



# Costs and Cost-Effectiveness of Biomedical, Non-Surgical HIV Prevention Interventions: A Systematic Literature Review

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## Abstract

**Background** Considerable evidence on the costs and cost-effectiveness of biomedical, non-surgical interventions to prevent human immunodeficiency virus (HIV) transmission has been generated over the last decade. This study aims to synthesize findings and identify remaining knowledge gaps to suggest future research priorities.

**Methods** A systematic literature review was carried out in August 2020 using the MEDLINE, Embase, Global Health and EconLit databases to retrieve economic evaluations and costing studies of oral pre-exposure prophylaxis (PrEP), injectable long-acting PrEP, vaginal microbicide rings and gels, HIV vaccines and broadly neutralizing antibodies. Studies reporting costs from the provider or societal perspective were included in the analysis. Those reporting on behavioural methods of prevention, condoms and surgical approaches (voluntary medical male circumcision) were excluded. The quality of reporting of the included studies was assessed using published checklists.

**Results** We identified 3007 citations, of which 87 studies were retained. Most were set in low- and middle-income countries (LMICs;  $n = 53$ ) and focused on the costs and/or cost-effectiveness of oral PrEP regimens ( $n = 70$ ). Model-based economic evaluations were the most frequent study design; only two trial-based cost-effectiveness analyses and nine costing studies were found. Less than half of the studies provided practical details on how the intervention would be delivered by the health system, and only three of these, all in LMICs, explicitly focused on service integration and its implication for delivery costs. ‘Real-world’ programme delivery mechanisms and costs of intervention delivery were rarely considered. PrEP technologies were generally found to be cost-effective only when targeting high-risk subpopulations. Single-dose HIV vaccines are expected to be cost-effective for all groups despite substantial uncertainty around pricing.

**Conclusions** A lack of primary, detailed and updated cost data, including above-service level costs, from a variety of settings makes it difficult to evaluate the cost-effectiveness of specific delivery modes at scale, or to evaluate strategies for services integration. Closing this evidence gap around real-world implementation is vital, not least because the strategies targeting high-risk groups that are recommended by PrEP models may incur substantially higher costs and be of limited practical feasibility in some settings.

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## Key Points for Decision Makers

Our literature review identified a large volume of literature on the costs and cost-effectiveness of biomedical, non-surgical interventions to prevent human immunodeficiency virus (HIV) transmission. Most literature focuses on oral PrEP regimens, is set in low- and middle-income countries and largely covers interventions targeting the general population.

PrEP technologies were generally found to be cost-effective only when targeting high-risk subpopulations, although relatively little evidence is available on more recently developed technologies. Single-dose HIV vaccines are expected to be cost-effective for all groups despite substantial uncertainty around pricing.

A lack of primary, detailed and updated cost data, including above service-level costs, from a variety of settings makes it difficult to evaluate the cost-effectiveness of specific delivery modes at scale, or to evaluate strategies for services integration. To effectively assist priority setting, more practical detail is needed on how modelled interventions would be implemented by the health system.

## 1 Background

The human immunodeficiency virus (HIV) epidemic continues to cause extensive morbidity and mortality globally. Despite global progress towards reaching the 90–90–90 targets, only 87% of people living with HIV who knew their status accessed antiretroviral therapy (ART) in 2020 [1], and gaps in HIV prevention and treatment contributed to 1.5 million new infections and 690,000 HIV-related deaths [2].

With the exception of voluntary medical male circumcision, the existing arsenal of biomedical HIV prevention tools, which includes oral pre-exposure prophylaxis (PrEP), condoms and medication-assisted treatment for people who inject drugs (PWIDs), requires frequent usage, which contributes to implementation challenges and high recurrent costs. Forthcoming products that offer longer duration of protection are poised to have a significant impact on HIV prevention efforts. For example, the dapivirine vaginal ring for women received a positive opinion from the European Medicines Agency as a monthly prevention option [3] and has been recommended by the World Health Organization (WHO) as a new choice for HIV prevention for women at substantial risk of HIV infection [4]. Phase III clinical trials

showed that the ring reduced HIV infection risk by approximately 30% overall [5]. Additionally, long-acting PrEP with cabotegravir administered as a bi-monthly injection was found to be 89% more effective than oral PrEP at preventing HIV acquisition [6], and has been approved by the US FDA [7]. Furthermore, several HIV prevention monoclonal antibody candidates are currently advancing through clinical development [8–10], and a number of putatively more potent combinations and engineered antibodies are also undergoing early clinical evaluation [11].

Information on the costs and cost-effectiveness of new HIV prevention interventions is required to inform priority setting, particularly drawing from and reflecting on ‘real world’ implementation. Funding for HIV programmes is not growing, which results in mounting pressure to improve the efficiency of HIV spending, for example by promoting the integration of HIV service delivery with other health services [12, 13]. Moreover, gaining insight into the drivers of cost and cost-effectiveness can help shape key choices in the early development of biomedical HIV prevention products that may have long-term implications for affordability and uptake, including pricing strategies, dosing regimens, coadministration strategies and delivery approaches.

