ONTARIO HIV TREATMENT NETWORK

Economic evaluations of pre- and post-exposure prophylaxis (PrEP and PEP) for HIV

Questions

- What is the cost-effectiveness of HIV pre-exposure prophylaxis (PrEP)?
- What is the cost-effectiveness of HIV post-exposure prophylaxis (PEP)?
- What are the gaps in literature?

Key Take-Home Messages

- Economic evaluations of health care interventions can inform resource allocation and policy development. However, interpreting and generalizing results can be challenging (1).
- PrEP can be cost-effective or cost-saving depending on the local context, adherence rates, and program coverage (1). Interventions that target individuals at high risk of HIV exposure may improve the cost-effectiveness of PrEP (1–3).
- Non-occupational PEP may be cost-effective, or even cost-saving, depending on the source or type of HIV exposure (4).
- Determining the best way to identify high-risk individuals (5), and the costs associated with these efforts (1), remain significant gaps in knowledge.

The Issue and Why It's Important

Health care decision-makers are often faced with the difficult choice of allocating health care resources, setting priorities, and forming health policy (6). As resources are limited, this choice is not solely dependent on the effectiveness of health care interventions, but also on which interventions are cost-effective – offering the best value for money (7). Health economic evaluation offers a number of analytic techniques that may allow for decision-making that is based on evidence of the relative value of interventions (6).

In 2015, it was reported that over CAD 70,000,000 of federal funding was contributed by the Federal Initiative to Address HIV/AIDS

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in Canada (8) towards HIV-related prevention, support programs reaching key priority populations, research, surveillance, public awareness, and evaluation (9). Despite this investment, in 2016 the number of new HIV diagnoses in Canada was the highest it had been in the previous five years (10). The increase in new diagnoses in Canada, as well as the large financial burden associated with HIV infection – which, in 2005, was calculated to be CAD 1,159 per patient per month (11) – highlights the economic and social importance of focusing on prevention of new HIV infections (5). Biomedical prevention interventions, such as PrEP or PEP, have the potential to prevent new HIV infections from occurring (5).

PrEP is highly protective against HIV acquisition across various populations and across different dosing schedules, however, the protective efficacy of oral PrEP is highly dependent on adherence to the prescribed regimen (12). PrEP relies on self-administration of antiretroviral medication before anticipated exposure to HIV (13). At the time of writing, the only regimens of PrEP approved by national and international guidelines are one daily oral dosage combining tenofovir disoproxil fumarate (TDF; 300mg) with emtricitabine (FTC; 200mg) (5, 14–16) or 300mg of TDF alone (14, 16). The efficacy of "on-demand" (also referred to as intermittent, time-driven, or event-driven) dosing schedules is also being explored (17).

PEP involves administering antiretroviral medications between two and 72 hours after exposures to HIV (5, 18–20), such as exposures to blood and/or other body fluids that may contain HIV in occupational contexts (19, 20) or non-occupational exposures to HIV such as sexual exposure and injection drug use (5, 18). PEP is highly effective against HIV, however due to ethical constraints that preclude the potential for randomized controlled trials in humans, the evidence regarding PEP efficacy is based on observational studies (18). Regimens typically involve the combination of two or more antiretroviral medications, but the most common preferred regimen is an oral dose of TDF/FTC (300mg/200mg) once daily plus raltegravir (RAL; 400mg) twice daily (5, 18–20).

To date, antiretroviral medication costs have limited the feasibility and acceptability of PrEP and PEP. However, the recent approval of generic TDF/FTC and the increasing availability of public drug coverage for PrEP in Canada may have considerable effects on their implementation (5). Nonetheless, the evidence supporting the effectiveness of PrEP and PEP leaves health care decision makers with the challenge of deciding whether to provide funding for them (2) – which may divert resources from treatment or other HIV prevention interventions – in order to achieve maximum health benefits at affordable costs (21).

This review summarizes economic evaluations measuring cost-effectiveness of PrEP and PEP as interventions for HIV prevention in high-income countries. It also outlines existing gaps in the literature.

