What do we know about the cost–effectiveness of HIV preexposure prophylaxis, and is it affordable?

Valentina Cambiano, Alec Miners, and Andrew Phillips

Purpose of review
The WHO recommends preexposure prophylaxis (PrEP) in populations at substantial risk of HIV. Despite a number of randomized controlled trials demonstrating its efficacy, and several ongoing implementation projects, PrEP is currently only available in a few countries. Modelling studies can provide useful insights into the long-term impact of introducing PrEP in different subgroups of the population. The review summarizes studies that either evaluated the cost–effectiveness or the cost of introducing PrEP, focusing on seven published in the last year.

Recent findings
These studies used a number of different types of models and investigated the introduction of PrEP in different settings. Among men having sex with men (MSM) in North America, PrEP ranged from being cost-saving (while benefiting population health) to costing US $160 000/quality-adjusted life-year gained. Among heterosexual sero-different couples, it varied from around US $5000 to US $10 000/disability-adjusted life-year averted, when PrEP was used until 6 or 12 months after the HIV-positive partner had initiated antiretroviral therapy (ART) in, respectively, Uganda and South Africa.

Summary
Future cost–effectiveness studies of PrEP should consider the HIV incidence, the level of uptake, the effect of its introduction on alternative prevention approaches, and the budget impact of rolling it out.

Keywords
affordability, cost–effectiveness, HIV prevention, modelling, preexposure prophylaxis

INTRODUCTION
Several guidelines and position statements have been issued recommending PrEP in people at high risk of contracting HIV to prevent HIV acquisition (see Table 1). The use of daily oral Truvada in HIV-negative people has been approved in the USA in 2012 [9], whereas, in most countries, including Europe and Australia, PrEP is not available so far. Importantly, the WHO and the position released by the relevant medical associations in the UK highlighted the importance of estimating the cost–effectiveness of PrEP. The WHO, in particular, reviewed the published literature on the cost–effectiveness of PrEP and took this into account when determining the strength of the evidence in the guidelines for key populations. The WHO announced in July 2015 that updated guidance on PrEP will be released soon [10].

The strong evidence for the effectiveness of PrEP leaves countries and health providers facing the decision of whether to fund PrEP on top of the other HIV prevention programmes already in place and, if so, to decide which subgroups should receive it. Mathematical models provide a framework to combine all the information available on PrEP (uptake, efficacy, effectiveness, adherence, sexual behaviour while on PrEP, monitoring on PrEP, and cost) to provide insights into the potential epidemiological impact, budget impact, and cost–effectiveness of PrEP at a population level. A cost–effectiveness analysis compares the cost and outcomes of two or more different options and usually involves calculation of the cost of obtaining a gain in health (years of life, quality-adjusted life-years (QALY), deaths averted, infections averted, or disability-adjusted life-years (DALYs) averted). The advantage of calculating the cost per QALY gained (or, similarly, per DALY averted) is that this...
‘incremental cost–effectiveness ratio’ (ICER) can be compared across other interventions in any disease area. Budget impact analysis, on the other hand, consists of ‘assessing the financial consequences of the introduction of a new technology in a specific setting in the short-to-medium term’ [11]. These methods have only been relatively recently developed, but they are becoming more and more popular, as countries need to understand, not only whether new interventions would be cost effective, but as well whether they can afford the introduction of these new technologies.

In this study, we review studies which evaluated the cost–effectiveness and/or affordability of PrEP-based HIV preventions, focussing on studies published in the past year. In particular, we aim to determine the settings and populations in which PrEP is likely to be cost effective and affordable.

A number of literature reviews on the cost–effectiveness of PrEP have been performed: some specific to the USA [12] and some more general [13]. A previous literature review of cost–effectiveness studies in the USA (all in MSM) concluded that there was substantial variation in the cost per QALY gained. The wide variation reflects the variation in the effectiveness assumed as well as the different type of models used, static rather than dynamic. Gomez et al. [13] systematically reviewed the literature on cost–effectiveness of PrEP. The populations modelled were heterosexual couples, MSM and people who inject drugs in generalized and concentrated epidemics from southern Africa, Ukraine, USA, and Peru. They pointed out that offering PrEP to key populations appeared to be the most cost-effective strategy and that PrEP had the potential to be a cost-effective component of HIV prevention. The factors found to be most influential were costs, epidemic context, coverage of the prevention programme, the degree to which PrEP is targeted at population with high HIV incidence, and adherence (affecting effectiveness). We now focus on the most recent studies to add to this literature.