Therefore, the aim of this literature review was to collate evidence on the costs and cost-effectiveness of biomedical, non-surgical HIV prevention interventions, to identify gaps and suggest future research priorities.

## 2 Methods

A systematic literature review was carried out using the Medline, Embase, Global Health, EconLit and Web of Science databases between 26 and 27 August 2020. The Cochrane Database of systematic reviews was also searched to retrieve other reviews on the same topic and hand search the reference lists of any relevant records. Searches were limited to full texts published after 2010, written in English and focusing on human subjects. The search strategy combined keywords on human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), HIV prevention interventions and economic evaluation. Published cost and cost-effectiveness filters were used for MEDLINE and adapted for other databases [14]. The full search strategies and number of records retrieved for each database are reported in the electronic supplementary material (ESM). Reporting follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist [15].

### 2.1 Screening, Data Extraction and Analysis

The abstract and titles of all unique records were screened and articles were further excluded based on the following criteria: (1) language other than English; (2) topic not related to human health; (3) no reference to HIV prevention interventions; (4) no reference to cost, cost-effectiveness, efficiency or priority setting models; and (5) ineligible article types (e.g. conference abstracts, comments, letters, review articles, methods papers). The full texts of the remaining articles were then reviewed and retained if they made reference to biomedical health products or technologies for preventing HIV infection in uninfected individuals (e.g. pre-exposure prophylaxis, or ‘PrEP’, or HIV vaccination). Behavioural methods of prevention, condoms and surgical approaches (voluntary medical male circumcision) were excluded. Articles reporting costs exclusively from the perspective of patients were also excluded.

Data were extracted from the retained records in the following categories: study setting; objective; population and demographics of interest; intervention and comparator; type of economic analysis, including perspective, cost analysis methods, data sources and types of costs; intervention delivery method (stand-alone or integrated) including any shared costs; type of model, if any, including disease transmission model characteristics where applicable; main results and

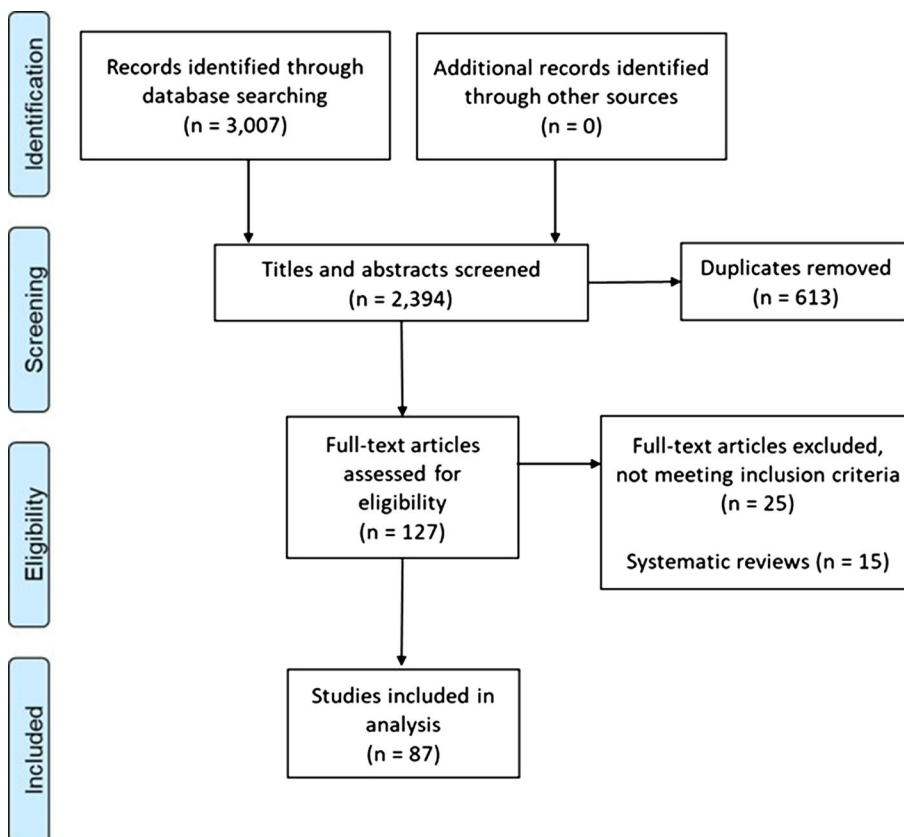
sources of uncertainty. The data were summarized using descriptive statistics and narratively following thematic analysis of the contents of the articles.

The quality of included studies was assessed using the Global Health Costing Consortium (GHCC) reference case for studies that have a substantial primary cost data collection component [16], and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist for economic evaluation studies [17]. While the GHCC reference case sets out methodological standards that costing studies should adhere to, the CHEERS checklist lays out reporting standards and is not intended to assess methodological quality.

