Modelling Risk Behaviour: The use of Behaviour Change Assumptions in Cost-Effectiveness Studies for Oral PrEP in the United Kingdom and United States

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Research Article

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Abstract

Background

HIV prevention policy and program implementation rely heavily on cost-effectiveness studies. They involve the use of some uncertain variables, serving as proxies for complex, emergent and unpredictable scientific, social and behavioural issues. The ongoing implementation and scale-up of oral pre-exposure prophylaxis (PrEP) requires the improvement and refinement of cost-effectiveness calculations, and the measures on which they are based.

Methods

We conducted a framework synthesis of the literature on cost-effectiveness for oral PrEP for men who have sex with men (MSM) in the US and UK between 2009 and 2021.

Results

Reviewing how behavioural risk variables were used in the studies, we found both significant increases and decreases in projected risk behaviour in MSM starting PrEP, and limited use of evidence for these variables. Studies that included increased ‘risk compensation’ scenarios inferred quantitative estimates from qualitative measures, appeared to group risk variables with assumptions about low adherence, and projected estimates of increased HIV incidence associated with PrEP use. Conversely, studies that included lower risk behaviour cited related research about behavioural risk reduction associated with treatment-as-prevention and referenced discussions about the importance of changing risk behaviour, rather than empirical evidence of changed behaviour.

Conclusion

Increased accuracy of cost-effectiveness models can be achieved through refining the use of behavioural risk variables, including reference to a common evidence base.

Background

HIV prevention policy and programmes that include the provision of oral HIV pre-exposure prophylaxis (PrEP) to prevent the acquisition of HIV are growing globally, and have been in place in the US and the UK for some time. In England, the aim is to make PrEP routinely available to end HIV transmission by 2030 (1). Impact assessments (IAs) are central to these policies, including projections about the cost-effectiveness of proposed therapies.

Several studies have evaluated the cost-effectiveness of PrEP interventions in different geographic locations and target populations (2–4). These studies consider a number of variables, including the clinical efficacy of the intervention, cost of the medication and associated sexual health services, local HIV incidence and prevalence among specific populations, and sexual behaviour associated with the risk of acquiring HIV, including condom-less sex (CLS).

The use of these variables have differed significantly across studies, leading to differing outcomes in the projected cost-effectiveness of PrEP implementation and scale-up. To improve cost-effectiveness studies, there is a need to strengthen the consideration given to evidence that underlies key variables related to PrEP implementation and scale-up among target populations, as Hoornenborg and colleagues (5) have observed. To accurately inform HIV prevention efforts, the careful use of variables in cost-effectiveness models must be ensured. Transparency and reflexivity in reporting the sources of assumptions about behaviour change are necessary to guide users’ interpretations of the inherently hypothetical nature of models.

Men who have sex with men (MSM) are the most at risk of acquiring HIV in the UK (6) and the largest group of people living with HIV in the USA (7).

Cost-effectiveness studies evaluating PrEP implementation and scale-up among MSM have been challenged by limitations in evidence to substantiate hypotheses about PrEP-driven ‘risk compensation’ on the part of MSM included in the models (5). Since the introduction of PrEP in the US in 2012 and the UK (as part of the IMPACT trial in 2017)(8), discussions about the potential for ‘risk compensation’ have been speculative, and much evidence about risk compensation has been based on research about the acceptability of PrEP and perceptions about its potential effects among MSM. This research has been limited because it was conducted with men who had not taken PrEP themselves and were thus discussing their potential future behaviours linked to a newly introduced therapeutic technology, rather than recounting their experiences as users (9–11). More recently, this evidence has been improved quantitatively and qualitatively through survey and interview-based research with MSM enrolled in PrEP care or using PrEP through different means [authors’ own]. While some MSM enrolled in PrEP care have reported more CLS since starting to use PrEP, results from clinical studies have reported no changes in CLS among PrEP users (12).

