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REVIEW OF THERAPEUTICS

Personalizing prevention: Advances in pharmacotherapy for HIV prevention

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Abstract

The HIV epidemic continues to pose a significant burden on the healthcare system. Although the incidence of annual new infections is decreasing, health disparities persist and most new infections remain concentrated into different racial, ethnic, and minority groups. Pre-exposure prophylaxis (PrEP), which involves those at high risk of acquiring HIV to take chronic medications to prevent acquisition of the virus, is key to preventing new HIV infections. The purpose of this article is to review medication therapies for PrEP and examine their role in personalizing PrEP in different patient populations. Additionally, new medications currently under development for PrEP are reviewed, as well as treatment as prevention (TasP) and post-exposure prophylaxis (PEP). There are currently four medications available for PrEP: the oral options of co-formulated emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or emtricitabine/tenofovir alafenamide (FTC/TAF); injectable long-acting cabotegravir (CAB-LA); and the vaginal ring dapivirine (DPV-VR). FTC/TAF is not currently

indicated for persons at risk for HIV through vaginal sex due to lack of studies, but trials are currently ongoing. DPV-VR is available in Zimbabwe and South Africa and has been endorsed by the World Health Organization but is not currently available in the United States. Several agents are also in development for use in PrEP: the novel long-acting injectable lenacapavir, a first-in-class capsid inhibitor, which has no cross-resistance to any existing HIV drug class; the subdermal implant islatravir, a first-in-class translocation inhibitor; and VRC01, a broadly neutralizing antibody (bnAb) which has been evaluated in proof-of-concept studies that may lead to the development of more potent bnAbs. Overall, PrEP is highly effective at preventing HIV infection in high-risk populations. Identifying optimal PrEP regimens in different patient populations is complex and must consider patient-specific factors and medication cost and access considerations. Lastly, providers should consider individual patient preferences with regard to prevention to improve access, retention in care, and adherence.

KEYWORDS
human immunodeficiency virus, pharmacotherapy, prophylaxis

1 | BACKGROUND

The Joint United Nations Program on HIV/AIDS (UNAIDS) 2022 global update identified that global progress against human immunodeficiency virus (HIV) stalled during the coronavirus disease 2019 (COVID-19) pandemic, with new HIV infections declining only 3.6% from 2020 to 2021, which is the smallest annual reduction in global HIV incidence since 2016.[1] Female sex workers, persons who inject drugs (PWID), men who have sex with men (MSM), and transgender women who have sex with men (TGWSM) were identified in this report as key population targets for HIV prevention interventions. Collectively, these populations account for less than 5% of the global population, yet they and their sexual partners comprise 70% of new HIV infections. In addition, young women (ages 15–24 years) are at increased risk of HIV infection and are three times more likely to acquire HIV compared with young men. Within the United States, The National HIV/AIDS Strategy for 2022–2025 from the White House is focused on expanding and improving implementation of safe and effective prevention interventions, syringe services programs (SSPs), and development of new prevention options.[2] Over the next 3 years, the White House aims to increase coverage in those indicated for pre-exposure prophylaxis (PrEP) to 50% from a 2020 baseline of 25%.[2,3] Although new HIV infections have declined in the United States, health disparities persist with Black, Hispanic or Latinx, and White gay and bisexual men, and Black heterosexual women are still bearing the greatest burden of new infections.[4]

Treatment as prevention (TasP), PrEP, and post-exposure prophylaxis (PEP) are all vital strategies to prevent HIV transmission and acquisition. TasP refers to people with HIV (PWH) taking antiretroviral therapy (ART) to prevent sexual transmission of HIV.[5] TasP is also commonly referenced by the concept of undetectable equals untransmittable (U=U) from multiple clinical trials, which demonstrated if PWH remain undetectable with HIV RNA < 200 copies/mL, then HIV cannot be transmitted sexually to a partner without HIV.[6–9] TasP relies on the partner with HIV to remain adherent to ART and maintain an undetectable viral load. On the other hand, PrEP allows the partner without HIV to protect themselves by taking medication chronically to prevent acquiring HIV from sex or injection drug use (IDU). Currently, there are two oral PrEP options, co-formulated emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or emtricitabine/tenofovir alafenamide (FTC/TAF); one injectable option, long-acting cabotegravir (CAB-LA); and one vaginal ring, dapivirine (DPV-VR).[5,10–13] However, not all of these are approved by the US Food and Drug Administration (FDA) for all patient groups. PEP involves a person without HIV taking ART after a known or suspected percutaneous or mucous membrane exposure to HIV to prevent infection but relies on rapid medication accessibility to be successful. Additionally, expansion of HIV testing should serve as an entry point for prevention and treatment through identification of new HIV infections and facilitating conversation about PrEP in patients who test negative.[1]

In this review, various approaches to prevent HIV transmission and acquisition will be presented, including a review of drug therapies currently available and under development, novel formulations for delivery, and updates on the use of prevention strategies across special populations. Pharmacists provide a unique opportunity to expand access to HIV prevention services through their accessibility, knowledge about medication therapies, and ability to address barriers to medication access. Pharmacists can personalize PrEP to patient needs based on individual characteristics and preferences to help combat new HIV infections in persons who may benefit from PrEP.

