The efficacy of post-exposure prophylaxis (PEP) for HIV

Questions

- What is the efficacy of PEP when used for non-occupational exposure?
- What is the efficacy of PEP when used for occupational exposure?
- Are specific PEP regimens more efficacious than others?
- What are key factors implicated in the efficacy or inefficacy of PEP?

Key Take-Home Messages

- PEP initiated soon after exposure can reduce the risk of HIV seroconversion after occupational and non-occupational exposures, provided adherence to medications is sufficient (1–4).
- Evidence suggests that individuals prescribed tenofovir-based two- or three-drug regimens are more likely to complete a course of PEP and have lower discontinuation rates due to adverse events compared to zidovudine-based regimens (5).
- Guidelines from Canada and the U.S. most commonly recommend a 28-day regimen of oral tenofovir disoproxil fumarate/emtricitabine (300mg/200mg) once daily plus raltegravir (400mg) twice daily for adults and adolescents as a preferred first-line regimen for both occupational and non-occupational PEP (1–3).
- The World Health Organization makes recommendations for PEP regimens based on differences in accessibility between high- and low-income settings (6).

References

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2. Tan DHS, Hull MW, Yoong D, Tremblay C, O'Byrne P, Thomas R, et al. Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational post-exposure prophylaxis: Updated version, June 13, 2018. Canadian Medical Association Journal. 2017;189(47):E1448–e58.

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4. 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.

The Issue and Why It's Important

In 2016, the Public Health Agency of Canada reported that the rate of new HIV diagnoses was the highest it had been in the last five years (7). Combining emerging biomedical prevention interventions with current prevention strategies may reduce new HIV infections (8).

One biomedical prevention strategy is post-exposure prophylaxis (PEP). PEP involves administering antiretroviral medications after exposure to HIV (1–3, 6). The World Health Organization (WHO), as well as Canadian and U.S. guidelines, recommend administering PEP within 72 hours following exposure (1-3, 6). Exposures are often distinguished into two types: occupational exposure to blood and/or other body fluids that may contain HIV in work contexts such as among health care personnel (3) and non-occupational exposure to HIV such as sexual exposure and injection drug use (1, 2).

Completion and adherence to the prescribed PEP regimen is crucial for effectiveness (6); however, medication costs have limited the feasibility and acceptability of biomedical strategies like PEP in Canada (2). Programs offering PEP have been slow to appear in the United States as well, mainly due to a lack of awareness in both providers and potential consumers (9). Expanding knowledge on biomedical interventions like PEP will contribute to the current efforts to eliminate new HIV infections (8). This review explores the efficacy of post-exposure prophylaxis for both occupational and non-occupational exposures to HIV, and the key factors implicated in its efficacy.

What We Found

Post-exposure prophylaxis (PEP)

Ideally, evidence from a randomized controlled trial comparing the effects of PEP with no intervention would provide the best evidence of the efficacy of PEP. However, conducting such a trial is neither ethical nor feasible, and none have been conducted (1). As a result, national and international PEP guidelines have based their recommendations on animal studies and observational studies in humans (1–3, 6). A single case-control study, conducted in 1997, reported the effect of occupational PEP (prescribed as ZDV monotherapy) on HIV seroconversion (4). The study identified risk factors for the transmission of HIV to health care workers from the U.S., France, Italy, and the UK who had experienced exposure to HIV-infected blood. Cases included those who had HIV seroconversion temporarily associated with the exposure, and no other reported exposures to HIV. Controls were HIV negative at the time of exposure, and for at least six months after. There was no difference in the rate at which PEP was offered to cases or controls after controlling for HIV transmission risk. However,

5. Ford N, Shubber Z, Calmy A, Irvine C, Rapparini C, Ajose O, et al. Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: A systematic review. Clinical Infectious Diseases. 2015;60 Suppl 3:S170–6.

6. World Health Organization Postexposure Prophylaxis Guideline Development Group. Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: Recommendations for a public health approach. 2014. Available from: https://apps.who.int/iris/bitstream/handle/10665/145719/9789241508193_eng.pdf;jsessionid=6783F9489D0A4891FE5D7691227235B4?sequence=1 Accessed March 7, 2019.

7. Bourgeois AC, Edmunds M, Awan A, Jonah L, Varsaneux O, Siu W. HIV in Canada-surveillance report, 2016. Canada Communicable Disease Report. 2017;43(12):248–56.