### 3 Results

We identified 3007 citations, of which approximately 1 in 20 were eligible for full-text screening. The PRISMA flowchart with details of the study screening and selection process is shown in Fig. 1. After the selection process was completed, 87 studies were retained for analysis. All studies meeting the inclusion criteria were included in the review, regardless of quality assessment score. The main study characteristics are summarized in the ESM.

Fig. 1 Screening and selection process for included studies



### 3.1 Study Characteristics

#### 3.1.1 Setting

Approximately two-thirds of the studies ( $n = 53$ ) focused on low- or middle-income countries (LMICs), with South Africa ( $n = 27$ ) and Kenya ( $n = 9$ ) being the countries most represented in the sample. Two of the largest PrEP demonstration projects were also based in these countries [18, 19]. Thirty-four studies analyzed data from high-income countries (HICs) and two studies were global. The majority of studies focusing on specific countries analyzed national-level data, while approximately one in four studies focused on individual regions, districts or urban areas. Countries in all UNAIDS regions were individually represented in the sample as follows: Eastern and Southern Africa (21%,  $n = 18$ ), Western and Central Europe and North America (18%,  $n = 16$ ), Asia and the Pacific ( $n = 6$ ), Latin America and the Caribbean (2%,  $n = 2$ ), Western and Central Africa (2%,  $n = 2$ ), Eastern Europe and Central Asia (1%,  $n = 1$ ), and Middle East and North Africa (1%,  $n = 1$ ).

#### 3.1.2 Study Populations

Most studies analyzed interventions for the general population ( $n = 49$ ). Studies focusing on key populations overwhelmingly evaluated interventions targeting men who have sex with men (MSM;  $n = 38$ ), nine studies focused on female sex workers (FSW), and eight studies focused on PWIDs. Some of the studies ( $n = 17$ ) compared the costs or cost-effectiveness of interventions across different populations or subgroups, such as adults versus adolescents/young adults or high-risk groups within a subpopulation. A breakdown of study populations investigated in the most represented geographical regions is presented in Fig. 2.

#### 3.1.3 Interventions and Comparators

The interventions analyzed in the retrieved records are also summarized in Fig. 2, stratified by study population. Eighty percent of retrieved studies ( $n = 70$ ) focused on the costs and/or cost-effectiveness of oral PrEP regimens, mostly on their own [18, 20–61] rather than in combination with other prevention interventions such as condom use, treatment as prevention, and HIV counselling and testing [35, 62–86]. All oral PrEP studies examined emtricitabine/tenofovir disoproxil fumarate regimens, whether branded or generic, except for one paper comparing this regimen with the newer emtricitabine/tenofovir alafenamide [58]. The most common comparator for cost-effectiveness studies was the status quo or no

intervention. A few studies compared the relative cost-effectiveness of PrEP between subpopulations (e.g. all adults) and high-risk groups (e.g. FSWs only). Another common comparison was the relative cost-effectiveness of daily PrEP and event-driven ('on-demand') PrEP, either limited to high-risk sexual encounters or around specific time periods, such as pregnancy and breastfeeding or as a bridge to ART for HIV-infected partners in serodiscordant couples.