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What We Found

Economic evaluation in HIV prevention

Health economic evaluations describe the extent to which health interventions represent value for money (22), and are intended to inform decisions (23). The measures used in economic evaluations are costs and outcomes (23). In any given health intervention, economic evaluation makes explicit the resources consumed (i.e. cost), as well as the outcomes (i.e. benefits and/or drawbacks) produced by the intervention (6). These costs and outcomes are evaluated relative to alternative strategies that can be used with the same available resources (6). Economic evaluation is defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences [outcomes]" (24).

Costs may be defined as direct (immediately associated with an intervention, such as staff time), indirect (such as patient's work lost due to treatment), or intangible (such as pain) (6). Some analyses may also consider cost as a measure of the benefits that are inevitably forgone by allocating resources to one alternative over another, referred to as the *opportunity cost* (7). In all types of economic evaluation, however, these costs are expressed in monetary units.

Outcomes are measured differently depending on the type of economic evaluation being performed (6). Two types of economic evaluation that are frequently used to appraise HIV-related health care interventions are *cost-effectiveness analysis* (which defines benefits of an intervention in terms of its direct effects on health, such as the number of HIV infections averted), and cost-utility analysis (which defines benefits in terms of the general impact on well-being, or "utilities"). A common measure of utility is the *quality-adjusted life year* (QALY), which combines the estimated quantity of life years that are gained or saved as a result of a health intervention, with some judgment as to the *quality* of those years (6). Cost-utility analysis is somewhat more sophisticated than cost-effectiveness analysis as it is able to compare very different health programs to one another, such as surgical, pharmaceutical, and health promotion interventions, in the same terms (6). In HIV prevention interventions, such as PrEP and PEP, costs usually occur immediately while benefits, such as HIV infections averted or QALYs gained, will not occur until years in the future (25). This differential timing can be incorporated into economic analyses by discounting future costs and benefits to their current value (6).

Both cost-effectiveness and cost-utility analyses are able to make comparisons between health interventions in terms of cost-effectiveness ratios, or costs per unit of benefit (e.g. dollar per HIV infection averted). In practice, implementing one intervention often results in changes to the costs and outcomes of another intervention, or means that another intervention cannot be implemented (22). In these cases, decision-makers need to know what these changes in

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cost and outcome may be when implementing one program over another (6). This can be derived through an incremental cost-effectiveness ratio (ICER), or the difference in costs between two programs per the difference in health outcomes between two programs (22). An ICER can provide objective guidance to health care decision-makers in reference to prior judgments regarding specific health-effect targets, budget constraints, or thresholds for what is to be considered "cost-effective" (26). According to the World Health Organization, the standard international threshold for determining the cost-effectiveness of an intervention is an ICER of less than three times the Gross Domestic Product (GDP) per capita of a given country (less than once the GDP per capita is considered highly cost-effective) (26). A threshold range between CAD 20,000 and CAD 100,000 per QALY gained is often used in Canada (27) and has been used to evaluate the cost-effectiveness of HIV prevention interventions in Canada (28). However, threshold values are often debated and are not always representative of recognized standards (27). Rather, the decision to label a health care intervention as cost-effective is often determined by the cost one is able or willing to pay per unit of benefit (27). While there is no "acceptable" limit for what one should be willing to pay to avert HIV infection or save a year of life, these ratios can be utilized to compare the economic and societal value of interventions to one another (29).

Regardless of the approach used, all economic evaluations require that relevant cost and outcome variables be identified, quantified, and assigned value (6). Mathematical models can be used to combine all the information available on the cost and outcome variables of a given intervention to produce estimates of the cost-effectiveness of an intervention. For example, uptake, efficacy, effectiveness, adherence, sexual behaviour, monitoring, and drug costs are some variables of interest when determining the costs and outcomes of HIV prevention interventions (2). A variety of model types can be used; some track both specific clinical events and their use of resources, others project clinical events over the lifetime of individual patients, and some predict changes in incidence and prevalence over long periods of time (29).