Related analyses have monitored STI incidence as a proxy measure for risk compensation linked to PrEP (12–17). These studies have also generated mixed results and faced significant limitations. Specifically, studies utilizing sexually transmitted infections (STI) incidence as a proxy measure for risk compensation have been limited by an ascertainment bias since MSM enrolled in PrEP care may get tested for STIs more frequently than they would otherwise. Therefore, while STI incidence among MSM enrolled in PrEP care may be observed, increased incidence is not on its own a perfect proxy measure for risk compensation. Although the implications of increased screening and diagnosis remain understudied, recent modelling studies that consider regular STI screening required for MSM in PrEP care have shown that PrEP implementation and scale-up are most likely to be associated with greater control of STIs, even if PrEP users choose to stop using condoms (18, 19). Thus studies of increased STI incidence may equally be demonstrating that PrEP implementation has the potential to contribute to additional positive health outcomes.
Such degrees of uncertainty in the evidence may result in a wide range of variables being used in cost-effectiveness studies evaluating PrEP implementation and scale-up among target groups. These would include variables that simulate different scenarios of PrEP-related behaviour change among MSM, and with their use changing over time as the evidence is refined. There is limited research to-date that has evaluated the ways this often very partial evidence has been used, specifically in cost-effectiveness models. Moreover, to our knowledge, no research has so far traced the use of evidence about PrEP-related behaviour change deployed in cost-effectiveness studies, and its effects. We begin to address the need for such an approach in this exploratory review.

Methods

As part of two linked anthropological studies of PrEP in the UK and the United States [authors' own], we began to observe the literature on cost-effectiveness relevant to our observation of public health discussions in each of our sites. As interesting patterns emerged with regards to assumptions and speculations of sexual risk behaviour in the cost-effectiveness models, we conducted a framework synthesis of the literature on cost-effectiveness for oral PrEP among MSM in the US and UK between 2009 and 2021, reported here. For this synthesis, we reviewed how different behavioural ‘risk’ variables were used in the included studies and we limited the analysis to include only studies evaluating daily PrEP use among (only) MSM in US and UK both for pragmatic reasons and to maintain relative consistency within the defined target group.

The initial key word query was first carried out in PubMed in September 2019, and subsequently updated in August 2021, and included terms such as: HIV pre-exposure prophylaxis, cost-effectiveness, and men who have sex with men. This search yielded 133 results (after the removal of duplicates). We excluded studies that were: non/applicable (not on PrEP or HIV prevention) (=20); not on cost-effectiveness (=11); not focused on MSM (=20); not in UK or US (=45); reviews on PrEP with only minimal info on cost-effectiveness (=11); or study protocols (=3).

Based on the exclusion criteria, we identified 17 studies of the cost-effectiveness of PrEP among MSM in US and UK, and 9 reviews of PrEP cost-effectiveness studies that discussed variables relevant to PrEP implementation and scale-up among MSM. After discussion between all authors 4 of the studies were excluded due to incomplete information presented.

To analyse the 13 cost-effectiveness models and 9 reviews, we utilized framework synthesis, a form of qualitative literature synthesis generally conducted to respond to specific policy questions through a combination of deductive and inductive reasoning, with a focus on concepts that are defined a priori, and refined through iterative synthesis (20). We approached original cost-effectiveness studies as texts we could read as qualitative data. First, we used the 9 reviews (Table I) to contextualise the 13 cost-effectiveness studies and to inform the types of questions we asked of the data, including to assess how evidence about PrEP-related behaviour change has been evaluated over the given time period.

[insert Table 1 here]

Secondly, we analysed how risk variables were used in the 13 cost-effectiveness studies, focusing on measures of behaviour change after the introduction of PrEP. We then traced the assumptions about behaviour change in the cost-effectiveness studies to the evidence offered in support, read this and noted what it suggested relative to how it was interpreted in the cost-effectiveness studies. We also noted any instances where no evidence was made available and where no reason was given for exclusion or inclusion of behaviour change variables.

This was an exploratory approach to cost-effectiveness studies that aimed to analyse modelling papers qualitatively, drawing from themes regarding changes in risk behaviours hypothesised in the literature that we initially identified through reading the 9 review articles. Although it was conducted rigorously, it was not a comprehensive review of all possible cost-effectiveness studies, but rather a focused synthesis ‘to clarify and gain insight’ (21) into the broader issue of forecasting of sexual behaviour change in economic studies and the uses of evidence in this process.