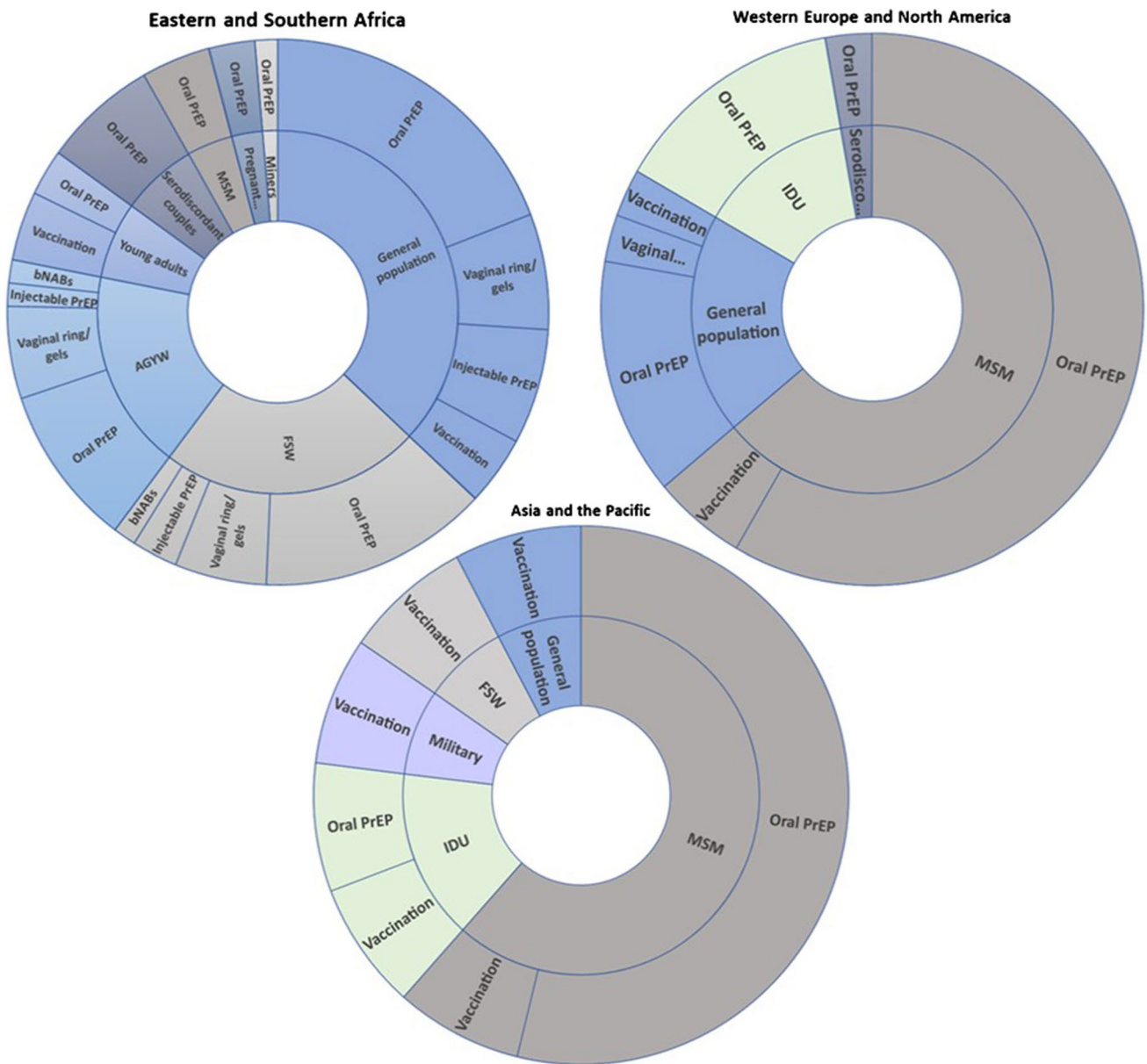
Eleven studies investigated the cost-effectiveness of HIV vaccines compared with no intervention [37, 82, 87–90]; comparing different vaccination strategies (e.g. one-off versus revaccination strategies, different target populations) [91–93]; or comparing HIV vaccination with oral PrEP [62, 94].

Fewer records retrieved focused on non-oral forms of PrEP, including six studies on microbicide gel [76, 80, 95–98] and four studies each on long-acting injectable PrEP [80, 82, 99, 100] and vaginal rings [80–82, 101]. Only one study reported results on broadly neutralizing HIV-1 antibodies (bNABs), a promising novel approach to prevention that engages with the host immune response to neutralize free virus, clear infected cells and inhibit cell-to-cell transmission of HIV-1 [82]. All of these studies compared the new prevention technologies, alone or in combination with other interventions, to current standards of preventive care, likely reflecting the early stage of development of the technologies and thus the exploratory nature of the research questions.

#### 3.1.4 Intervention Design

Less than half of the studies (43%) provided practical details on the platforms through which the intervention of interest would be delivered, either through routine public health services, pharmacies or other distribution systems, and only three of these explicitly focused on service integration and its implication for delivery costs [45, 52, 100].

Among the studies that explicitly mentioned delivery modes, 11 stated that the intervention was delivered through a stand-alone vertical programme, with dedicated resources (diagnostics, staff, program management) but likely assuming no shared costs; 10 studies described interventions delivered through routine HIV services; 7 studies reported on interventions integrated with an existing HIV service (e.g. a vaginal microbicide programme integrated with a condom distribution programme); and another 10 studies reported on interventions integrated with other non-HIV health services (e.g. HIV vaccine delivered through the expanded programme on immunization, or long-acting injectable PrEP delivered during family planning visits for injectable contraception).



**Fig. 2** Summary of populations and technologies studied, by region. *PrEP* pre-exposure prophylaxis, *MSM* men who have sex with men, *bNABs* broadly neutralizing HIV-1 antibodies, *FSW* female sex worker, *AGYW* adolescent girls and young women

### 3.2 Study Methods

#### 3.2.1 Cost and Cost-Effectiveness Analyses

A small number of studies carried out cost analyses (10%) only, while the majority were economic evaluations. Of these, more than half were cost-utility analyses, using either cost per quality-adjusted life-year (QALY) gained or per disability-adjusted life-year (DALY) averted as outcome measures. Approximately 30% were cost-effectiveness analyses,

most commonly reporting cost per infection averted or per life-year gained. The majority of economic evaluations that used cost-effectiveness thresholds to establish whether the interventions represented good value for money used gross domestic product-based thresholds proposed by the WHO.

Lastly, 10% of the studies sought to optimize resource allocation or intervention scale-up for a given budget. Common objectives of these studies included maximizing intervention impact and/or coverage under a set of budget constraints.