Given the variety of methods available and potential variations in the estimates of key cost and outcome variables, economic evaluations often have considerable uncertainty associated with their findings (22). Assuming that results are sensitive to these variables, any changes may also impact whether or not an intervention would be deemed cost-effective (6). It is therefore imperative that a sensitivity analysis be performed to test the level of uncertainty of measured variables (22). This allows decision-makers to be aware of the possible impact on the baseline estimates. Sensitivity analysis may, therefore, demonstrate the confidence that can be placed in an estimated ICER (22). Different sensitivity analyses can also modify variables to determine the value a variable would have to reach to change results (6). For example, if an intervention is currently not cost-effective, analyses can determine under what

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conditions it may become so (29). Thus, it is crucial to consider that model methodologies, inputs, and assumptions vary significantly between different types of economic evaluation, and can largely affect results (29). Their complexity and inherent uncertainty make interpretation and generalization of the results of economic evaluations difficult (1).

Economic evaluations included in this review were mainly cost-utility analyses examining interventions for populations including men who have sex with men, people who inject drugs, health care workers, and heterosexual serodiscordant couples. Costs were reported in a number of currencies, including Canadian, U.S., and Australian Dollars (CAD; USD; AUD), Euros (EUR), and Great Britain Pounds (GBP). Studies mainly reported ICERs using cost per QALY gained. Cost-effectiveness ratios were also presented, and outcomes were measured in HIV infections averted, HIV-associated deaths averted, HIV-positive pregnancies averted, or life-years saved. A variety of mathematical models were also utilized. Due to the heterogeneity of methodologies, readers are advised to interpret the sections below with caution, and encouraged to explore original publications and methods sections.

Economic evaluations of PrEP

Cost-effectiveness estimates, as well as model input parameters in economic evaluations on PrEP vary widely across countries and target populations (29). Due to the variations between methodologies and assumptions made, synthesizing these results can be difficult (1).

The most recent systematic review and quantitative synthesis of economic evaluations of PrEP includes 49 full economic evaluations of PrEP with antiretrovirals (oral, injectable, and topical), 19 of which were from high-income countries (3, 30). Key populations of included studies were comprised of men who have sex with men, people who inject drugs, heterosexuals, women, heterosexual serodiscordant couples, and the general population. Outcomes reported included QALYs gained, HIV infections averted, disability-adjusted life-years (DALYs) averted, and life years gained (3). Review authors concluded that within a threshold of CAD/USD 50,000-150,000, PrEP would be deemed cost-effective in studies from high-income countries. They also noted that PrEP is more cost-effective when targeted at individuals at highest risk of HIV infection, compared to the general population (3).

Overall, studies included in this review report similar findings, which are outlined by key population groups below.

Men who have sex with men

A 2013 systematic review of cost-effectiveness studies of PrEP included 13 studies, four of which investigated daily oral PrEP for

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men who have sex with men in the U.S. (1). All four studies used transmission models and reported thresholds ranging from USD 50,000 to USD 297,000 per QALY gained. Two of these studies, however, were published before sufficient efficacy data for TDF-based PrEP was available (31, 32). The remaining two articles estimated that PrEP provided to this population generally would not be cost-effective, despite having a significant impact on the HIV epidemic (33, 34). PrEP for 20% of all men who have sex with men led to incremental costs of USD 95 billion. Cost per HIV infection averted was USD 2,000,000 when given to 20% of men who have sex with men (33), and USD 870,590 when given to all men who have sex with men (34). Costs per QALY gained were estimated to be USD 172,091 (33) and USD 570,273 (34) for baseline assumptions, and both studies suggested that high drug costs made PrEP unaffordable. One of these studies did find, however, that PrEP could be cost-effective with targeting to high-risk individuals, reporting cost per QALY gained as low as USD 40,279 relative to the status quo when this strategy was used with 20% coverage of individuals (33). In sensitivity analyses, cost-effectiveness was influenced by adherence rates (31, 34), PrEP's impact on quality of life (33), and the efficacy and cost of PrEP (32, 33). Review authors concluded that delivery of PrEP to key populations at highest risk of HIV appeared to be the most cost-effective approach. They cautioned, however, that included studies did not consider any extra costs related to identifying and engaging these populations – and executing these strategies may pose a challenge for decision makers (1).