Findings

Behavioural risk variables in the models consisted of baseline behaviour measures and behaviour change measures. The first varied by location but were well evidenced. For the behaviour change set of variables we found, firstly, that the direction of the estimate varied (risk increase, decrease, or no change); and, secondly, that the use of the evidence-base for the change scenarios also varied depending on whether increased or decreased risk scenarios were assumed. We describe these findings in turn.

Baseline risk measures

Baseline risk measures differed slightly by geographic location, and were directly linked to evidence from trials relevant to each location and informed by national clinical guidelines. For example, in US studies, behavioural risk measures for PrEP eligibility were associated with clinical trial data from the American iPrEx trial (13) and guidelines from the US Centers for Disease Control and Prevention (22). In the UK studies, behavioural risk measures for PrEP eligibility were associated with clinical trial data from the English PROUD trial (23) and guidelines from the British HIV Association (24). Since the trials were designed to test ‘real world’ interventions, eligibility criteria with regards to risk were drawn, in each site, from: the national epidemiological picture; available surveillance data (e.g., frequency and recency of testing); and participants self-reporting of sexual risk during the respective trials recruitment, leading to different choices of measures.

Behaviour change assumptions

Assumptions concerning PrEP-related behaviour change varied greatly across the 13 cost-effectiveness studies (Table II): just under half of the studies (= 6) did not include assumptions about behaviour change, 4 hypothesised increased risk behaviour, 2 hypothesised decreased risk behaviour, and 1 included a range of possible effects, including increased risk behaviour, decreased risk behaviour, and no effect on risk behaviour. Of the 6 that did not include PrEP-
related behaviour change, 2 provided a justification for not including this assumption in the model, and the remaining studies 4 either did not address the inclusion of behaviour change as a relevant factor or only included 'no behavioural change' in a base scenario, not in an estimate associated with PrEP implementation.

Insert table II here

**Uses of evidence**

Variations in assumptions of behaviour change and their inclusion in studies were linked to different uses of evidence.

In studies where it was acknowledged that assumptions about PrEP-related behaviour change were not included, authors mentioned other several possible clinical, behavioural and social variables also not included in the analysis. For example, Kessler et al int heir study explain:

"There are critical elements relating to the norms of people of various sexual identities and behavioural patterns, including differential condom use with casual partners, serosortive and seroadaptive practices, and alterations in risk behaviour as a result of HIV awareness, that are not explicitly accounted for in our computer simulation due to inherent choices and trade-offs made between model complexity and transparency" (25).

These authors also acknowledged that, "Many of these elements may act to reduce individual level risk for HIV acquisition" (Ibid), thus it would be challenging to isolate the effect of PrEP use itself, given such a range of possible variables. Furthermore, it would be difficult to determine if PrEP use influenced any related element of risk reduction, so assuming PrEP had such effects may even "overestimate the actual health benefits of PrEP" (Ibid).

In a second article that acknowledged not including assumptions about PrEP-related behaviour change, authors explained the "analysis does not explicitly account for many complexities of HIV transmission and treatment, including effects of PrEP use on treatment resistance, correlations between sexual risk behaviour and treatment outcomes" (26).

In studies with assumptions of increased risk behaviour associated with PrEP, authors related to available evidence in three ways. Firstly, they inferred quantitative estimates from qualitative studies about perceptions of likely behaviours among potential PrEP users, some of whom reported behaviour change was possible. For example, a study about the cost-effectiveness of PrEP in the US (27) based assumptions of increased risk behaviours associated with PrEP on three qualitative studies conducted before PrEP was approved by the FDA: one conducted from 2007 to 2009 (28); a second conducted in 2009 (29); and a third completed in 2011 (30). These studies solicited preferences and perceptions among men who have sex with men in New York, couples in San Francisco, and African-American men in Atlanta. In these studies, investigators found 10% of men were concerned that PrEP could lead to behaviour change (30), however "participants differed about whether risk-reduction behaviours would change, and in which direction" following the introduction of PrEP (29). Based on these findings, the authors of the cost-effectiveness study represented behavioural disinhibition in three ways, including: "15% decrease in condom use, 15% increase in sexual encounters, and resulting 15% increase in STI prevalence among those taking PrEP" (27).