2 | TREATMENT AS PREVENTION

2.1 | Review of data supporting TasP

The concept of TasP, where a PWH takes ART to prevent sexual transmission to a person without HIV, has been considered for over a decade, when the Swiss HIV Advisory Committee formulated "The Swiss Statement," which indicated that, for PWH with virologic suppression for 6 months, unprotected sex with an informed partner was unlikely to transmit virus.[14] In 2011, Cohen and colleagues[6] published one of the first controlled trials evaluating the concept. The HIV Prevention Trials Network (HPTN) 052 trial evaluated the impact of early versus delayed initiation of ART on rates of HIV transmission in 1763 PWH who were in primarily heterosexual serodiscordant partnerships. Individuals in the early therapy arm were initiated on ART at study enrollment while individuals in the delayed arm were initiated on ART after two consecutive CD4+ counts below 250 cells/mm^3 or if an AIDS-defining illness developed. Participants were followed for 5 years resulting in a 96% lower risk of partner infections in the early ART initiation group compared with the delayed ART initiation group. Importantly, no genetically linked HIV infections were seen when the positive individual maintained virologic suppression, defined as HIV RNA < 200 copies/mL. Subsequently, TasP gained universal acceptance following the publication of a series of clinical studies validating the concept beginning in 2016. The PARTNER1 trial, which was a prospective, observational study, investigated the risk of HIV transmission among serodiscordant couples engaging in condomless sexual intercourse.[7] Partners with HIV had an HIV RNA of <200 copies/mL on suppressive ART. After a median follow-up of 1.3 years per couple and approximately 58,000 condomless sex acts, there were no linked transmissions of HIV to the negative partner. Although PARTNER1 confirmed the ability of suppressive ART to prevent transmission of HIV, most couples included in the trial were heterosexual. The Opposites Attract observational cohort study included serodiscordant, homosexual, male couples engaging in condomless anal intercourse in which the partner with HIV had an HIV RNA of <200 copies/mL on suppressive ART.[8] No linked HIV transmission occurred after following patients for 588.4 couple-years. Later, as an extension to PARTNER1, PARTNER2 included only serodiscordant homosexual male partners and further demonstrated that PWH who maintained virologic suppression did not transmit HIV to their partners after >75,000 condomless sexual encounters.[9] Collectively, these results supported the development of the U=U campaign, focused on reducing stigma and spreading awareness that PWH receiving ART, who achieve and maintain virologic suppression, cannot transmit virus sexually.

2.2 | Personalizing TasP

To ensure TasP is successful, HIV treatment must be personalized to individual needs. In treatment-naïve individuals, initial regimens should be tailored to patient preferences on dosage form, adverse-effect profiles, and comorbid conditions and medications. In treatment-experienced patients, personalizing treatment often involves simplification to address barriers to adherence. Treatment simplification involves the modification of effective ART to achieve a reduction in pill burden, pill size, dosing frequency, and/or to update a regimen to one that is safer and more convenient.[15] Perhaps the most obvious benefit of treatment simplification is to reduce the number and/or frequency of pills to maintain virologic suppression. This can be achieved by switching patients to fewer tablets via single tablet regimens (STRs) and/or less frequent dosing through once-daily regimens or long-acting injectables. Multiple studies have demonstrated that a lower pill burden results in improved medication adherence and high rates of virologic suppression.[15,16] Furthermore, modernizing ART to an updated regimen containing fewer medications with increased barriers to resistance and decreased likelihood of adverse effects may lead to less problematic drug–drug interactions, adverse effects, inconvenient dietary requirements, and a lower propensity for antiviral resistance.[17] Overall, the goal of treatment simplification is to improve quality of life while maintaining virologic suppression.

Early treatment regimens consisted of patients taking numerous tablets many times per day. In 1997, the first nucleoside reverse transcriptase inhibitor (NRTI) fixed-dose combination tablet, lamivudine/zidovudine (3TC/AZT), was approved and utilized as a backbone to HIV treatment. Although rarely used today due to the adverse effects of AZT, this fixed-dose combination tablet opened the possibility for reducing ARV pill burden. In 2006, the first STR came to market containing efavirenz/FTC/TDF, which was a non-nucleoside reverse transcriptase inhibitor (NNRTI) and NRTI combination tablet. Since then, another 10 STR options came to market and offered the convenience of one pill, once-per-day, which may limit toxicities, drug–drug interactions, increase patient satisfaction, potentially reduce medication cost, and maintain virologic suppression in PWH.[17] In 2021, the first intramuscular (IM) combination option, long-acting cabotegravir/rilpivirine (CAB/RPV-LA), provided an alternative to daily pills for the management of HIV in adults and adolescents weighing ≥35 kg who were virologically suppressed on current ART.[18] CAB/RPV-LA is available as either monthly or bi-monthly IM injections administered in the ventrogluteal or dorsogluteal region by a healthcare provider and has an optional oral lead-in of cabotegravir (CAB) 30 mg and rilpivirine (RPV) 25 mg daily for 30 days leading up to the first injection appointment to assess for tolerability. IM administration of CAB and RPV obviate absorption-related issues, specifically food requirements and drug–drug interactions (e.g., cationic supplements or proton pump inhibitors). Providing additional routes and frequencies of long-acting (LA) ARV administration addresses barriers to long-term adherence including pill fatigue, privacy- and stigma-related fears, convenience, and pill dysphagia.