### 3.2.2 Model-Based and Trial-Based Analyses

Only two of the studies presented the results of trial-based cost-effectiveness analyses [26, 46]. The majority of studies (83%) were instead based on mathematical models of disease transmission. The three main transmission model types—deterministic compartmental models, stochastic models and agent-based simulations—were present. No pattern was observed in terms of the chosen mathematical model structure for specific interventions, with different structures being used interchangeably to accommodate different technologies and answer diverse study questions (Fig. 3).

Thirty-three (44%) of the transmission model-based analyses were pre-trial analyses that posed exploratory strategic questions (e.g., is oral PrEP cost-effective in a given population?), while the remainder addressed more tactical questions of relevance once the efficacy of the technology has been demonstrated (e.g. which population groups should be targeted during scale-up? What is the most cost-effective way of delivering HIV vaccines?). The most common time horizons for the models were in the 10- to 20-year range (62%), and 21% of the models projected costs and outcomes over a lifetime horizon.

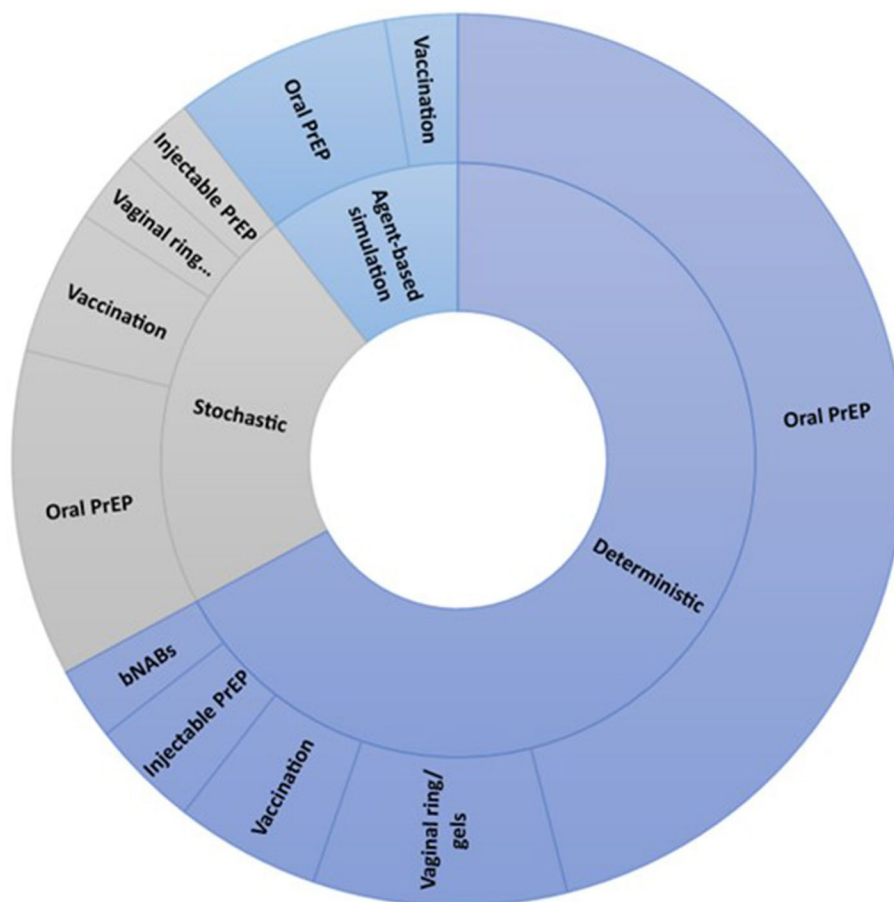
### 3.2.3 Costing Methods

The vast majority of studies took a provider or payer perspective (86%) and calculated economic costs, taking opportunity costs into account (90%) rather than financial costs. Only approximately 30% of studies mentioned the inclusion of above service-level costs, defined as the costs of support services provided by central administrations such as training, laboratory services or sensitization campaigns.

Only nine studies (10%) in the sample collected primary data, seven from bottom-up microcosting exercises [18, 26, 31, 44, 46, 71, 86] and two allocating programme costs using top-down gross costing methods [27, 52]. Most studies (93%) used secondary cost data sources to parameterize economic models, including published and grey literature, public procurement price lists and other national-level routine sources such as insurance reimbursement prices (particularly in HICs), and ‘off-the shelf’ estimates such as the Lives Saved Tool [82]. The remaining studies either made assumptions about the prices of novel drugs or technologies, or validated assumptions or costs extrapolated from the literature through key informant/expert consultations.

Lastly, 10 studies modelled the optimal costs of the intervention or programme of interest for it to achieve a certain

**Fig. 3** Intervention frequency by type of model structure. *PrEP* pre-exposure prophylaxis, *bNABs* broadly neutralizing HIV-1 antibodies



objective, such as remaining cost-effective or optimizing resource allocation under a budget constraint [20, 22, 61, 65, 66, 73, 87, 89, 90, 93].

### 3.2.4 Quality Assessment

The quality of studies collecting primary cost data was high overall, with an average score of 80% based on the criteria laid out in the GHCC reference case. Overall, the reference case principles with the lowest average scores were #14 (reporting on the use of shadow prices), #15 (reporting variation in costs by size and subpopulation) and #16 (uncertainty is appropriately characterized).