Secondly, authors grouped assumptions about behaviour compensation with estimates of lower adherence. As a result, behavioural disinhibition was unduly associated with reductions in clinical efficacy. For example, the authors suggested, "some individuals on PrEP may engage in behavioural disinhibition (be willing to adopt riskier sexual behaviour as a result taking PrEP), and adherence to a daily preventive regimen may vary widely, leading to different levels of clinical effectiveness"(27). The authors associated both "riskier sexual behaviour" and variable adherence with decreases in clinical efficacy. "PrEP efficacy decreased from 44–28%, thus increasing the number needed to treat to 97 (95% UR: 46 to 222)." (27). Page 4).

Thirdly, studies projecting increased risk associated with PrEP use cited evidence of increased STI diagnoses. Two studies presented a conflicting picture with one reporting that whilst STI rates were high, the increase was not necessarily linked with PrEP use, with the other concluding that increased STI incidence was attributable to risk compensation when taking PrEP: '30% of patients were diagnosed with a STI after 6 months and 50% after 12 months on PrEP....there were no incidences of accompanying HIV infection' (31). Another used the increase in STIs to justify estimates of increased HIV incidence over the lifetime of PrEP users, whether or not they continued to use PrEP. For example, one study assumed "Risk compensation would also lead to an increase in HIV exposure" and resulting 20% increase in HIV incidence (32). To justify this assumption, the authors wrote, "published evidence suggests increased frequency of anal CLS subsequent to PrEP use and increased STI diagnoses" (32, 33). While the evidence cited in this instance does show moderate increases in STIs over time, the same cited evidence also clearly observes, "no HIV seroconversions occurred during PrEP use" (23), and does not provide data to suggest that PrEP-related risk compensation will lead to 20% increase in HIV incidence over lifetime of those given PrEP.

In studies with scenarios of decreased risk behaviour associated with PrEP, authors leveraged evidence in two key ways. In the first instance, the authors referred to previous research about risk reduction associated with related elements of HIV care and prevention, including counselling associated with HIV testing, knowledge of one's own HIV status and treatment as prevention (TASP) (34–36). For example, one study citing this evidence observed, "Providing counselling with HIV testing has been found to reduce risky sexual behaviour; thus, we assumed a 20% reduction in risky behaviour for both infected and uninformed persons after HIV screening" (37). In the second instance, studies cited literature that argues for the importance of reducing risk behaviour in order to improve the cost-effectiveness of HIV care, not empirical studies that demonstrate reduced risk behaviour. In one such study citing this literature, authors also assumed, "20% reduction in risky sexual behaviour owing to testing and counselling associated with PrEP" (38).

The single study that assumed a wide range of possible effects on user behaviour reasoned there was the potential for behavioural disinhibition, as evidenced by research about previous risk reduction methods (39) however the authors also recognized the "issue remains to be resolved empirically for the particular case of PrEP," thus they "considered a broad range of behavioural assumptions"(40).

Across all studies, whether assuming increased risk behaviour, decreased risk behaviour or no change in behaviour associated with PrEP use, authors made use of available evidence for different ends, referring to different resources, at times incomplete. In some cases, the particular use of evidence had significant
effects on cost-effectiveness results. For example, when authors constructed a scenario that grouped behavioural disinhibition with lower adherence and thus suggested both would be associated with a reduction in the clinical effectiveness of daily PrEP, they lowered the relative risk reduction of the intervention from 44–28%, elevated the projected number needed to treat (NTT): from 64 [26-175] to 97 [46-222], and raised the cost per quality-adjusted life-years gained from $160,000 to $320,000 (27; table II).