8. Hull M, Tan D. Setting the stage for expanding HIV pre-exposure prophylaxis use in Canada. Canada Communicable Disease Report. 2017;43(12):272–8.

9. Beymer MR, Kofron RM, Tseng CH, Bolan RK, Flynn RP, Sayles JM, et al. Results from the post-exposure prophylaxis pilot program (P-QUAD) demonstration project in Los Angeles County. International Journal of STD & AIDS. 2018;29(6):557–62.

10. Wiboonchutikul S, Thientong V, Sutha P, Kowadisaiburana B, Manosuthi W. Significant intolerability of efavirenz in HIV occupational postexposure prophylaxis. Journal of Hospital Infection. 2016;92(4):372–7.

the odds of HIV seroconversion among health care workers who had received PEP after occupational exposure was reduced by approximately 81%, compared to those who did not receive PEP (4). This study is considered the strongest example of the benefit of PEP in humans (1). Evidence from more recent studies suggests that the administration of antiretroviral medications as PEP soon after exposure, and continued for 28 days, can reduce the risk for acquiring HIV infection after occupational and non-occupational exposures, provided adherence to medications is sufficient (1).

Below is a table of approved antiretroviral medications used in PEP regimens that are discussed in this review.

Class of antiretroviral drug	Antiretroviral drug generic name & acronym
Nucleoside reverse transcriptase inhibitors (NRTIs)	Abacavir (ABC) Emtricitabine (FTC) Lamivudine (3TC) Tenofovir disoproxil fumarate (TDF) Zidovudine (ZDV*; AZT)
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz (EFV) Nevirapine (NVP) Rilpivirine (RPV)
Protease inhibitors (PIs)	Atazanavir (ATV) Darunavir (DRV) Indinavir (IDV) Lopinavir (LPV) Nelfinavir (NFV)
Entry inhibitors (EIs)	Maraviroc (MVC)
Integrase strand transfer inhibitors (INSTIs)	Dolutegravir (DTG) Elvitegravir (EVG) Raltegravir (RAL)
Booster drugs	Cobicistat (c) Ritonavir (r)

*this review uses ZDV as the acronym for zidovudine

The following sections, divided by exposure type and population, summarize observational studies published between 2014 and 2019 that report HIV seroconversion outcomes among participants receiving PEP.

11. Abubakar S, Iliyasu G, Dayyab FM, Inuwa S, Tudun Wada RA, Sadiq NM, et al. Post-exposure prophylaxis following occupational exposure to HIV and hepatitis B: An analysis of a 12-year record in a Nigerian tertiary hospital. Journal of Infection Prevention. 2018;19(4):184–9.

12. Sheth SP, Leuva AC, Mannari JG. Post exposure prophylaxis for occupational exposures to HIV and hepatitis B: Our experience of thirteen years at a rural based tertiary care teaching hospital of Western India. Journal of Clinical and Diagnostic Research 2016;10(8):OC39–44.

13. Tetteh RA, Nartey ET, Lartey M, Mantel-Teeuwisse AK, Leufkens HG, Nortey PA, et al. Outcomes of a post-exposure prophylaxis program at the Korle-Bu teaching hospital in Ghana: A retrospective cohort study. Journal of the International Association of Providers of AIDS Care. 2015;14(6):544–52.

14. O'Byrne P, MacPherson P, Orser L. Nurse-led HIV PEP program used by men at high risk for HIV seroconversion. Journal of the Association of Nurses in AIDS Care. 2018;29(4):550–9.

15. McDougal SJ, Alexander J, Dhanireddy S, Harrington RD, Stekler JD. Non-occupational post-exposure prophylaxis for HIV: 10-year retrospective analysis in Seattle, Washington. PLoS ONE. 2014;9(8):e105030.

16. Beymer MR, Bolan RK, Flynn RP, Kerrone DR, Pieribone DL, Kulkarni SP, et al. Uptake and repeat use of postexposure prophylaxis in a community-based clinic in Los Angeles, California. AIDS Research & Human Retroviruses. 2014;30(9):848–55.

Efficacy of PEP for occupational HIV exposure

Health care workers

Four retrospective studies reported outcomes in health care workers who had received PEP following occupational exposure to HIV (10–13). Review periods ranged from five to 19 years. Studies were conducted in Thailand (10), Nigeria (11), India (12), and Ghana (13) and used two- to three-drug PEP regimens that were mainly ZDV-based. Of the 527 total participants who received PEP in these studies, no seroconversions occurred (10–13).