Another review summarized cost-effectiveness studies of introducing PrEP in both high- and low-income settings published between 2014 and 2016 (2). Three studies on the cost-effectiveness of PrEP among men who have sex with men in high-income settings (Canada and the U.S.) were included. PrEP regimens investigated were either once daily (35, 36) or on-demand (37) TDF-based oral dosages. All three studies compared PrEP to an alternative scenario where PrEP was not introduced. Compared to these "no-PREP" alternatives, the cost-effectiveness of PrEP for men who have sex with men across studies was considered cost-saving (i.e. a cost per QALY gained ratio of less than zero) in an on-demand regimen (except when discounted at 5% where the ICER was between CAD 47,338 and CAD 60,223 per QALY gained and between CAD 135,584 and CAD 172,489 per HIV infection averted) (37). PrEP was considered highly cost-effective – between USD 27,863 (36) and USD 160,000 (35) per QALY gained – in a daily regimen. One study also compared PrEP (as well as six different "enhanced" PrEP strategies that included variations in HIV testing frequency and PrEP initiation times) to strategies involving the expansion of HIV testing and early antiretroviral treatment (36). While not considered the most cost-effective strategies overall, PrEP and four of the six enhanced PrEP strategies were identified as cost-effective (below USD 150,000 per QALY gained). ICERs ranged from USD 63,269 to USD 145,956 per QALY gained when compared to their next best alternatives (36).

31. Desai K, Sansom SL, Ackers ML, Stewart SR, Hall HI, Hu DJ, et al. Modeling the impact of HIV chemoprophylaxis strategies among men who have sex with men in the United States: HIV infections prevented and cost-effectiveness. AIDS. 2008;22(14):1829–39.

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Sensitivity analyses were performed in two of the included studies, finding that factors such as HIV prevalence (35, 36), antiretroviral therapy and PrEP adherence/initiation rates (36), PrEP efficacy (35), behavioural disinhibition (35), baseline risk of HIV acquisition (35, 36), QALYs gained per case of HIV averted (35), rates of sexual partner mixing (36), and PrEP annual cost (35) had an impact on cost-effectiveness. Review authors concluded that targeting PrEP to high-risk individuals improves cost-effectiveness, but identification and successful targeting of these individuals may be a challenge (2).

In addition to these reviews, nine economic evaluations, published between 2014 and 2018, of PrEP in men who have sex with men in high-income countries were identified (28, 38–45). These studies were conducted in the U.S. (41, 44), Canada (28), Hong Kong (38), Spain (40), Australia (45), the Netherlands (43), and the United Kingdom (39, 42). Once daily PrEP (at varying rates of effectiveness and coverage) among the general population of men who have sex with men led to costs per HIV infection averted between USD 671,857 and USD 939,657 (28), and EUR 417,241 (40). Costs per HIV-associated death averted exceeded USD 12,000,000 (28). Estimates for cost-effectiveness of once daily PrEP among men who have sex with men varied. Four studies found a daily regimen not cost-effective with costs per QALY gained between CAD 495,175 and CAD 792,763 (28), greater than USD 1,400,000 (38, 44), and greater than AUD 400,000 (45). Others found it cost-effective but not affordable with up to USD 132,520 per QALY gained but five times the annual given budget (41); cost-effective (cost per QALY gained EUR 6,281.62 undiscounted, and EUR 16,706.73 when discounted 3% (40), cost per QALY gained between EUR 7,800 and EUR 26,000 (43); or cost-saving (42) compared to alternatives. However, on-demand PrEP for the general population of men who have sex with men was considered cost-effective (cost per QALY gained less than EUR 17,000) (40), cost-saving (39, 40), or potentially both cost-effective and cost-saving depending on the context of the epidemic and effectiveness of PrEP (43). Costs per HIV infection averted was reported as EUR 246,488 in one study (40).