Discussion

Considering the ongoing implementation and scale-up of oral PrEP in the US, UK and many other locations, it is important to improve cost-effectiveness studies, including by refining the use of behavioural risk variables. As shown, the inclusion of estimates of ‘risk compensation’ in the cost-effectiveness studies reviewed would benefit from more reflexivity and contextualization, which we would argue are even more needed where there is limited evidence available to hypothesize either scenario.

Since studies about PrEP implementation and its effects are relatively nascent, variation in the use of evidence is generally expected as researchers construct a variety of hypotheses from a limited pool of data to respond to implementation questions. To the same effect, since the evidence base is growing through ongoing studies, we expect future cost-effectiveness models will have more robust data, in particular about STI control.

We recognize the intention of modelling. Much of the work of estimation in modelling is done to demonstrate potential effects. Within the models, some authors state they are constructing hypothetical scenarios. Some also acknowledge their assumptions are not or would not be based on published evidence precisely because they are speculations on novel interventions yet to be implemented. Attempting to calculate the cost of ‘risk compensation’ and changes in CLS is thus part of understanding the future of PrEP provision. PrEP is a technology developed to address the prevention needs of those who do not or cannot use condoms, and anticipating changes in condom use for PrEP users is as important as it is challenging.

However, the lack, or limits, of the evidence base for behavioural risk variables – such as identified in this review – need to be made transparent. Such categories have significant impact on the overall outcome of the studies, and cost-effectiveness studies may be read and interpreted with varying degrees of caution and beyond their original use. In the process of reporting findings then translating them into policy to inform implementation, such estimations could inadvertently contribute to the construction of apparent empirical evidence about the cost-effectiveness of PrEP and about PrEP users. In other words, evidence is not only translated but also ‘transformed’ in the process of its use in practice (41).

Our analysis has found that cost-effectiveness models include evidence-based and non-evidence-based information, which may at times be presented in ways that do not accurately guide interpretation. For example, when authors infer quantitative estimates from qualitative evidence about participants’ views about hypothetical effects of PrEP on risk behaviour, claims that may be indicative, but are nonetheless largely abstract, are presented as possible and measurable. Such scenarios, speculative in nature, may appear factual and become fixed (41) by the time models reach other readers, such as policymakers, commissioners, the media and wider public.

Through the process of interpreting evidence to inform implementation, perceptions about the potential effects of PrEP could be rendered into empirical realities, and embedded within scientific, public and political discourse. Increased reflexivity in cost-effectiveness studies, particularly with regards to the uncertainty of variables concerning user or patient behaviour, is necessary to aid what is an already complex policy cycle in the context of PrEP implementation.

This study is limited in so far as it is based on a small selection of models from two countries and for one target population of MSM. As PrEP efforts are expanding globally (42) and across populations, the literature on cost effectiveness from other countries may prove insightful with regards to addressing the degree of speculation in the models. Further claims about PrEP cost-effectiveness models would also need to address different designs of the models, choice of data input, sensitivity analysis, and levels of complexity, among other factors beyond the scope of the analysis presented here.

Conclusion

We found that cost-effectiveness models include a range of assumptions about risk behaviour, including increased and decreased risk associated with PrEP use, and the variability of assumptions has been linked to limitations in and different uses of the evidence base. The degree of speculation, uncertainty and potential contestation with regards to the relationship with available evidence need to be made transparent to aid accurate and moderate interpretation of modelled scenarios. While there will continue to be gaps in evidence, as PrEP implementation and scale-up continue including among populations and across geographies where less is known about risk behaviour, it will be increasingly important to ensure evidence is used appropriately and consistently in order to guide the effective use of novel methods to prevent HIV.

Declarations

Ethics approval and consent to participate
Ethics approval not required; no original research data used.

Consent for publication
Not applicable.

Availability of data and materials
All primary data used in the study is publicly available.

**Competing interests**

The Authors declare that there is no conflict of interest.

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**Authors' contributions**

Author 1 [SP] and Author 2 [RW] conceptualised the study and wrote the first draft of the manuscript. All three authors conducted final data analysis and wrote the final draft of the manuscript.