Efficacy of PEP for non-occupational HIV exposure

Mixed populations

Three studies retrospectively reviewed medical records of patients seeking PEP (14–16). The first study found that 112 individuals (103 male; 84 men who have sex with men) sought PEP from two STI clinics in Ottawa between 2013 and 2015 (14). All patients were prescribed TDF/FTC (300mg/200mg) plus RAL (400mg) twice daily for a 28-day course. Five individuals were diagnosed with HIV within 12 months of using PEP, all of which reportedly completed the prescribed regimen (14).

The second study found that 324 patients (266 male, 215 men who have sex with men) were prescribed PEP at a publicly-funded HIV clinic in Seattle between 2000 and 2010 (15). A total of 89% of patients completed the prescribed regimen. Two cases were considered potential PEP failures, as they tested HIV positive at two and five months following PEP, respectively. One additional patient tested negative at his baseline visit and at 11 days following the completion of PEP, but tested HIV positive at five months – indicating another potential PEP failure. The fourth case was considered unlikely to be a PEP failure, as they tested HIV negative as late as one year after receiving PEP (15).

The third study found that 649 individuals enrolled in the Los Angeles LGBT Center's PEP-LA program were prescribed a 28-day course of once daily TDF/FTC (300mg/200mg) PEP between 2011 and 2012 (16). Seven seroconversions occurred within the study period. Among those who seroconverted, the mean time from exposure to first PEP medication dose was 51.5 hours (16).

An additional study evaluated a PEP pilot program (P-SQAUD) in two community-based clinics in Los Angeles County (9). Between 2010 and 2011, PEP was offered to 267 individuals with sexual exposure to HIV. Participants were mainly men who have sex with men (84%) and most had been prescribed TDF/FTC-based two- or three-drug regimens (90%). Seven seroconversions were reported. Of these,

17. Whitlock G, McCormack C, Fearnley J, McOwan A. High HIV incidence in men who have sex with men attending for postexposure prophylaxis: A service evaluation. Sexually Transmitted Infections. 2017;93(3):214–6.

18. Jain S, Oldenburg CE, Mimiaga MJ, Mayer KH. Subsequent HIV infection among men who have sex with men who used non-occupational post-exposure prophylaxis at a Boston community health center: 1997-2013. AIDS Patient Care and STDs. 2015;29(1):20–5.

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20. Mukhtar-Yola M, Otuneye AT, Mairami AB, Wey Y, Nwatah V, Audu LI. Audit of prevention of mother-to-child transmission programme interventions in HIV-exposed children at national hospital, Abuja, Nigeria. Nigerian Postgraduate Medical Journal. 2018;25(1):27–31.

21. Muriuki EM, Kimani J, Machuki Z, Kiarie J, Roxby AC. Sexual assault and HIV postexposure prophylaxis at an urban African hospital. AIDS Patient Care & STDs. 2017;31(6):255–60.

22. Ebert J, Sperhake JP, Degen O, Schroder AS. The use of HIV post-exposure prophylaxis in forensic medicine following incidents of sexual violence in Hamburg, Germany: A retrospective study. Forensic Science, Medicine & Pathology. 2018;14(3):332–41.

23. Al-Hajjar SH, Frayha HH, Al-Hazmi M, Batawi R, McIntosh K, Sax PE, et al. Prevention of HIV-1 transmission with postexposure prophylaxis after inadvertent infected blood transfusion. AIDS. 2014;28(10):1539–41.

six had had ongoing sexual exposure. One reported no subsequent re-exposure. Four of the seven participants who seroconverted initiated PEP more than 48 hours after initial HIV exposure (9).

Men who have sex with men

One study retrospectively reviewed electronic case-notes of men who have sex with men prescribed PEP in 2013 at a sexual health service in London, UK (17). The specific PEP regimen was not recorded. During this period 530 individuals received PEP. Of them, 183 received more than one course. The number of seroconversions was 57, resulting in an HIV incidence of 7.6 per 100 person-years. Of those who seroconverted, 40 individuals had negative HIV tests following their PEP course, and prior to diagnosis. Another five received a positive diagnosis more than two months following their initiation of PEP. It was not possible to rule out PEP failure in the remaining 12 individuals. However, study authors concluded that PEP failure was unlikely given ongoing sexual risk behaviours in this group. They concluded that men who have sex with men who access repeat PEP may also be candidates for pre-exposure prophylaxis (17).