Targeting PrEP to higher risk men who have sex with men (e.g. those who are in serodiscordant regular partnerships) tended to make ICERs cost-effective: cost per QALY gained less than CAD 45,000 (28); less than USD 43,000 (44); less than AUD 12,000 (45). Targeting PrEP to high-risk men who have sex with men led to costs per HIV infection averted between USD 42,508 and USD 66,809 and costs per HIV-associated death averted between USD 711,931 and USD 1,440,334 (28). One study in Hong Kong, however, found that targeted PrEP was still not cost-effective (cost per QALY gained between USD 1,583,136 and USD 2,162,072) in an area of low-incidence and a low-proportion of high-risk men who have sex with men (38).

37. Ouellet E, Durand M, Guertin JR, LeLorier J, Tremblay CL. Cost effectiveness of 'on demand' HIV pre-exposure prophylaxis for non-injection drug-using men who have sex with men in Canada. The Canadian Journal of Infectious Diseases & Medical Microbiology. 2015;26(1):23–9.

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Sensitivity analyses showed improving adherence rates (28, 42, 45), reducing PrEP prices (38–42, 45), higher PrEP effectiveness (42), higher cost of antiretroviral treatment (39, 43), lower PrEP coverage (41), and event-based dosing schedules (40, 42) resulted in PrEP having lower cost per QALY gained. Other factors such as HIV incidence (40, 42), QALY discounting rate (43), and behavioural disinhibition (39, 45) also influenced cost-effectiveness in these analyses.

People who inject drugs

Three economic evaluations, investigating PrEP delivery among people who inject drugs in the U.S. (46–48) estimated that PrEP would not be cost-effective compared to alternatives when delivered to people who inject drugs in general. PrEP could be cost-effective when delivered in communities with high HIV incidence (46), when high-risk individuals are enrolled in PrEP programs (47), or if PrEP prices are substantially decreased (48). In sensitivity analyses, cost-effectiveness was significantly influenced by drug costs (46–48), PrEP adherence (46, 47), HIV transmission risks (46), and community HIV prevalence (46).

The first study compared the cost-effectiveness of PrEP alone, PrEP with frequent HIV screening, and PrEP with frequent screening as well as enhanced provision of antiretroviral treatment for individuals who become HIV infected (46). Compared to other strategies, PrEP with frequent screening and treatment had a lower cost per QALY gained (USD 253,000), but was still above the cost-effectiveness threshold of USD 100,000 per QALY gained (46). The second study compared PrEP to other HIV prevention interventions with demonstrated efficacy for people who inject drugs (e.g. opioid agonist therapy, needle and syringe programs, and HIV testing and treatment), and also used a threshold of USD 100,000 per QALY gained (48). Compared to other strategies, PrEP cost USD 300,000 per QALY gained, while the other strategies were estimated to achieve similar benefits at substantially lower costs (48). The third study compared the cost-effectiveness of four different strategies for enrolling people who inject drugs into a PrEP program recommended by the U.S. Centers of Disease Control and Prevention (CDC) (47). The first strategy, which randomly selected individuals without prioritization, had a cost per QALY gained of USD 272,000 and was not cost-effective compared to the status quo (threshold of USD 170,000 per QALY gained). The other three strategies, however, which enrolled individuals based on information about sexual and needle-sharing partnerships (indicators for risk of HIV acquisition) were cost-effective. The most cost-effective strategy enrolled individuals based on their number of HIV-infected sexual and needle-sharing partnerships (USD 101,000 per QALY gained) (47).

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HIV-negative female/HIV-positive male couples who wish to conceive

Three economic evaluations investigated the cost-effectiveness of different conception strategies, including PrEP, for heterosexual serodiscordant couples (HIV-negative female/HIV-positive male) in Canada (49), France (50), and the U.S. (51). Two of these studies assumed HIV-infected partners were on antiretroviral therapy, and virologically suppressed (49, 50). Both of these studies found that PrEP was not cost-effective when compared to other conception strategies, including condomless sex limited to ovulation (in either cost per QALY gained or cost per life year saved). These results were robust to sensitivity analyses in both studies (49, 50). The third study found similar results, in that PrEP was not cost-effective when partners were virologically suppressed (USD 725,960 per QALY gained, threshold USD 100,000 per QALY gained; USD 723,950,000 per HIV-positive pregnancy averted) (51). However, sensitivity analyses showed that PrEP could be cost-effective or cost-saving when the probability of viral suppression (determined by rate of adherence to antiretroviral therapy) was low and generic pricing of PrEP was assumed (51).