**RECENT STUDIES: SEARCH CRITERIA AND SUMMARY OF MODELLING CONSIDERATIONS**

To identify the most recent studies of interest the following terms (‘cost’ AND (‘tenofovir’ OR ‘preexposure prophylaxis’ OR ‘chemoprophylaxis’ OR ‘PrEP’) AND ‘HIV’) were used to search all databases in the Web of Science, starting from 1st July 2014. Eighty-three abstracts were retrieved and seven were identified as eligible as they contained either an evaluation of the cost–effectiveness of PrEP or an estimation of the cost of delivering PrEP (see Table 2).

In terms of the type of mathematical model used in these seven studies, one used a static decision model [14*], three a dynamic deterministic compartmental model [15*,18*,19*], one a dynamic stochastic microsimulation model [17*], whereas two did not use mathematical models, either because they simply used the number needed to treat to estimate the average cost of the PrEP interventions to prevent one infection [16**] or estimated the resources required to deliver PrEP and did not evaluate the cost–effectiveness of introducing it [24]. The difference between static and dynamic models is that static models, typically used in health economics, do not take into account the fact that HIV is an infectious diseases and therefore that by preventing directly one infection, more (secondary) infections are likely to be averted [25].
<table>
<thead>
<tr>
<th>Year</th>
<th>Setting</th>
<th>Body</th>
<th>Title</th>
<th>Issues of costs, cost–effectiveness and affordability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 2011</td>
<td>USA</td>
<td>CDC</td>
<td>Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men</td>
<td>Not mentioned. In the Editorial note it is highlighted the importance of ensuring 'patients understand the financial implications of starting PrEP'</td>
</tr>
<tr>
<td>Jan 2012</td>
<td>UK</td>
<td>BHIVA/BASHH</td>
<td>The British HIV Association/British Association for Sexual Health and HIV Position Statement on preexposure prophylaxis in the UK</td>
<td>Cost is mentioned as a concern if PrEP had to be widespread used in the UK. In addition, they stated that 'It is imperative to gather evidence for the value of PrEP in the UK'</td>
</tr>
<tr>
<td>Jun 2012</td>
<td>South Africa</td>
<td>Southern African Clinicians Society</td>
<td>Southern African guidelines for the safe use of preexposure prophylaxis in men who have sex with men who are at risk for HIV infection</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Jul 2012</td>
<td>Worldwide</td>
<td>WHO</td>
<td>Guidance on pre-exposure oral prophylaxis (PrEP) for serodiscordant couples, men, and transgender women who have sex with men at high risk of HIV: recommendations for use in the context of demonstration projects</td>
<td>The authors highlighted that despite resource costs being collected during the trials, there is poor understanding of their applicability outside this context. They reviewed the cost–effectiveness studies published at the time and recommended PrEP, taking into account the estimated potential cost–effectiveness of PrEP. Out of pocket costs are mentioned one of the factors influencing PrEP acceptability. They underlined the need for demonstration projects and specified that countries will need to evaluate the best allocation of their available resources for HIV prevention, taking in account of the potential role of PrEP.</td>
</tr>
<tr>
<td>Aug 2012</td>
<td>USA</td>
<td>CDC</td>
<td>Interim guidance for clinicians considering the use of preexposure prophylaxis for the prevention of HIV infection in heterosexually active adults</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>May 2014</td>
<td>USA</td>
<td>US Public Health Service</td>
<td>Preexposure prophylaxis for the prevention of HIV infection in the United States – 2014 a clinical practice guidelines</td>
<td>Low out-of-pocket costs are mentioned as one of the most important factor for being adherent to medications by chronic diseases patients</td>
</tr>
<tr>
<td>Jul 2014</td>
<td>Worldwide</td>
<td>WHO</td>
<td>Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations</td>
<td>Costs and financial implications have been taken into account when establishing the strength of the recommendations, included in these guidelines. Regarding PrEP, they concluded that there was variability regarding its cost-effectiveness, highly dependent on the drug price.</td>
</tr>
<tr>
<td>Apr 2015</td>
<td>Europe</td>
<td>ECDC</td>
<td>Evidence suggests that the use of preexposure prophylaxis (PrEP) for men who have sex with men (MSM) is an effective HIV prevention tool for Europe</td>
<td>Not mentioned</td>
</tr>
</tbody>
</table>