Another study examined risk factors associated with HIV acquisition among men who have sex with men who presented for PEP at a large community centre in Boston between 1997 and 2013 (18). During this time period, 894 patients (including 788 men who have sex with men) were prescribed 1,244 courses of PEP. Of these, 39 seroconversions occurred, all of which were men who have sex with men. This resulted in an HIV incidence of 2.2 cases per 100 person-years within this population. Repeated use of PEP was not associated with incident HIV infection. All seroconversions occurred greater than 90 days after initially presenting for PEP (35 of which occurred greater than 180 days after PEP). Three of the remaining four individuals reported completing the 28-day regimen, but adherence or ongoing sexual risk behavior were not reported (18).

Infants exposed to HIV

Two retrospective studies reviewed outcomes following PEP administered to infants born to HIV-positive mothers (19, 20). The first study reviewed case notes of 79 infants receiving care in Brighton, UK between 2003 and 2014 (19). Seventy-eight percent of infants received PEP, of which 88% received ZDV and 12% received a combination of antiretroviral medications. One seroconversion occurred. Both mother and infant received care in accordance with guidelines, including neonatal PEP within 4 hours (19).

The second study reviewed the rate of mother-to-child transmission of HIV in exposed infants at a tertiary hospital in Nigeria between 2011 and 2014 (20). Out of 699 infants (599 of which received PEP; 554 NVP and 45 ZDV for 6 weeks), 22 seroconversions occurred. Analysis

24. McAllister JW, Towns JM, McNulty A, Pierce AB, Foster R, Richardson R, et al. Dolutegravir with tenofovir disoproxil fumarate-emtricitabine as HIV postexposure prophylaxis in gay and bisexual men. AIDS. 2017;31(9):1291–5.

25. Foster R, McAllister J, Read TR, Pierce AB, Richardson R, McNulty A, et al. Single-tablet emtricitabine-rilpivirine-tenofovir as HIV postexposure prophylaxis in men who have sex with men. Clinical Infectious Diseases. 2015;61(8):1336–41.

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27. Chauveau M, Billaud E, Bonnet B, Merrien D, Hitoto H, Bouchez S, et al. Tenofovir DF/emtricitabine/rilpivirine as HIV post-exposure prophylaxis: Results from a multicentre prospective study. Journal of Antimicrobial Chemotherapy. 2019. [Epub ahead of print].

28. Mulka L, Annandale D, Richardson C, Fisher M, Richardson D. Raltegravir-based HIV postexposure prophylaxis (PEP) in a real-life clinical setting: Fewer drug-drug interactions (DDIs) with improved adherence and tolerability. Sexually Transmitted Infections. 2016;92(2):107.

29. Milinkovic A, Benn P, Arenas-Pinto A, Brima N, Copas A, Clarke A, et al. Randomized controlled trial of the tolerability and completion of maraviroc compared with Kaletra in combination with Truvada for HIV post-exposure prophylaxis (MiPEP Trial). Journal of Antimicrobial Chemotherapy. 2017;72(6):1760–8.

showed that PEP use by infants was independently associated with a reduction in HIV transmission rate (20).

Sexual assault survivors

Two retrospective studies explored outcomes related to PEP administration following sexual assault (21, 22). One study reviewed hospital charts of survivors of sexual violence attending the Gender Based Violence Recovery Center between 2009 and 2012 in Nairobi, Kenya (21). Survivors were mainly female, and 16% were children under 10 years old. Of 385 survivors, 207 initiated PEP (ZDV/3TC plus LPV/r). Only 70 completed the full 28-day course and 21 returned for a three-month follow up. No seroconversions were reported among those who came for a repeat HIV test (21).

The second study reviewed forensic clinical examinations carried out by the Hamburg Department of Legal Medicine following incidents of sexual violence from 2009 to 2016 in Germany (22). The study reviewed 1,218 cases of sexual violence (96% female) and PEP (TDF/FTC plus RAL) was prescribed in 223 cases. Only 39 victims returned for follow-up testing after at least 6 weeks. No seroconversions occurred in any of these cases (22).

Blood transfusion

One case report was found of a 12-year-old girl in Saudi Arabia with sickle-cell disease who had inadvertently received a transfusion with HIV-infected packed red blood cells (23). The donor had not been receiving antiretroviral therapy. A 13-week PEP regimen of TDF/FTC plus DRV/r (later changed to LPV) and RAL was started approximately 24 hours later. No HIV was detected in her blood eight months after the exposure, strongly suggesting that PEP had successfully prevented HIV acquisition (23).

