSW). Similarly, the current review found only one study focusing on FSWs, although there are published studies on these populations in settings outside of Africa [66,82]. The continuing dearth of studies on these vulnerable populations in sub-Saharan Africa ought to be addressed by future research, as costing studies can inform policymaking.

Several limitations were recognized while conducting this review. First, behavioral and structural interventions, like partner concurrency reduction and condom use, have historically been included in HIV prevention programs [71]. Although the studies in this paper suggest that these strategies are cost-effective, most analyses do not separate the effect of behaviour change on HIV incidence from other interventions, thus not allowing us to understand the effectiveness of these interventions in isolation [67,71]. Second, comparability across studies was difficult since parameters, settings, and assumptions vary. Unless studies present cost-effectiveness estimates using the same assumptions, base year, time horizon, and discount rate, we should take caution when comparing study estimates.

Third, many of the cost-effectiveness studies offer evidence for a specific intervention in a number of scenarios, but few address the potential effects of an intervention in scenarios outside the scope of the study. This makes it difficult to generalize a study’s results to other country settings, creating an obstacle for policy makers in determining how and when a single intervention is the most cost-effective for a specific country. The limited geographic coverage among the studies additionally does not allow for broad generalizability. South Africa was the setting in 24 of the 60 studies (40%) and just three countries (South Africa, Zambia, and, Malawi) comprise over 60% of the studies.

Fig. 7. Cost-effectiveness measures of structural interventions. Data points reflect the measures from structural intervention studies reporting cost per HIV infection averted (above) and cost per DALY averted (below). Points represent study-specific cost-effectiveness estimates; error bars represent estimate ranges, if provided in study results.
### Table 3: CHEERS quality assessment, by intervention type.

| Study Reference | Rating | Item 1 | Item 2 | Item 3 | Item 4 | Item 5 | Item 6 | Item 7 | Item 8 | Item 9 | Item 10 | Item 11 | Item 12 | Item 13 | Item 14 | Item 15 | Item 16 | Item 17 | Item 18 | Item 19 | Item 20 | Item 21 | Item 22 | Item 23 | Item 24 |
|-----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Rutstein et al. (2014) | Y | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Fasowe et al. (2013) | Y | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Granich et al. (2012) | Y | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Barnighausen et al. (2012) | Y | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Awad et al. (2011) | Y | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Utman et al. (2011) | Y | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Duffy et al. (2013) | Y | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Menon et al. (2014) | Y | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Awad et al. (2015) | Y | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Tastr | Y | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Njeuhmeli et al. (2016) | Y | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

**Abbreviations:** Y = item completely fulfilled; P = item partially fulfilled; N = item not fulfilled; N/A = item not applicable to the study
Lastly, this review is not immune to publication bias. Studies that do not demonstrate interventions as cost-effective are less likely to be submitted to peer-reviewed journals or to be published by journals [83]. It is possible that some cost-effectiveness results of current HIV interventions are not available to key policy makers, which poses a large problem. Despite the aforementioned limitations, this review included studies of good quality, highlighting the strength of the available evidence. The large number of studies included in this review reflects the increasing importance of considering cost-effectiveness as a factor in implementing HIV prevention interventions in sub-Saharan Africa. The studies demonstrated intervention cost-effectiveness under a variety of scenarios and emphasized interventions targeting high-risk populations. In contrast to the 2009 Galarraga review, which concluded that sufficient cost-effectiveness data did not exist to inform large-scale decision making, the results from emergent, more robust and varied costing studies may serve as an aid to inform evidence-based decisions. Key stakeholders, such as international donors and government agencies, should consider cost-effectiveness results and affordability when developing national guidelines and protocols for HIV prevention to maximize prevention impact under resource constraints. However, important gaps in the research persist: a lack of focus on vulnerable populations remains an important concern in this region, and additional studies that discuss the cost-effectiveness of different combinations of interventions are needed to reflect the reality of HIV programs in this region [84].

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Contributors

KW conceived the study. SS and SE conducted the literature search. PK, SE, and SC conducted the data extraction. SS wrote the first draft, and KW, PC, SE, SC, and PK reviewed and provided feedback. All authors approved the final paper.

Declaration of Interests

The authors declare that they do not have any competing interests.

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Appendix A. Supplementary Material

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