Economic evaluations of PEP

There is considerable variation in the estimates of cost-effectiveness of PEP as an HIV prevention intervention reported in the literature (18). It has been stated that there is currently no conclusive evidence regarding the cost-effectiveness of PEP (52). This can be mainly attributed to the limited data available for its clinical effectiveness, as well as other model parameters such as per-exposure transmission probabilities, treatment compliance rates, and the prevalence of HIV among different population groups (4). Studies that demonstrate the potential cost-effectiveness of PEP for both non-occupational and occupational exposures are discussed in the sections below.

Non-occupational PEP

One systematic review investigated the cost-effectiveness of PEP for non-occupational exposures, and found four economic evaluations conducted between 1998 and 2006 (4). Three of these studies investigated only non-occupational exposures to HIV, while the fourth study looked at both non-occupational and occupational exposure types. Three studies were conducted in the U.S. (53–55) and reported costs in USD, and one study was conducted in France (56) and reported costs in EUR. Thresholds for cost-effectiveness varied (ranging between USD 50,000 and USD 200,000; EUR 50,000 per QALY gained), and results regarding the overall cost-effectiveness of PEP were mixed: PEP did not appear to be cost-effective in the French study (EUR 996,104 per HIV infection averted and EUR 88,692 per QALY gained) (56), while cost per QALY gained ranged between USD 4,137 and greater than USD 750,000

50. Mabileau G, Schwarzinger M, Flores J, Patrat C, Luton D, Epelboin S, et al. HIV-serodiscordant couples desiring a child: 'Treatment as prevention,' preexposure prophylaxis, or medically assisted procreation? American Journal of Obstetrics & Gynecology. 2015;213(3):341.e1–12.

51. Leech AA, Burgess JF, Sullivan M, Kuohung W, Horny M, Drainoni ML, et al. Cost-effectiveness of preexposure prophylaxis for HIV prevention for conception in the United States. AIDS. 2018;32(18):2787–98.

52. Cresswell F, Waters L, Briggs E, Fox J, Harbottle J, Hawkins D, et al. UK guideline for the use of HIV post-exposure prophylaxis following sexual exposure, 2015. International Journal of STD & AIDS. 2016;27(9):713–38.

53. Pinkerton SD, Holtgrave DR, Bloom FR. Cost-effectiveness of post-exposure prophylaxis following sexual exposure to HIV. AIDS. 1998;12(9):1067–78.

54. Pinkerton SD, Martin JN, Roland ME, Katz MH, Coates TJ, Kahn JO. Cost-effectiveness of postexposure prophylaxis after sexual or injection-drug exposure to human immunodeficiency virus. Archives of Internal Medicine. 2004;164(1):46–54.

55. Pinkerton SD, Martin JN, Roland ME, Katz MH, Coates TJ, Kahn JO. Cost-effectiveness of HIV postexposure prophylaxis following sexual or injection drug exposure in 96 metropolitan areas in the United States. AIDS. 2004;18(15):2065–73.

56. Herida M, Larsen C, Lot F, Laporte A, Desenclos JC, Hamers FF. Cost-effectiveness of HIV post-exposure prophylaxis in France. AIDS. 2006;20(13):1753–61.

in the three U.S. studies (53–55). However, all studies revealed that non-occupational PEP could be cost-effective or even cost-saving, depending on the population receiving it, or the source or type of HIV exposure (4). For example, PEP for men who have sex with men following receptive anal intercourse was considered cost-effective (EUR 31,862 per QALY gained) when the source partner was of unknown HIV status (56), highly cost-effective (USD 6,354 per QALY gained) (53), or cost-saving when the source partner was known to be HIV-positive (54). PEP for injection drug use was considered moderately cost-effective (USD 86,462 per QALY gained) (54), or cost-saving for those who have shared needles with a known HIV-positive person (56). PEP was considered cost-saving for receptive anal intercourse among heterosexual men and women (55, 56). PEP was also possibly cost-effective for non-occupational needle stick injuries in the general population (USD 159,686 per QALY gained) (55).