PEP regimens

The following sections describe studies that assess the safety, tolerability, and/or effectiveness of different PEP regimens. Guideline recommendations for PEP regimens are also outlined.

Adults and adolescents

A 2015 systematic review assessed the safety and efficacy of two- and three-drug antiretroviral regimens (the majority of which were TDF- or ZDV-based) for PEP after occupational or non-occupational exposures to HIV (5). Overall, PEP HIV seroconversion was rare, however an association between PEP efficacy and regimen could not be determined. Among studies assessing two-drug regimens, PEP completion rates were significantly higher for TDF-based regimens (78.4%) compared to ZDV-based regimens (58.8%). The pooled proportion of PEP discontinuation due to adverse events was also

30. Fatkenheuer G, Jessen H, Stoehr A, Jung N, Jessen AB, Kummerle T, et al. PEPDar: A randomized prospective noninferiority study of ritonavir-boosted darunavir for HIV post-exposure prophylaxis. HIV Medicine. 2016;17(6):453–9.

31. Inciarte A, Leal L, Gonzalez E, Leon A, Lucero C, Mallolas J, et al. Tenofovir disoproxil fumarate/emtricitabine plus ritonavir-boosted lopinavir or cobicistat-boosted elvitegravir as a single-tablet regimen for HIV post-exposure prophylaxis. Journal of Antimicrobial Chemotherapy. 2017;72(10):2857–61.

32. Leal L, Leon A, Torres B, Inciarte A, Lucero C, Mallolas J, et al. A randomized clinical trial comparing ritonavir-boosted lopinavir versus maraviroc each with tenofovir plus emtricitabine for post-exposure prophylaxis for HIV infection. Journal of Antimicrobial Chemotherapy. 2016;71(7):1982–6.

33. Leal L, Leon A, Torres B, Inciarte A, Lucero C, Mallolas J, et al. A randomized clinical trial comparing ritonavir-boosted lopinavir versus raltegravir each with tenofovir plus emtricitabine for post-exposure prophylaxis for HIV infection. Journal of Antimicrobial Chemotherapy. 2016;71(7):1987–93.

34. Mayer KH, Jones D, Oldenburg C, Jain S, Gelman M, Zaslow S, et al. Optimal HIV postexposure prophylaxis regimen completion with single tablet daily elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine compared with more frequent dosing regimens. Journal of Acquired Immune Deficiency Syndromes. 2017;75(5):535–9.

significantly lower for TDF-based regimens (0.3%) compared to ZDV-based regimens (3.2%). Among studies examining three-drug regimens (including seven different drug combinations), pooled completion rates were highest for TDF/FTC plus DRV/r (93.9%) and lowest for ZDV/3TC plus LPV/r (59.1%). Discontinuations were lowest for TDF/FTC plus RAL (1.9%) and highest for ZDV/3TC plus ATV/r (21.2%). Authors supported the use of co-formulated TDF with either 3TC or FTC as the two-drug backbone for PEP. They concluded that this combination may improve PEP completion rates, produce fewer treatment discontinuations, and result in fewer new HIV infections compared to ZDV-based regimens. As for the third drug, authors concluded that this should depend on short-term tolerability, cost, availability, and possible risk of transmitted drug resistance. In the context of high-income settings, they supported the use of TDF/FTC plus RAL (5).

An additional 13 studies, published between 2015 and 2019, assessed the safety and tolerability of different PEP regimens in adults. Studies were conducted in Australia (24, 25), France (26, 27), the UK (28, 29), Germany (30), Spain (31–33), the U.S. (34), Canada (35), and Denmark (36). Four of these were open-label, single-arm, non-randomized studies that assessed the safety and tolerability of a single PEP regimen containing TDF/FTC (24–27). Two of these studies assessed men who have sex with men only (24, 25). Drug regimens examined were as follows: TDF/FTC (300mg/200mg daily) plus DTG (50mg daily) (24); co-formulated TDF/FTC (245mg/150mg) with EVG/c (200mg/150mg) as a single tablet daily regimen (26); and co-formulated TDF/FTC (300mg/200mg) plus RPV (25mg) as a single tablet daily regimen (25, 27). These studies reported high tolerability as well as high adherence and completion rates; furthermore, no seroconversions were reported in these four studies (24-27).