BASHH, British Association for Sexual Health and HIV; BHIVA, British Association for Sexual Health and HIV; CDC, Centers for Disease Control and Prevention; ECDC, European Centre for Disease Control and Prevention; UK, United Kingdom; USA, United States of America.
Table 2. Recent studies of the cost-effectiveness of preexposure HIV prophylaxis

<table>
<thead>
<tr>
<th>Chen et al. [14**]</th>
<th>Drabo et al. [15*]</th>
<th>Ouvellet et al. [16***]</th>
<th>Jewell et al. [17**]</th>
<th>Mitchell et al. [18**]</th>
<th>Ying et al. [19**]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of publication</td>
<td>Peer-reviewed paper</td>
<td>Conference abstract</td>
<td>Peer-reviewed paper</td>
<td>Peer-reviewed paper</td>
<td>Peer-reviewed paper</td>
</tr>
<tr>
<td>Setting and population</td>
<td>MSM in the USA</td>
<td>MSM in LA County (USA)</td>
<td>Noninjection drug-using MSM in Canada</td>
<td>Heterosexual sero-different couples in KwaZulu-Natal (South Africa)</td>
<td>Heterosexual sero-different couples in Nigeria</td>
</tr>
<tr>
<td>Model type</td>
<td>Static decision</td>
<td>Dynamic deterministic compartmental</td>
<td>No mathematical model used. NNT used to estimate the ICER</td>
<td>Dynamic stochastic microsimulation</td>
<td>Dynamic deterministic compartmental</td>
</tr>
<tr>
<td>Duration and type of PrEP intervention</td>
<td>1 year of daily PrEP</td>
<td>NA</td>
<td>1 year of on demand PrEP</td>
<td>Daily PrEP used by the HIV uninfected partner before the HIV-positive partner initiates ART and for 1 year thereafter</td>
<td>PrEP used by 60% of HIV uninfected partners, until the first event among: ART initiation of the HIV-positive partner, HIV acquisition or death</td>
</tr>
<tr>
<td>Comparator scenario</td>
<td>No PrEP (ART initiation at CD4⁺ ≤ 500 cells/μl)</td>
<td>No PrEP (ART initiation at CD4⁺ ≤ 500 cells/μl)</td>
<td>No PrEP (ART initiation at CD4⁺ ≤ 350 cells/μl)</td>
<td>No PrEP (ART initiation at CD4⁺ ≤ 350 cells/μl)</td>
<td>No PrEP (ART in 60% of those with CD4⁺ ≤ 200 cells/μl, in 50% of those with CD4⁺ 200–350 cells/μl and 10% of those with CD4⁺ 350–500 cells/μl; overall 40%)</td>
</tr>
<tr>
<td>HIV incidence or prevalence</td>
<td>0.53% baseline risk of HIV acquisition per sex act (0.19 HIV prevalence)</td>
<td>NA</td>
<td>HIV incidence of 2.7 per 100 person-years</td>
<td>HIV incidence between 2 and 9 per 100 person-years (median 5 per 100 person-year)</td>
<td>NA</td>
</tr>
<tr>
<td>PrEP effectiveness</td>
<td>44% based on IPrEx study (92% in alternative)</td>
<td>NA</td>
<td>44% based on IPrEx study</td>
<td>90% based on Partners PrEP study</td>
<td>70% (44–90%) based on Partners PrEP study</td>
</tr>
<tr>
<td>Cost of PrEP (US$)</td>
<td>$10,000 (range: $5000–$15,000) per year</td>
<td>NA</td>
<td>$117,600 (Canadian $12,000) per year</td>
<td>$250 per year</td>
<td>$118 (range: $82.6–$153.4) for PrEP initiation, $233 (range: $163.1–$302.9) per year</td>
</tr>
<tr>
<td>Perspective of the analysis</td>
<td>Societal</td>
<td>Societal</td>