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**References**

1. Care DoHaS. HIV drug PrEP to be available across England. In: Care DoHaS, editor. https://www.gov.uk/government/news/hiv-drug-prep-to-be-available-across-england2020.
2. Cambiano V, Miners A, Phillips A. What do we know about the cost-effectiveness of HIV preexposure prophylaxis, and is it affordable? 2016.
3. Gomez GB, Borquez A, Case KK, Wheelock A, Vassaila A, Hankins C. The cost and impact of scaling up pre-exposure prophylaxis for HIV prevention: a systematic review of cost-effectiveness modelling studies. PLoS Med. 2013;10(3):e1001401.
4. Schackman BR, Eggman AA. Cost-effectiveness of pre-exposure prophylaxis for HIV: a review. Curr Opin HIV AIDS. 2012;7(6):587-92.
5. Hoornenborg E, Krakower DS, Prins M, Mayer KH. Pre-exposure prophylaxis for MSM and transgender persons in early adopting countries. AIDS. 2017;31(16):2179-91.
6. England PH. HIV in the United Kingdom: Towards Zero HIV transmissions by 2050. In: England PH, editor. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/le/965765/HIV_in_the_UK_2019_towards_zero_HIV_transmissions.pdf.
7. Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, et al. Preexposure Prophylaxis for the Prevention of HIV Infection: US Preventive Services Task Force Recommendation Statement. JAMA. 2019;321(22):2203-13.
8. Prepster T. IMPACT trial: The Love Tank CIC; 2021 [Available from: https://prepster.info/impact/.
9. Aghaizu A, Mercey D, Copas A, Johnson AM, Hart G, Nardone A. Who would use PrEP? Factors associated with intention to use among MSM in London: a community survey. Sex Transm Infect. 2013;89(3):207-11.
10. Frankis J, Young I, Flowers P, McDaid L. Who will use pre-exposure prophylaxis (PrEP) and why?: Understanding PrEP awareness and acceptability amongst men who have sex with men in the UK - A mixed methods study. PLoS One. 2016;11(4):e0151385-e.
11. Young I, Li J, McDaid L. Awareness and Willingness to Use HIV Pre-Exposure Prophylaxis amongst Gay and Bisexual Men in Scotland: Implications for Biomedical HIV Prevention. PLoS One. 2013;8(5):e64038-e.
12. Marcus JL, Glidden DV, Mayer KH, Liu AY, Buchbinder SP, Amico KR, et al. No Evidence of sexual risk compensation in the iPrEx trial of daily oral HIV preexposure prophylaxis. PLoS One. 2013;8(12):e81997-e.
13. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. N Engl J Med. 2010;363(27):2587-99.
14. Lal L, Audsley J, Murphy DA, Fairley CK, Stove M, Roth N, et al. Medication adherence, condom use and sexually transmitted infections in Australian preexposure prophylaxis users. AIDS (London). 2017;31(12):1709-14.
15. Liu AY, Cohen SE, Vittinghoff E, Anderson PL, Doblecki-Lewis S, Bacon O, et al. Preexposure Prophylaxis for HIV Infection Integrated With Municipal-and Community-Based Sexual Health Services. JAMA Intern Med. 2015;175(1):1-11.
16. Montaño MA, Dombrowski JC, Dasgupta S, Golden MR, Duerr A, Manhart LE, et al. Changes in Sexual Behavior and STI Diagnoses Among MSM Initiating PrEP in a Clinic Setting. AIDS Behav. 2018;23(2):548-55.
17. Volk JE, Marcus JL, Phengrasamy T, Blechinger D, Nguyen DP, Follansbee S, et al. No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting. Clin Infect Dis. 2015;61(10):1601-3.
18. Jenness SM, Sharma A, Goodreau SM, Rosenberg ES, Weiss KM, Hoover KW, et al. Individual HIV risk versus population impact of risk compensation after HIV preexposure prophylaxis initiation among men who have sex with men. PLoS One. 2017;12(1):e0169484-e.
19. Jenness SM, Weiss KM, Goodreau SM, Gift T, Chesson H, Hoover KW, et al. Incidence of gonorrhea and chlamydia following human immunodeficiency virus preexposure prophylaxis among men who have sex with men: A modeling study. Clin Infect Dis. 2017;65(5):712-8.
20. Dixon-Woods M. Using framework-based synthesis for conducting reviews of qualitative studies. BMC Med. 2011;9(1):39-.
21. Greenhalgh T, Thorne S, Malterud K. Time to challenge the spurious hierarchy of systematic over narrative reviews? Eur J Clin Invest. 2018;48(6):e12931-n/a.
22. Centers for Disease Control and P. Preventing New HIV Infections | Guidelines and Recommendations | HIV/AIDS | CDC.