One case control and five open-label randomized trials assessed the tolerability, safety, completion, or number of seroconversions associated with 28-day PEP regimens (28-33). All studies compared regimens containing daily TDF/FTC plus LPV/r twice daily (in varying dosages) with another 28-day TDF/FTC-based three-drug regimen (28-33). The majority of participants in these studies were men who have sex with men. The third drug used in comparison regimens included RAL (400mg twice daily) (28, 33), or MVC (300mg twice daily) (29, 32), or DRV/r (800mg/100mg daily)(30), or EVG/c (150mg/150mg) (combined with TDF/FTC [245mg/200mg] as a combination single tablet daily regimen) (31). Compared with TDF/FTC plus LPV/r regimens, alternative drugs had greater completion rates (30-32), fewer side-effects or adverse events (28–33), less drug-drug interactions (28), and higher adherence rates (31, 33). Authors concluded that these were well-tolerated alternatives for first-line PEP. While no HIV seroconversions were observed among participants completing follow-up in four of these studies (28–30, 32), one participant seroconverted at 90-day follow-up in each of the remaining two studies (31, 33). One of these participants had

35. Thomas R, Galanakis C, Vezina S, Longpre D, Boissonnault M, Huchet E, et al. Adherence to post-exposure prophylaxis (PEP) and incidence of HIV seroconversion in a major North American cohort. PLoS ONE. 2015;10(11):e0142534.

36. Lunding S, Katzenstein TL, Kronborg G, Storgaard M, Pedersen C, Morn B, et al. The Danish PEP registry: Experience with the use of post-exposure prophylaxis following blood exposure to HIV from 1999–2012. Infectious Diseases. 2016;48(3):195–200.

37. Penazzato M, Dominguez K, Cotton M, Barlow-Mosha L, Ford N. Choice of antiretroviral drugs for postexposure prophylaxis for children: A systematic review. Clinical Infectious Diseases. 2015;60 Suppl 3:S177–81.

38. Kakkar FW, Samson L, Vaudry W, Brophy J, Le Meur JB, Lapointe N, et al. Safety of combination antiretroviral prophylaxis in high-risk HIV-exposed newborns: A retrospective review of the Canadian experience. Journal of the International AIDS Society. 2016;19(1):20520.

39. BC Centre for Excellence in HIV/AIDS PEP Guidelines Committee. HIV post-exposure prophylaxis (PEP) guidelines May 2017. Available from: http://cfenet.ubc.ca/sites/default/files/uploads/publications/centredocs/pep_guidelines_final_may_2017.pdf Accessed January 21, 2019.

40. Siegfried N, Beanland RL, Ford N, Mayer KH. Formulating the future research agenda for postexposure prophylaxis for HIV: Methodological challenges and potential approaches. Clinical Infectious Diseases. 2015;60 Suppl 3:S205–11.

received TDF/FTC plus EVG/c (31), while the other had received TDF/FTC plus RAL (33). Both participants had reported multiple high-risk exposures before and after PEP use (31, 33).

Two studies compared three or more PEP regimens (34, 35). The first study was a small case-control study that compared the tolerability of a single daily tablet containing TDF/FTC plus EVG/c compared to daily TDF/FTC plus twice daily RAL or twice daily ZDV/3TC and a protease inhibitor (34). Authors concluded that the combination TDF/FTC plus EVG/c was safe and well-tolerated for PEP, with higher regimen completion rates than more frequently dosed PEP regimens. No participants seroconverted (34). The second was a prospective cohort study that reported the incidence of PEP failures among patients at a Montreal clinic receiving PEP after sexual exposure between 2000 and 2014 (35). A total of 2,731 patients received PEP, of which 74% received TDF/FTC plus LPV/r, 10% received ZDV/3TC plus LPV/r, and 8% received TDF/FTC plus RAL. Authors found that patients were significantly more likely to be adherent to TDF/FTC-based regimens. Ten treated patients seroconverted (less than 1%) during the study period. One seroconversion was attributed to PEP failure and the other nine were attributed to high-risk behaviour following treatment (35).