<td>Societal</td>
<td>Healthcare</td>
<td>Provider</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Source for disability weights/utilities</th>
<th>Chen et al. [14**]</th>
<th>Drabo et al. [15*]</th>
<th>Ouellet et al. [16**]</th>
<th>Jewell et al. [17***]</th>
<th>Mitchell et al. [18***]</th>
<th>Ying et al. [19***]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time horizon</td>
<td>Lifetime</td>
<td>NA</td>
<td>Lifetime</td>
<td>20 years</td>
<td>20 years</td>
<td>10 years</td>
</tr>
<tr>
<td>Annual discount rate</td>
<td>3%</td>
<td>NA</td>
<td>0, 3, and 5%</td>
<td>3%</td>
<td>10% [3 and 15% in sensitivity analyses]</td>
<td>3% [0 and 10% in sensitivity analyses]</td>
</tr>
<tr>
<td>Outcome measure</td>
<td>ICER [Cost per QALY gained]</td>
<td>ICER [Cost per QALY gained]</td>
<td>ICER [Cost per QALY gained]</td>
<td>ICER [Cost per DALY averted]</td>
<td>ICER [Cost per DALY averted and per infection averted]</td>
<td>ICER [Cost per DALY averted and per infection averted]</td>
</tr>
<tr>
<td>ICER of PrEP intervention in the base care (US$ if not specified)</td>
<td>$160 000/QALY gained (95% UR: cost-saving $74 000)</td>
<td>$26 000/QALY gained</td>
<td>At 0 and 3% discount rate: cost-saving</td>
<td>$97 577/DALY averted, assuming 33% efficacy of PrEP against HSV-2 and $10 383/DALY averted, assuming no efficacy against HSV-2</td>
<td>Condom promotion was the most cost-effective strategy ($12 065/DALY averted) effective in condom promotion in combination with ART at diagnosis ($16 007/DALY averted) and only at this point the addition of PrEP would be cost-effective ($78 707/DALY averted)</td>
<td>A programme of PrEP and ART: $13 400 per infection averted and $5 334 per DALY averted</td>
</tr>
<tr>
<td>CE threshold</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Cost effective if ICER &lt; 3 times South Africa GDP per capita</td>
<td>Cost effective if ICER &lt; 3 times Nigeria GDP per capita ($8 226) per DALY averted; highly cost effective if ICER &lt; 3 times Nigeria GDP ($27 427)</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost effective if ICER &lt; 3 times Nigeria GDP ($27 427)</td>
<td>Cost effective if ICER &lt; 3 times 2012 Uganda GDP per capita ($1 681)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 5% discount rate: range from $46 000/QALY gained in the most expensive scenario to $59 000 in the least expensive</td>
<td>A programme of ART alone in 90% of those with CD4&lt;sup&gt;+&lt;/sup&gt; &lt; 500 cells/µL: $1 452 per infection averted and 1075 per DALY averted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ICER (expressed in US$) in sensitivity analyses | Higher level of HIV prevalence and high adherence to PrEP: cost-saving | NA | Range presented in the base case | If all couples sero-different for HIV both HIV and HSV-2: $1445/DALY averted | With 15% discount rates cost-effectiveness is reduced. With 3% discount rate the order of cost-effectiveness among interventions is the same but the ICERs are lower |