23. McCormack SP, Dunn DTP, Desai MMPH, Dolling DIM, Gafo MP, Gilson RMD, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet. 2016;387(10013):53-60.
24. British HIVA. BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis (PrEP) 2018.
25. Kessler J, Myers JE, Nucifora KA, Mensah N, Toohey C, Khademi A, et al. Evaluating the impact of prioritization of antiretroviral pre-exposure prophylaxis in New York. AIDS. 2014;28(18):2683-91.
26. Ross EL, Cinti SK, Hutton DW. Implementation and Operational Research: A Cost-Effective, Clinically Actionable Strategy for Targeting HIV Preexposure Prophylaxis to High-Risk Men Who Have Sex With Men. J Acquir Immune Defic Syndr. 2016;72(3):e61-e7.
27. Chen A, Dowdy DW. Clinical effectiveness and cost-effectiveness of HIV pre-exposure prophylaxis in men who have sex with men: risk calculators for real-world decision-making. PloS one. 2014;9(10):e108742.
28. Golub SA, Kowalczyk W, Weinberger CL, Parsons JT. Pre-exposure prophylaxis and predicted condom use among high-risk men who have sex with men. J Acquir Immune Defic Syndr. 2010;54(5):548-55.
29. Smith DK, Toledo L, Smith DJ, Adams MA, Rothenberg R. Attitudes and program preferences of African-American urban young adults about pre-exposure prophylaxis (PrEP). AIDS Educ Prev. 2012;24(5):408-21.
30. Saberi P, Garemel KE, Nelands TB, Comfort M, Sheon N, Darbes LA, et al. Ambiguity, Ambivalence, and Apprehensions of Taking HIV-1 Pre-Exposure Prophylaxis among Male Couples in San Francisco: A Mixed Methods Study. PLoS One. 2012;7(11):e50061-e.
31. Adams JL, Shelley K, Nicol MR. Review of Real-World Implementation Data on Emtricitabine-Tenofovir Disoproxil Fumarate as HIV Pre-exposure Prophylaxis in the United States. Pharmacotherapy. 2019;39(4):486-500.
32. Ong KJ, Desai S, Field N, Desai M, Nardone A, van Hoek AJ, et al. Economic evaluation of HIV pre-exposure prophylaxis among men-who-have-sex-with-men in England in 2016. Euro Surveill. 2017;22(42):15-24.
33. Cambiano V, Miners A, Dunn D, McCormack S, Ong KJ, Gill ON, et al. Cost-effectiveness of pre-exposure prophylaxis for HIV prevention in men who have sex with men in the UK: a modelling study and health economic evaluation. Lancet Infect Dis. 2018;18(1):85-94.
34. Long EF, Brandeau ML, Owens DK. The cost-effectiveness and population outcomes of expanded HIV screening and antiretroviral treatment in the united states. Annals of internal medicine. 2010;153(12):778-89.
35. Marks G, Crepaz N, Senterfitt JW, Janssen RS. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: Implications for HIV prevention programs. J Acquir Immune Defic Syndr. 2005;39(4):446-53.
36. Sanders EJ, Okuku HS, Smith AD, Mwangome M, Wahome E, Fegan G, et al. High HIV-1 incidence, correlates of HIV-1 acquisition, and high viral loads following seroconversion among MSM. AIDS. 2013;27(3):437-46.
37. Juusola JL, Brandeau ML, Owens DK, Bendavid E. The Cost-Effectiveness of Preexposure Prophylaxis for HIV Prevention in the United States in Men Who Have Sex With Men. Annals of internal medicine. 2012;156(8):541-U144.
38. Drabo EF, Hay JW, Vardavas R, Wagner ZR, Sood N. A Cost-effectiveness Analysis of Preexposure Prophylaxis for the Prevention of HIV Among Los Angeles County Men Who Have Sex With Men. Clin Infect Dis. 2016;63(11):1495-504.
39. Philipson TJ, Posner RA. Private choices and public health : the AIDS epidemic in an economic perspective. Cambridge, Mass ; London: Harvard University Press; 1993.
40. Paltiel AD, Freedberg KA, Scott CA, Schackman BR, Losina E, Wang B, et al. HIV Preexposure Prophylaxis in the United States: Impact on Lifetime Infection Risk, Clinical Outcomes, and Cost-Effectiveness. Clinical Infectious Diseases. 2009;48(6):806-15.
41. Rhodes T, Lancaster K. Evidence-making interventions in health: A conceptual framing. Social Science & Medicine.
2019;238:TYPE=IssueAR=ark:/81055/vdc_100091535912.0x000001|ENUMA=238|CHRONI=2019|DATE=2019|PAGES=.
42. Hodges-Mameletzis I, Dalal S, Sismangma-Radebe B, Rodolph M, Baggaley R. Going global: the adoption of the World Health Organization's enabling recommendation on oral pre-exposure prophylaxis for HIV. Sexual Health. 2018;15:489-500.