In general, the sensitivity analyses of these studies did not significantly change baseline results (4). Review authors noted that the studies were constrained by lack of published data on the clinical effectiveness of non-occupational PEP, as all effectiveness data were derived from a case-control study of occupational PEP using the antiretroviral medication zidovudine (57, 58), which is not currently the preferred first-line PEP regimen recommended by Canadian and U.S. guidelines (5, 18). It is also not known whether the effectiveness of PEP would be the same in a non-occupational setting (4). Studies were also constrained by lack of data on per-exposure transmission risk, compliance with medication, and the prevalence of HIV infection among population groups. The results should, therefore, be used with caution (4).

In addition to the above systematic review, one study estimating the cost-effectiveness of non-occupational PEP was found (59). Authors compared a "no-PEP" alternative to a PEP program described in a population-based observational cohort study of 1,601 participants eligible for PEP between 1998 and 2004 in Australia. PEP treatment costs were modelled and combined with effectiveness outcomes of the observational cohort study to calculate the cost per HIV infection averted and the cost per QALY gained. Overall, cost per HIV infection averted was AUD 1,647,476 in baseline analysis and cost per QALY gained was AUD 176,772. Using a threshold of AUD 50,000, and assuming lowest risk of transmission, the intervention was only cost-effective after unprotected receptive anal intercourse with a known HIV-positive source (AUD 23,618 per QALY gained). Sensitivity analyses showed that cost-effectiveness results were very sensitive to the transmission risk of exposure types. Assuming the maximal risk of HIV transmission, PEP was cost-effective overall (AUD 40,673 per QALY gained and AUD 512,410 per HIV infection averted) and cost-saving for unprotected receptive anal intercourse with HIV-positive source, but still not cost-effective after insertive anal exposure (AUD 450,466 per QALY gained) or heterosexual exposure (AUD 421,765 per QALY gained).

57. Cardo DM, Culver DH, Ciesielski CA, Srivastava PU, Marcus R, Abiteboul D, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. New England Journal of Medicine. 1997;337(21):1485–90.

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59. Guinot D, Ho MT, Poynten IM, McAllister J, Pierce A, Pell C, et al. Cost-effectiveness of HIV nonoccupational post-exposure prophylaxis in Australia. HIV Medicine. 2009;10(4):199–208.

60. Scheid DC, Hamm RM, Stevens KW. Cost effectiveness of human immunodeficiency virus postexposure prophylaxis for healthcare workers. Pharmacoeconomics. 2000;18(4):355–68.

61. Kerr CC, Stuart RM, Gray RT, Shattock AJ, Fraser-Hurt N, Benedikt C, et al. Optima: A model for HIV epidemic analysis, program prioritization, and resource optimization. Journal of Acquired Immune Deficiency Syndromes: JAIDS. 2015;69(3):365–76.

62. Juusola JL, Brandeau ML. HIV treatment and prevention: A simple model to determine optimal investment. Medical Decision Making. 2016;36(3):391–409.

Authors noted that the study was limited due to lack of evidence on the effectiveness of non-occupational PEP and on HIV transmission rates after single risk exposures, but concluded that the results suggest non-occupational PEP should be limited to the highest-risk exposures (59).

Occupational PEP

No recent economic evaluations of occupational PEP were identified. One 2000 study analyzed the cost-effectiveness of the 1998 U.S. Public Health Service (USPHS) PEP guidelines compared to two other occupational PEP strategies and no PEP (60). The analysis supported the use of the USPHS PEP guidelines, and all three PEP strategies were found to be cost-effective compared to no PEP (60). Similarly, according to a 2006 French study, PEP was cost-effective (EUR 20,077 per QALY gained) for health care workers after percutaneous exposure (e.g. needle stick injury) to a known HIV-positive source (56).