100% condom use: $840/ QALY gained | With a time-frame of 10 (rather than 20) years, TasP is the most cost-effective intervention, followed by condom promotion + TasP | Clinical capacity: high (1500 couples annually) ICER of $4648/DALY averted; low (200 couples): $18151/DALY averted |

With ART cost at $100/ person-year, 0% annual discounting, 10% dropout from ART and PrEP programme is cost-effective for averted DALY but not very cost-effective. PrEP remains the most cost-effective strategy for averting HIV infections across all ranges of assumptions.

The initial PrEP coverage (40 and 80% rather than 60%) had a small impact on DALYs averted, although had an impact on total costs.

Lower initial condom promotion coverage (40 or 60% rather than 80%) reduced to some extent both costs and DALYs averted, and cost per DALY, but the order remained the same.

Costs are in US dollars if indicated as $.

ART, antiretroviral therapy; CE, cost-effectiveness ratio; LA, Los Angeles; NA, not available; NNT, number needed to treat; PrEP, preexposure prophylaxis; QALY, quality-adjusted life-year; STI, sexually transmitted infections; UR, uncertainty range; USA, United States of America.

*The costing study by Homan et al. is not included in this table, as it did not evaluate the PrEP cost-effectiveness.

**Defined as couples where the HIV-negative partner is aged < 25 years and belongs to the top 15th percentile in the number of casual sex partners.
RECENT STUDIES: MODEL COMPARISONS AND MAIN EPIDEMIOLOGICAL ASSUMPTIONS

Summary details of the studies are provided in Table 2. Of the seven studies we identified, three were among MSM [14**,15*,16**], three in heterosexual sero-different couples [17**–19**], and one in the general population attending primary healthcare clinics [24]. Those conducted among MSM were all North American – from the USA in general [14**], Los Angeles [15*], and Canada [16**]. The studies that focused on sero-different couples were conducted from an African perspective – South Africa [17**], Nigeria [18**], and Uganda [19**] and finally there was one based on attendees at primary healthcare clinics in South Africa [24]. We will focus here primarily on the five published cost–effectiveness studies (not the abstract [15*]).

All of the cost–effectiveness studies compared the introduction of PrEP to a scenario in which PrEP is not introduced [14**,15*,16**–18**], although some studies also considered the potential expansion of HIV testing and/or eligibility criteria for ART initiation [15*,19**]. A couple of them considered the introduction of PrEP in combination either with condom promotion and ART to all those diagnosed with HIV [18**] or with an increase in ART coverage in couples at high risk [19**].

Only two studies provided the HIV incidence in the comparator scenario in which PrEP was not introduced, being 2.7 per 100 person-years [17**] and a median of five per 100 person-years [18**].

The effectiveness of PrEP against HIV was assumed to be 44% by Chen and Dowdy and Ouellet et al. [14**,16**], based on the PrEx study conducted among MSM in several countries including the USA [26] (92% in an alternative scenario in Chen and Dowdy), 70% (range: 44–90%) by Mitchell et al. [18*], 90% by Jewell et al. [17**], and 92% (range: 77–98%) by Ying et al. [19**], all based on the Partners PrEP study [27].

The duration of the PrEP intervention was 1 year in the studies conducted among MSM in North America [14**,16**], for a variable length of time, from enrolment to respectively 6 months and 1 year since ART initiation of the HIV-positive partner in sero-different couples in Uganda [19**] and South Africa [17**], while until HIV acquisition or ART initiation of the positive partner for the HIV-negative partners in the sero-different couples in Nigeria [18**].

Only one study considered the potential impact of a decrease in condom use in people receiving PrEP [14**] and none of them considered other possible negative consequences of PrEP: such as the development of resistance or toxicities because of PrEP, however, there is no evidence from the randomized controlled trials for these to be major issues.

RECENT STUDIES: COST–EFFECTIVENESS PARAMETERS

The cost assumed for 1 year of PrEP varies substantially across studies, mainly driven by the setting. In South Africa and Nigeria this was assumed to be around $250 per year [17**–18**], in Uganda this was estimated to be respectively $408 and $92 in the study and government settings [19**], whereas in North America it was assumed around $10 000 per year (range $5000–$15 000) (including the cost of documenting HIV-negative status, renal function tests prior to PrEP initiation, quarterly clinic visits, HIV testing, biannual screening for sexually transmitted infections, and biannual renal function testing) by Chen et al. [14**] and $11 760 (Canadian $12 000) by Ouellet et al. [16**].

Three of the seven studies considered a societal perspective [this means that the cost and benefit incurred by the society as a whole are taken into account: direct medical and nonmedical costs (e.g. patient transportation to attend the clinic), indirect costs (e.g. time lost from work), and intangible costs (e.g. pain and suffering)] [14**,15*,16**–18**], one study took a healthcare system perspective [17**], two the provider perspective [18**,19**]. The studies conducted among MSM in North America considered a lifetime horizon [14**,16**], whereas the studies among sero-different couples in Nigeria and South Africa used a time horizon of 20 years [17**,18**] and the one in Uganda 10 years [19**].