Tables
Table I: Reviews of cost-effectiveness studies for PrEP among MSM
| Authors                  | Title                                                                 | Setting     |
|-------------------------|-----------------------------------------------------------------------|-------------|
| Cambiano et al 2016     | What do we know about the cost-effectiveness of HIV preexposure prophylaxis, and is it affordable? | Worldwide   |
| Desai et al 2017        | Recent advances in pre-exposure prophylaxis for HIV                   | Worldwide   |
| Garnett et al 2017      | Cost-Effectiveness of Interventions to Prevent HIV Acquisition         | Worldwide   |
| Gomez et al 2013        | The cost and impact of scaling up pre-exposure prophylaxis for HIV prevention: a systematic review of cost-effectiveness modelling studies | US, UK     |
| Hankins et al 2015      | Translating PrEP effectiveness into public health impact: key considerations for decision-makers on cost-effectiveness, price, regulatory issues, distributive justice and advocacy for access | UK         |
| Hoornenborg et al 2017  | Pre-exposure prophylaxis for MSM and transgender persons in early adopting countries | US, UK     |
| Mitchell et al 2018     | In what circumstances could nondaily preexposure prophylaxis for HIV substantially reduce program costs? | UK         |
| Schackman and Eggman 2012 | Cost-effectiveness of pre-exposure prophylaxis for HIV: a review     | Worldwide   |
| Adams et al 2019        | Review of real-world implementation data on emtricitabine-tenofovir disoproxil fumarate as HIV pre-exposure prophylaxis in the United States | USA        |

Table II: Behaviour change assumptions in cost-effectiveness studies for PrEP among MSM in the UK and US

| Authors                  | Setting | Behaviour change                      |
|-------------------------|---------|---------------------------------------|
| Juusola et al 2012      | US      | decreased risk behaviour              |
| Drabo et al 2016        | US      | decreased risk behaviour              |
| Chen and Dowdy 2014     | US      | increased risk behaviour, condom-less sex |
| Cambiano et al 2018     | UK      | increased risk behaviour, condom-less sex |
| Ong et al 2017          | UK      | increased risk behaviour, lifetime    |
| Koppenhaver et al 2011  | US      | none                                  |
| Kessler et al 2014      | US      | none                                  |
| Juusola and Brandeau 2016 | US       | none                                  |
| Ross et al 2016         | US      | none                                  |
| Adamson et al 2017      | US      | none                                  |
| Shen et al 2018         | US      | none                                  |
| Paltiel et al 2009      | US      | range: increased, decreased, and no effect |
| Adams et al 2019        | US      | Increased risk behaviour, increase in STI incidence |