The quality of economic evaluations, assessed using the CHEERS checklist, was also good overall, with an average score of 70%. The criteria with the lowest average score were #13 and #14 (supplying details of resources and costs estimation and currency conversion), and #18 (reporting values, ranges, references and, if used, probability distributions of all study parameters).

## 3.3 Study Findings

### 3.3.1 Oral PrEP

Daily oral PrEP was generally found to be costly, with the potential to become cost-effective only at lower or generic prices, or when targeting high-risk groups, although findings were not conclusive across settings and subpopulations. In settings with generalized HIV epidemics, with sustained transmission in the general population, PrEP programmes targeting the general population would not be included in an optimal package of prevention interventions, which would rather favour scaling-up existing interventions such as universal or early ART and voluntary medical male circumcision [20, 21, 48, 64, 76, 77, 79, 82, 102].

Findings among subpopulations are less uniform. Several studies across both high- and low-income settings found that daily oral PrEP can be cost-effective when high-risk population groups are targeted, while uniform scale-up to the entire population (or subpopulation) is usually not cost-effective [34, 39, 42, 59, 65, 103]. For example, MacFadden et al. found an incremental cost-effectiveness ratio (ICER) of between US\$640,000 and US\$1,025,600 per QALY gained by introducing oral PrEP for all MSM in Toronto, Canada, while targeting the highest-risk decile yielded an ICER of US\$45,000–90,000 per QALY [39]. Similar findings were reported by Nichols et al. in Macha, Zambia, where targeting the highest sexual activity groups in the population was found to be highly cost-effective compared with no targeting of oral PrEP [42]. Jamieson et al. found that in South Africa, self-selection of higher-risk individuals in subpopulations (adolescents, young adults) can be up to 10 times

more cost-effective compared with targeting the entire subpopulation to receive daily oral PrEP [32].

Oral PrEP was also found to be cost-effective among young women and FSWs in LMICs [48, 80, 97]. However, there is evidence that it might not be cost-effective in all high-risk groups and across settings. Roberts et al. report that the costs of daily oral PrEP delivery targeting young women could be up to 40% lower when the intervention is integrated into the routine family planning services provided at Kenyan government clinics [52]. Among PWIDs, adding PrEP to existing interventions such as methadone maintenance therapy, needles and syringe exchange programmes, naloxone and addiction counselling was found to not be cost-effective at current PrEP drug prices in the USA and Ukraine [36, 63, 67, 68, 84], while one study found that daily oral PrEP coupled with increased frequency of HIV testing (every 6 months) among PWIDs in India was cost-effective at a reference price negotiated with manufacturers [35].

Among MSM, several studies in high- and upper middle-income settings found daily oral PrEP was not cost-effective at current prices [22, 24, 26, 27, 40, 46, 50, 55, 60, 73, 75]. Two stochastic modelling analyses, one with a global scope and one focusing on the USA, found that in addition to high prices, PrEP among MSM is not cost-effective at low levels of adherence (defined as efficacy <92%, as observed in clinical trials) and low background levels of HIV prevalence [24, 40]. Similarly, studies from Lima, Peru and Hong Kong found that PrEP for MSM is not cost-effective at coverage levels currently attainable within the budget envelope [28, 60]. Studies from The Netherlands and San Francisco, USA, respectively, found that PrEP for MSM is more likely to be cost-effective in the absence of risk compensation (the increase in risk-taking behaviour triggered by a decrease in perceived risk) [50], and when background ART coverage is low [54]. In contrast, other studies found that PrEP is cost-effective among MSM in The Netherlands [43] and England [45] at efficacy levels between 65 and 80%; among MSM and transgender women in Brazil [38]; and among transgender FSWs and their clients in Lima, Peru [69].

Among serodiscordant couples, the general consensus in the literature is that due to the high cost of PrEP drugs, PrEP for the uninfected partner is generally not cost-effective compared with early ART for the HIV-infected partner [29, 72, 104], although a study from Kampala, Uganda, concluded that PrEP in serodiscordant couples as a bridge to sustained ART use for the HIV-infected partner is slightly more cost-effective (US\$1340 per DALY averted) than scaling up ART for the whole HIV-infected population (US\$1452 per DALY averted) [86]. Similarly, Schneider et al. found that oral PrEP is only cost-effective when targeting MSM in serodiscordant partnerships in Australia, compared with targeting 10–30% of all MSM or all high-risk MSM [53]. Other time-limited uses of PrEP, such as during pregnancy and breastfeeding

[49] and sexual event-driven PrEP, were found to be cost-effective both in the general population and among MSM in most high- and upper middle-income countries, where PrEP prices are higher [27, 41, 43, 51], as well as among the partners of migrant miners during home visits in Mozambique [25]. No studies of PrEP in paediatric populations were retrieved.