All the cost–effectiveness studies discounted the costs and effects using an annual discount rate of 3% per year [14**,16**–17**,19**], with the exception of Mitchell et al. [18**] that used an annual discount rate of 10% per year, because of the high predilection for present in Nigeria.

All cost–effectiveness studies used as measure of health benefit used either the DALYs averted [17**–19**] or the QALYs gained [14**,16**], and some in addition considered infections averted [18**,19**]. The disability weights for HIV-positive people used were taken either from a metaanalysis [20] conducted few years ago [14**,16**], or from the Global Burden of Disease study performed in 2004 [21], or in 2010 [18**,19**,22].

Finally, regarding the cost–effectiveness threshold used, only the studies set in Africa [18**,19**] reported this explicitly. They used a cost–effectiveness threshold of three times gross domestic product (GDP) per capita to be cost effective and one time GDP per capita to be considered very cost-effective [28], as was used in previous WHO material, which is
What do we know about the cost–effectiveness of HIV pre-exposure prophylaxis

COST–EFFECTIVENESS OF PREEXPOSURE PROPHYLAXIS IN MSM IN NORTH AMERICA

Chen and Dowdy [14**] estimated the introduction of PrEP for 1 year (44% efficacious) among HIV-negative MSM living in the USA will cost $160 000/QALY gained over a lifetime horizon (95% uncertainty range: cost-saving to $740 000) in the base case. However, they considered alternative scenarios which made PrEP cost-saving (when an HIV prevalence of 0.35 and high adherence to PrEP – such that the PrEP efficacy was 92% – were assumed) and on the other hand scenarios which increased the ICER up as far as $840/QALY gained (in the case of 100% condom use).

Most recently, Ouellet et al. [16**] evaluated the cost–effectiveness of 1 year of ‘on demand’ PrEP (as used in the IPERGAY trial [30]), among non-injection drug-using MSM in Canada. They used the number – needed-to-treat ($1.78), estimated from the iPrEx trial, to calculate the total number of non-injection drug-using MSM needed to be on PrEP to prevent one HIV infection and estimated the lifetime cost of living with HIV, assuming infections occur at age 30, with a life-expectancy of 35.2 years. They found that at 0 and 3% discount rates the PrEP intervention was cost-saving, whereas when using a 5% discount rate the ICER varied from Canadian $47 338/QALY gained, in the most expensive scenario (1 Canadian $ = 0.98 US$), to Canadian $60 223 in the least expensive case.

The three studies [14**,15*,16**] present significant differences in the base case ICER: from cost-saving [16**] to $160 000/QALY gained [14**]. However, given Chen and Dowdy used a static model, which does not take into account secondary infections averted, we would expect this study to obtain less favourable ICERs. In addition, even this study found PrEP to be a cost-saving option in situations characterized by high adherence (corresponding to a PrEP efficacy of 92%) and being used in a high HIV prevalence population (0.35).

Importantly, studies recently published on the cost–effectiveness of PrEP in high-income countries have started taking a societal perspective, allowing them to take into account the cost incurred by the entire society and therefore some of the advantages of keeping people free from HIV. Unfortunately, none of these studies conducted a budget impact analysis necessary to determine its affordability.

Before this last year, only one study had evaluated the cost–effectiveness of PrEP among sero-different couples [31]. They had found that PrEP could be highly cost effective in this population group and even cost-saving. They estimated that if the annual cost of PrEP is less than 40% the annual cost of ART and if PrEP is more than 70% effective then offering PrEP to the HIV-negative partner could be at least as cost effective as initiating ART earlier in the positive one.

Recently, three studies evaluated the cost–effectiveness of PrEP among sero-different couples in Africa [17**–19**].

Jewell et al. [17**] envisaged an intervention where PrEP (90% efficacious against HIV) would be used by the HIV uninfected partner of sero-different couples living in South Africa before the HIV-positive partner initiates ART and for one year thereafter. They found that this intervention with (33% efficacy against herpes simplex virus-2 (HSV-2)) or without protection against HSV-2, would be cost effective, with ICERS (over 20 year time horizon) of respectively $9757 and $10 383/DALY averted (South Africa GDP in 2012 $7314). In the sensitivity analyses they found that if all couples were sero-different not only for HIV but for HSV-2 as well, the ICER could be further reduced to $1445/DALY averted.