Finally, one study described all PEP prescriptions following non-sexual exposure (12.4% of which were non-occupational) to HIV in Denmark between 1999 and 2012 (36). Regimens included TDF/FTC plus ATV/r, ZDV/3TC plus LPV/r, ZDV/3TC plus IDV, or "other regimens" (exact dosages not reported). Adverse effects were reported by more than 50% of the study population (n=411); however, no particular regimen was linked to these events. One patient, who had initiated ZDV/3TC plus LPV/r, seroconverted. This individual had been lost to follow-up 3 days after PEP initiation, and was diagnosed with HIV one year later. Therefore, it was not possible to conclude whether this was a case of PEP failure, or if the individual had been re-exposed to HIV (36).

Children and infants

A lack of availability of age-appropriate formulations limits regimen choice for children (6). One systematic review assessed PEP regimens for children and adolescents (37). Three prospective cohort studies, reporting outcomes of children given ZDV plus 3TC as a two-drug PEP regimen, were included. Sixty-four percent of children completed the full 28-day course of PEP and 4.5% discontinued due to adverse events. One randomized trial was also included in this review that compared ABC plus 3TC and ZDV plus 3TC as part of a two- or three-drug regimen. Better efficacy was demonstrated in the ABC-containing combinations. Another three randomized trials included in this review compared LPV/r to NVP for antiretroviral therapy. LPV/r was associated with a lower risk of treatment discontinuations than NVP, however there was no significant difference between groups in drug-related adverse

41. Kijak GH, Kim JH. Timing, adherence, resistance, and ... persistence? New insight into the mechanisms of failure of HIV type 1 postexposure prophylaxis. Journal of Infectious Diseases. 2013;208(10):1542–4.

42. de la Tribonniere X, Dufresne MD, Alfandari S, Fontier C, Sobazek A, Valette M, et al. Tolerance, compliance and psychological consequences of post-exposure prophylaxis in health-care workers. International Journal of STD & AIDS. 1998;9(10):591–4.

43. Sultan B, Benn P, Waters L. Current perspectives in HIV post-exposure prophylaxis. HIV/AIDS Research and Palliative Care. 2014;6:147–58.

44. Heuker J, Sonder GJ, Stolte I, Geskus R, van den Hoek A. High HIV incidence among MSM prescribed postexposure prophylaxis, 2000-2009: Indications for ongoing sexual risk behaviour. AIDS. 2012;26(4):505–12.

events. Overall, the quality of evidence among the included studies was rated as low (37).

One additional study reviewed PEP-exposed infants identified from four urban Canadian centres between 1997 and 2013 (38). Combination antiretroviral therapy (defined as any regimen of three or more antiretroviral agents for a minimum of six weeks) was administered to 148 infants. Regimens included 3TC (2 mg/kg twice daily for six weeks) plus either NVP (150 mg/m^2 daily for 14 days followed by 150 mg/m2 twice daily for 14 days) or NFV (40-50 mg/kg twice daily for six weeks), or LPV/r (300 mg/m^2 twice daily) for six weeks. ZDV monotherapy was given to 145 infants (either 2mg/kg every six hours or 4mg/kg twice daily). Results showed that combination antiretroviral therapy administered for PEP was generally well tolerated, though a higher incidence of non-specific signs and symptoms and early treatment discontinuation occurred among combination antiretroviral therapy recipients. No infants receiving ZDV monotherapy and 13 infants given combination antiretroviral therapy seroconverted. Five of these infants had HIV detected within 48 hours of birth, suggesting in utero infection. The timing of infection could not be ascertained among eight of these infants, as initial testing took place after 48 hours of life. Authors concluded that comparison of the risk of transmission among combination antiretroviral therapy versus ZDV-treated infants was not appropriate, as the latter group would have received better antenatal preventive management (38).

Guidelines for PEP regimens

Adults and adolescents

In the absence of randomized controlled trials, PEP guidelines are recommended based on drug combinations that have been effective in suppressing viral replication (1), are tolerated well, and have sufficient completion rates of these drugs as PEP (1–3, 6). These particular regimens almost always consist of a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone plus an integrase strand transfer inhibitor (INSTI), a protease inhibitor (PI; boosted with ritonavir), or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (3).

Currently, the Canadian guidelines for adults and adolescents recommend an oral dose of TDF/FTC (300mg/200mg) once daily plus either RAL (400mg) twice daily, DTG (50mg) once daily, or DRV/r (800mg/100mg) once daily as a preferred first-line regimen (2). Alternate regimens are also provided (2).

Guidelines from the U.S. also recommend a preferred first-line regimen for adults and adolescents with normal renal function (including pregnant women) of oral dose of TDF/FTC (300mg/200mg) once daily plus either RAL (400mg) twice daily (1, 3) or DTG (50mg) once daily (1).