### 3.3.2 Other Forms of Pre-Exposure Prophylaxis (PrEP) and Broadly Neutralizing HIV-1 Antibodies (bNABs)

Evidence on other forms of PrEP, including dapirivine-containing intravaginal rings, tenofovir-based vaginal microbicides, injectable long-acting PrEP (rilpivirine) and bNABs, also found that they are unlikely to be cost-effective outside of specific high-risk groups. A study by Smith et al. seeking to identify an optimal package of HIV prevention interventions for the South African population that includes both existing interventions (oral PrEP, condoms, voluntary medical male circumcision, early ART) and new interventions (vaginal microbicides/rings, bNABs, long-acting antiretrovirals, HIV vaccine) concluded that a cost-effective package would include all established technologies with the addition of a vaccine, while the newer PrEP technologies would be excluded unless their price could be lowered [82].

However, other studies from South Africa found that targeting specific risk groups could be cost-effective. Evidence on long-acting injectable PrEP in South Africa, for example, concludes that it would be cost-effective for young women and FSWs [80, 99, 105] but not for heterosexual men [102]. Another study assessing the use of injectable antiretrovirals among long-acting contraceptive users attending family planning clinics in Limpopo province, South Africa, found that despite the economic benefit of service integration, the intervention would not be cost-effective unless the price of PrEP decreased by 16% and coverage was sustained at 85% [100].

Early models exploring the cost-effectiveness of vaginal microbicide gels concluded that they had the potential to be cost-effective for women of reproductive age in a generalized epidemic setting such as in South Africa [97, 98], but not in the USA, even in areas with higher relative HIV prevalence such as Washington, DC [96]. Terris-Prestholt et al. calculated that tenofovir gel could be cost-effective for women in Gauteng Province, South Africa, at a maximum price of US\$0.12 per dose, which could be increased to more realistic threshold prices (US\$0.25 or US\$0.33, respectively) if administered as a single dose or if highly effective [95]. Dapirivine-containing intravaginal rings could also be cost-effective among young women and other high-risk groups such as FSWs and women with multiple sexual partners in South Africa [81, 101].

### 3.3.3 HIV Vaccines

HIV vaccines are generally expected to achieve high impact even if imperfectly efficacious (i.e., allowing for breakthrough infections among vaccinated individuals), although much uncertainty remains around costs. The three retrieved studies focusing on an HIC (USA) found that the vaccine would be highly cost-effective among MSM compared with oral PrEP [62, 94], but even a single dose regimen would not be cost-effective compared with no intervention in the general population, and repeated booster doses every 3 years would make it no longer cost-effective even among MSM and PWIDs [93].

Six studies focused on vaccines in LMICs. Modelling evidence from these concluded that a vaccine administered to the reproductive-age population of LMICs would be cost-effective under most coverage, product profile and efficacy scenarios except for very high prices and a 3-year duration of protection [87]. A study from Thailand, modelling a prime-boost combination of the LVAC-HIV and AIDSVAX B/E vaccines, found that the vaccine would remain cost-effective at a high price per dose (\$353) with 70% efficacy, lifetime protection and no change in post-vaccination risk behaviour, but would not be cost-effective at any price if efficacy was low (30%) and the vaccine induced even a relatively small increase (10%) in risk behaviour [37]. Evidence from South Africa suggested that a partially effective and rapidly waning vaccine could still be cost-effective under targeted delivery to age groups with the highest HIV incidence [90], and that campaign-based vaccination is consistently less costly and more effective than routine vaccine delivery [88, 89, 91].

## 4 Discussion

This systematic review summarized data from a large number of studies on the costs and cost-effectiveness of non-surgical, biomedical interventions to prevent HIV. Despite the substantial amount of literature retrieved, relatively few data were found on newer preventive technologies such as injectable long-acting PrEP, vaginal rings and bNABs. Moreover, the cost and cost-effectiveness evidence on these preventive technologies is limited in geographical scope, with most studies focusing on a single LMIC (South Africa), a consideration that also applies to the literature on HIV vaccines.

While the evidence seems to point towards high costs and limited efficacy in the general population, most forms of PrEP were demonstrated to be cost-effective in high-risk population subgroups and/or for specific use cases (e.g. sexual event-based use of oral PrEP, or as a bridge to sustained ART use in serodiscordant couples). These findings are in line with existing literature reviews which conclude that despite being cost-effective among selected key populations,



oral PrEP could be less cost-effective than expanding existing prevention interventions [106, 107]. However, as the range of PrEP products with different durations of protection expands, greater analytical nuance will be required to understand how risk varies over time and its effect on cost-effectiveness. Different products may be more cost-effective at different points in an individual's life.

For some of the technologies, the evidence is too scarce to draw firm conclusions across settings and populations. In particular, fewer than 10 studies each were retrieved on injectable PrEP, intravaginal rings and microbicide gels, and only one study on bNABs. More evidence should be generated comparing intervention strategies that include these modern technologies, focusing on head-to-head comparisons in different settings and for different delivery options. Furthermore, the gross domestic product-based cost-effectiveness thresholds used in the majority of published economic evaluation studies are outdated, as it is now recommended that analysts make use of country-specific opportunity cost-based thresholds [108]. More generally, cost-effectiveness thresholds, particularly early in the life of a product, need to be interpreted with caution. Prices of active ingredients decrease as patents expire; cost and cost-effectiveness research should present findings in a disaggregated manner, allowing for the recalculation of costs and ICERs as prices change.