Mitchell et al. [18**] compared the cost–effectiveness of condom promotion, treatment as prevention (TasP), PrEP, and their combination against a baseline scenario characterized by eligibility criteria for ART initiation of CD4+ ≤ 350 cells/µL for sero-different couples in Nigeria. They found that the most cost-effective strategy was condom promotion with an ICER of $1206/DALY averted, followed by condom promotion in combination with TasP (ICER: $1607/DALY averted), followed by the addition of PrEP (ICER: $7870/DALY averted).

The order of incrementally cost-effective interventions remained the same when varying the discount rate (range: 3–15%), initial PrEP coverage (range: 40–80%), or initial condom promotion coverage (range: 40–80%). However, with a discount rate of 3% (more commonly used, rather than 10%) and with lower initial condom promotion coverage, the ICERS are reduced. When considering a time frame of 10 years (rather than 20), the most cost-effective intervention became TasP, followed by condom promotion along with TasP, whereas when considering a lifetime frame, the ICERS are improved. This is because of the fact that TasP will have a more immediate effect in averting DALYs by improving

considered unlikely for low and middle-income countries, given in the UK it has been estimated to be around 0.4 of the GDP per capita [29].

COST–EFFECTIVENESS OF PREEXPOSURE PROPHYLAXIS AMONG SERO-DIFFERENT COUPLES IN AFRICA

In situations characterized by high adherence (corresponding to a PrEP efficacy of 92%) and being used in a high HIV prevalence population (0.35). Importantly, studies recently published on the cost–effectiveness of PrEP in high-income countries have started taking a societal perspective, allowing them to take into account the cost incurred by the entire society and therefore some of the advantages of keeping people free from HIV. Unfortunately, none of these studies conducted a budget impact analysis necessary to determine its affordability.
survival in people at low CD4\(^+\), whereas the introduction of PrEP has an effect on DALYs later in time, by averting HIV infections. Ying et al. [19**] estimated the cost–effectiveness of a short-term use of PrEP in HIV-negative partners of high-risk sero-different couples in Uganda. The PrEP intervention is similar to the one described by Jewell et al. [17**], but until 6 rather than 12 months after the HIV-positive partner’s ART initiation and in combination with an increase in ART coverage (assumed currently 40% in Uganda) among the HIV-positive partners of high-risk sero-different couples. They reported that this intervention would be very cost effective in terms of HIV infections averted, but not cost effective in terms of cost per DALY averted ($5334/DALY). They found that clinical capacity played an important role with ICER varying from $4648/DALY averted with high-clinical capacity (1500 couples annually) to $18 151/DALY averted with low-clinical capacity (200 couples annually). When varying other relevant assumptions (ART cost at $100/person-year, rather than $269/person-year, discount rate of 0%, rather than 3% and drop-out from ART and PrEP programme of 10%, rather than 3%) the PrEP intervention remains cost effective for averting DALYs but not very cost-effective, whereas it remains the most cost-effective strategy for averting HIV infections across all ranges of assumptions.

These three studies considered a relatively similar PrEP intervention in sero-different couples, all using dynamic models and with a relatively short time frame, either 10 or 20 years. The cost-effectiveness of the PrEP intervention alone, assessed by Mitchell et al. and Jewell et al., varied from being dominated (meaning that the intervention costs more and is no more effective than the comparator) in Nigeria to a cost of around $10 000/DALY averted in South Africa, where it is cost-effective. When considering the combination of the PrEP intervention with condom promotion and TasP in Nigeria, the addition of PrEP was cost effective only after condom promotion and condom promotion in combination with TasP at an ICER of $7870/DALY averted, whereas in Uganda a programme of PrEP and ART in high-risk couples cost $5334/DALY averted, which means PrEP is unlikely to be cost effective in these circumstances. The ICER threshold for an intervention to be considered cost effective is the subject of much debate, and the often used threshold of one or three time the per capita GDP is widely considered to be too high [32].