The WHO 2014 PEP guideline recommends that PEP should be offered based on HIV risk rather than actual type of exposure (6). The preferred backbone regimen for adults and adolescents recommended by WHO is TDF plus 3TC (or FTC), based on safety and affordability. However, recommendations for a potential third drug are less defined. LPV/r or ATV/r is recommended as the preferred third drug for adults and adolescents for use in antiretroviral therapy and is widely available in low- and middle-income countries. WHO also recommends RAL, DRV/r or EFV, though these drugs are costly and access remains limited in low- and middle-income settings (6).

Children and infants

For children two years or older, Canadian guidelines recommend TDF plus 3TC once daily and RAL twice daily for 28 days as a preferred first-line regimen. Exact dosages of these drugs are dependent on bodyweight (39).

U.S. guidelines also recommend a three-drug regimen consisting of TDF/FTC and RAL with each drug dosed to age and weight (1). The preferred first-line regimen for children four weeks to two years is a three-drug regimen consisting of ZDV oral solution and 3TC oral solution combined with RAL or LPV/r oral solution, with each drug dosed to age and weight (1).

Conversely, WHO recommends ZDV/3TC as the preferred backbone regimen for children 10 years and younger in combination with LPV/r (6). TDF plus 3TC or FTC is provided as an alternative

regimen for children three years or older, however concerns regarding potential bone toxicity are cited (6).

Key factors implicated in the efficacy of PEP

There is a wide-scale lack of knowledge about PEP among health care providers (40) and research regarding implementation and supporting awareness of PEP is greatly needed (2).

The timing of initiation and the duration of treatment are crucial to the success of PEP (6). Ensuring the timely and appropriate prescription of PEP, and understanding barriers to access, remain a challenge (40). Maintaining sufficient antiretroviral drug levels is also important in preventing replication of the HIV virus (41). Adherence to the prescribed regimen is therefore a determinant in the effectiveness of PEP (6). Adherence and completion rates of PEP are generally low in most settings (6) as adherence can be impacted by side effects that can impact individuals physically and psychologically (42). As a result, it is important that research continues to determine tolerable and convenient antiretroviral drug regimens in addition to investigating adherence interventions (6).

Continued exposure to HIV while on PEP may also be a key determinant in its efficacy (43). While studies have described HIV infection following PEP use, in many cases it is unclear whether seroconversions occurred due to PEP failure or continued exposure to HIV (44). Understanding factors associated with continued exposure is crucial (35). Furthermore, it may be appropriate to promote the transition to pre-exposure prophylaxis (PrEP) in cases of repeated exposure to HIV (6). Identifying optimal strategies for this transition (2), and ways for front-line workers to determine potential PrEP candidates (40), remain critical gaps in knowledge.

In the absence of randomized controlled trials, monitoring individual and population-level outcomes will provide vital information regarding the effectiveness of PEP delivery and follow-up, adverse effects, and PEP failure (6). The World Health Organization Guideline Development Group has recommended a global PEP registry be established (40). This would provide information regarding follow-up and linkage to care and inform future recommendations for PEP drug regimens (40).

Factors That May Impact Local Applicability

The safety of antiretroviral medications used for PEP, including the occurrence of serious adverse effects from use by people without HIV infection, use during pregnancy, and potential selection for drug-resistant strains of virus, have been explored and discussed in guidelines (1). Further information and alternative drug regimen recommendations are also provided (1). These topics, however, are outside the scope of this review.

The availability of certain antiretroviral medications remains limited and costly in low- and middle-income countries (6). Antiretroviral medications are also expensive in high-income countries (1). Identifying budgetary, human resource, infrastructure, and health system requirements within the local context are important for decision-makers to consider in the implementation of PEP programs (6).

Moreover, the achievement of global and national commitments requires timely and equitable delivery of HIV treatment and prevention (6). Addressing barriers to access, particularly those faced by populations that are marginalized or criminalized, will be critical for decision-makers (6).

What We Did

We searched Medline (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations) using a combination of text term HIV with text terms post-exposure prophylaxis or postexposure prophylaxis or PEP or MeSH term Post-Exposure Prophylaxis. All searches were conducted on January 17, 2019 and results limited to English articles without publication date restrictions.

Reference lists of identified systematic reviews were also searched. The search yielded 542 references from which 44 were included. Sample sizes of primary studies ranged from 1 to 3,547.

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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