Substantial uncertainty remains around the price of preventive technologies, their efficacy in the event of less than optimal uptake and adherence (including vaccine hesitancy) or risk compensation in the form of lower condom use. Background rates of HIV prevalence and ART coverage, as well as duration of protection for HIV vaccines, were also found to drive uncertainty in cost-effectiveness estimates. While several model-based analyses conduct threshold analyses to define a price for the technologies to remain cost-effective, the majority of cost parameters in the models are based on secondary estimates or assumptions that are often not comprehensively listed, as revealed by the quality assessments of the included studies. The most frequently cited secondary sources of cost data on intervention delivery include PrEP demonstration projects conducted in South Africa, Kenya and Uganda, not all of them published and often extrapolated to other contexts without making the methods explicit, as well as a few other costing studies from the mid-2000s and early 2010s.

Our sample included relatively few primary costing studies or model-based analyses parameterized with primary data. Moreover, fewer than 15% of studies took a societal perspective and fewer than 30% mentioned the inclusion of above service-level costs. Collecting and reporting comprehensive cost data, including the costs of above service-level activities is particularly important in the case of interventions targeting specific population groups that are often

harder to reach [109]. Excluding the additional spending that is necessary to expand coverage might lead to overestimating the cost-effectiveness of the intervention. Interestingly, the only study comparing existing and newer forms of PrEP and HIV vaccines in a range of populations, and also the only study that builds a cost function to model scale-up costs, concludes that while newer technologies might not be cost-effective in an ideal scale-up scenario, they might be included in the optimal package if health system constraints to the expansion of existing interventions (voluntary medical male circumcision, early ART) were taken into account [82]. In this case, for an equivalent benefit, the additional costs of increasing coverage of existing interventions among harder-to-reach groups may outweigh the costs of newer preventive technologies.

Only a small proportion of retrieved studies detailed the delivery mechanism of the interventions, specifying whether these were integrated with other services or stand-alone. Service integration is an area that deserves increased attention, given the emphasis on its potential for improving efficiency. Evidence from empirical studies of integration at the service delivery level is currently mixed [110], particularly from LMICs where health systems are overstretched, and adding new services onto existing platforms that are facing input constraints might actually reduce rather than boost efficiency [111]. A meta-analysis of the effects of HIV services integration concluded that uptake and retention improved with integration for both HIV and non-HIV services, although no difference in treatment outcomes was detected because of an insufficient number of eligible studies [112]. A recent study of oral PrEP in Zimbabwe further demonstrated that delivery modes that improve continuation rates achieve lower unit costs per person-year [113]. More updated evidence that also captures 'real-world' delivery modes and any health system constraints affecting the feasibility of implementation and scale-up is therefore essential for informing priority setting [106].

Modelling studies should also acknowledge the acceptability and equity implications of suggesting PrEP options be made available only to certain population groups. Beyond the equity implications of restricting access to prevention for at-risk individuals that fall outside defined risk groups, there is also evidence that expanding access may ultimately reduce costs and improve cost-effectiveness by substantially reducing new infections in HIV-endemic countries [114].

## 5 Conclusions

Evidence on the cost-effectiveness of biomedical, non-surgical HIV prevention interventions rests largely on transmission model-based analyses that to date have concentrated on oral PrEP while overlooking more modern prevention

technologies, including long-acting injectable PrEP, intra-vaginal rings and bNABs. The evidence seems to suggest that given the relatively high anticipated costs of these drugs and devices compared with established interventions such as voluntary medical male circumcision and early ART, these interventions might be cost-effective only in higher-risk population subgroups and/or for specific time-limited use cases. However, the scenarios modelled do not include head-to-head comparisons of the more recently developed interventions, and studies are not representative of a wide variety of settings and are rarely explicit about delivery strategies.

More generally, the ‘real world’ mechanisms and costs of intervention delivery are rarely considered or made explicit in the papers analysed in this review. This is an important gap given that reaching some of the high-risk groups that made the delivery of different forms of PrEP cost-effective in model-based analyses may incur substantial additional costs in day-to-day implementation and may, in addition, be of limited practical feasibility in some settings. Similarly, the general lack of primary, detailed and updated cost data from a wider range of settings, including above service-level costs, makes it difficult to evaluate the cost-effectiveness of specific delivery modes at scale, as well as to evaluate strategies for services integration.

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**Conflict of interests** Fiammetta M. Bozzani, Fern Terris-Prestholt, Matthew Quaipe, Mitzy Gafos, Pitchaya P. Indravudh, Rebecca Giddings, Graham F. Medley, Shelly Malhotra and Sergio Torres-Rueda declare they have no conflicts of interest in relation to this article.

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