The difficulty in comparing these estimates comes from the fact the possible scenarios included differs and so do the countries where these studies are set. In particular there are substantial differences in terms of HIV incidence assumed in these couples (2.7 per 100 person-years in the study set in South Africa [17**] to 5 per 100 person-years in the study set in Nigeria [16**]), ART eligibility and coverage in the reference scenario (CD4\(^+\) < 350 cells/\(\mu\L\)) in the studies set in South Africa and Nigeria, with assumed ART coverage of 100% in Nigeria and of CD4\(^-\) < 500 cells/\(\mu\L\) with 40% ART coverage in the study in Uganda) and the cost–effectiveness threshold, which is based on the GDP per capita ($11 440 for South Africa, $2742 for Nigeria, and $1681 for Uganda). When considering the parameters varied in sensitivity analyses in these three studies, they do not overlap. The parameters that were significantly affecting the results are the proportion of couples sero-different for both HIV and HSV-2 in Jewell et al. [17**], the discount rate and the time frame in Mitchell et al. [18**], and the clinical capacity in Ying et al. [19**].

**RECENT STUDIES: COSTING OF DELIVERING PREEXPOSURE PROPHYLAXIS**

Only two studies presented a costing for delivery of a PrEP programme. Homan et al. [24] estimated the additional cost of using a quality improvement approach to integrate the offer of tenofovir gel (topical PrEP) in primary healthcare clinic and strengthen family planning services in KwaZulu-Natal (South Africa). They estimated the resources necessary to introduce the quality improvement approach are minimal ($18 660) compared with the cost for gel delivery ($89 500). Ying et al. conducted a microcosting study within a PrEP implementation project and estimated the cost in the research setting and in government setting to be respectively $408 and $92 per couple per year.

**CONCLUSION**

There has been a move for studies of cost–effectiveness of PrEP to focus on populations at high risk of contracting HIV. All the studies published in the last year all focused on some of the key populations: MSM in high income countries and sero-different couples in African countries. In addition, those among sero-different couples envisaged a short-term PrEP intervention but in a period of time in which the HIV-negative person is considered at high risk of contracting HIV. Clearly offering PrEP to subgroups of the population and for periods of time where the person is at particularly high risk helps to improve the cost-effectiveness of PrEP. However, identification and successful targeting of these subgroups at higher risk of contracting HIV is not always straightforward.
In addition, some studies [13] concluded that the maximum benefit from PrEP introduction could be realized if introduced in combination with HIV prevention programmes.

Compared with the previous cost-effectiveness studies of PrEP reviewed, some of the recent studies developed further investigation of the role of other prevention interventions (such as expansion of HIV testing and ART) in combination or as alternatives to PrEP, some [18**] found that PrEP would not be the most cost effective, but all found it to be cost effective as an addition (when considering a time frame of 20 years). Unfortunately, most studies do not report the HIV incidence which is clearly a key parameter in determining the cost–effectiveness of PrEP introduction (with PrEP more likely to be cost-effective if incidence is high) and that could help explain the difference in results. The appropriate cost–effectiveness threshold to be used in a given setting remains a key issue that is not fully resolved.

The other crucial element to determine the cost-effectiveness of any intervention is clearly its cost and the cost of its delivery. Ongoing implementation projects are paramount to inform countries on how to deliver PrEP (who, where, how), how much it will cost and what level of capacity is necessary to make it cost effective. Most of the studies presented cost-effectiveness analyses, but not budget impact analyses, with the exception of Ying et al. which estimated, by conducting a microcosting study, the expenditure within a PrEP implementation project, and extrapolated the cost if the programme was to be run by the government. Budget impact analyses are extremely important for health providers when increasing a new technology and are increasingly requested by reimbursement authorities [33]. The cost–effectiveness of an intervention does not in itself imply affordability. This means that even if an intervention is found cost effective and if the country typically uses this criterion to decide on how to distribute the resources on health, this does not mean it will make the policy decision to pay to introduce them. The use of sofosbuvir for treatment of hepatitis C is an example of this in the UK [34]).

Acknowledgements
We would like to acknowledge KohJun Ong, who contributed in reviewing some of the studies.

Financial support and sponsorship
None.

Conflicts of interest
V.C. has received in the past honorarium from Merck Sharp & Dohme Limited, outside the submitted work. The remaining authors have no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


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