Gaps in knowledge

Overall, health economic analyses have suggested that PrEP and PEP may have high cost-effectiveness when targeted to individuals with the greatest risk of HIV acquisition, or who engage in behaviours that have a high risk of HIV transmission, such as receptive anal intercourse (5). Determining the best way to identify these individuals (especially individuals who are not men who have sex with men) (5), and the costs associated with these efforts (1), remain significant gaps in knowledge.

Ethical constraints prevent randomized controlled trials of non-occupational PEP in humans from being carried out (18). As a result, critical data on the efficacy of PEP after sexual or injection drug exposures is lacking (18). The use of effectiveness estimates from an occupational setting in economic evaluations of non-occupational PEP is of concern, as the same conditions may not exist in situations involving sexual exposures or injection drug use (4). Knowledge gaps related to the use of newer antiretroviral medications, transitioning high-risk individuals on PEP to PrEP, and the ideal timing of follow-up HIV testing (5) may also inform future economic evaluations.

With respect to PrEP, there is little data from high-income countries regarding populations other than men who have sex with men, and on the cost-effectiveness of on-demand regimens (5). Comparing PrEP with treatment as prevention remains an important gap in knowledge as well (1). Economic evaluations should continue to focus on efficiently funding current prevention, testing, treatment, and retention strategies, while investigating the potential cost-effectiveness of new interventions (29).

Health economic evaluations on HIV prevention are useful for determining if interventions are of good value, but do not determine if they are affordable (29). This means that, while an intervention may have benefits in the long-term, policy makers may not be able to make the initial investment required. Incorporating assessments of affordability and feasibility of resource allocation for interventions would be valuable to include in health economic evaluations on HIV prevention (29). Some models have been developed to assist decision makers with concerns of resource allocation given certain budget restrictions (61, 62), which are important steps in this direction. Decision-makers are also collectively working towards defining new thresholds of cost-effectiveness that better reflect a country's actual ability to pay for health care (27).

Factors That May Impact Local Applicability

Model input parameters in economic evaluations can vary significantly across different countries and target populations, making it difficult to accurately compare studies and make generalizations (29). Although the risk of HIV transmission for specific exposures are likely to be the same, other data, such as HIV incidence, may not be similar between different countries, and local costs may be different (4). It is important to note, as well, that monetary values reported in studies may not reflect current costs, due to inflation or changes in market prices over time. Furthermore, the recent approval of generic pricing for TDF/FTC in some countries may greatly impact the implementation of PrEP and

PEP (5). Future evaluations should adjust cost estimates accordingly.

It is important to keep in mind that, while an economic evaluation may deem certain HIV prevention interventions cost-effective, limited HIV budgets can make the initial investment in these interventions economically impossible for some governments and agencies (29). Moreover, decisions to include specific interventions within combination prevention packages will require more than just cost-effectiveness data. Ensuring the accessibility of these interventions to populations who would most benefit from them, and who are often marginalized or criminalized, will be critical for decision-makers (1).

Due to the heterogeneity of methods, readers are encouraged to examine original publications for outcomes, model inputs, and assumptions used to interpret data.

What We Did

We searched Medline (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations) using a combination of text terms HIV and cost-effective* and (preexposure prophylaxis or pre-exposure prophylaxis or PrEP or post-exposure prophylaxis or postexposure prophylaxis or PEP). All searches were conducted on November 13, 2018 without language or publication date restrictions. Reference lists of identified systematic reviews were also searched. The search yielded 180 references from which 62 were included.

Rapid Response: Evidence into Action

The OHTN Rapid Response Service offers quick access to research evidence to help inform decision making, service delivery and advocacy. In response to a question from the field, the Rapid Response Team reviews the scientific and grey literature, consults with experts, and prepares a brief fact sheet summarizing the current evidence and its implications for policy and practice.

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