With modern day ART providing multiple routes of administration including injectable administration, this also provides simplified options in treatment-experienced patients with drug resistance who may be on multi-tablet regimens with a high pill burden. In this

population, it is recommended to have at least two fully active ARVs if one has a high barrier to resistance (i.e., dolutegravir [DTG] or boosted darunavir [DRV]).[17] If no options are available with a high barrier to resistance, ideally three fully active agents should be included in the regimen. Drug resistance testing will guide ARV selection, but efforts should be made to provide patients with the lowest pill burden and frequency of dosing as possible to help with adherence. Simplification of ART in treatment-experienced patients with complex regimens have demonstrated improved patient outcomes and reduced HIV transmission, highlighting its role in TasP.[19]

2.3 | TasP in serodiscordant couples

In many settings, HIV transmission between stable serodiscordant couples accounts for the majority of new HIV infections.[20] Therefore, there has been significant focus on serodiscordant couples, and the World Health Organization (WHO) has referred to them as a "key population" in their guidance for HIV prevention, testing, treatment, service delivery, and monitoring.[21] This population has also been pivotal in HIV transmission research as well as establishing the effectiveness of TasP as a viable strategy. HPTN 052, Opposites Attract, and the PARTNER studies, summarized previously, demonstrated zero transmissions of HIV sexually in serodiscordant couples when the seropositive partner was virologically suppressed.[6–9]

Pharmacotherapy of TasP in serodiscordant couples is not vastly different from other populations and is largely dependent on successful suppression of the seropositive partner. The same factors that ensure optimal treatment apply. Although risk of HIV transmission may differ by route of exposure, to date, there is no evidence that supports personalization based on whether the biological sex of the index partner is male or female, or the route of sexual transmission (oral, penile, vaginal, or rectal).[22] One study which followed 3777 serodiscordant couples in Rwanda found that HIV transmission was significantly influenced by age of either partner, with lower ages associated with greater risk of HIV acquisition.[23] The largest predictor of successful TasP is achieving virologic suppression in PWH; therefore, the seronegative partner should seek PrEP or other prevention strategies if the PWH discontinues ART or is no longer virologically suppressed. The highest risk of transmission is before and within the first weeks of starting ART, prior to virologic suppression, which is an important counseling point for serodiscordant couples.[24]

2.4 | TasP: access to TasP

ART access is crucial to the success of TasP and ending the HIV epidemic. At the end of 2021, 28.7 million of the 38.4 million PWH globally (75%), were able to obtain ART.[1] Women with HIV are more likely to access treatment and become virologically suppressed compared with men with HIV. The inequality of access to HIV treatment between children and adults continues to grow, with only 50% of children worldwide receiving ART due to profound gaps in testing and treatment. Globally, wealth-related inequalities also impact ability to acquire ART, which highlights the influence of social and economic determinants of health on HIV testing, linkage to care, and treatment adherence in PWH. Key barriers to ART access include stigma and discrimination, especially in PWID. The UNAIDS goal for 2025 is to provide 90% of people with HIV, at risk for HIV, or affected by HIV, equitable and patient-centered care.

In the United States, insurance and finances continue to be reported as barriers to care by patients, despite residing in areas with essentially universal access to HIV care.[25] The AIDS Drug Assistance Program (ADAP) provides ART to low-income PWH with limited or no health insurance and serves as a payer of last resort after all available programs have been pursued for payment.[26] Despite federal funding, individual states are responsible for defining financial eligibility requirements, which are usually determined as a percentage of the federal poverty level. Despite these programs being available in the United States, patients may be unaware of their existence and therefore may not seek access to ART based on perceived financial barriers.[25] Patient assistance programs via drug manufacturers are also available for uninsured or underinsured patients, including copay assistance for patients with private health insurance plans. Involving HIV-specialized pharmacists in patient care has been associated with increased rates of adherence and positives outcomes related to virologic suppression.[27] Pharmacists play a key role in ensuring patients have access to ART, remain engaged in care, and remain virologically suppressed, which all are essential to using TasP to limit the spread of new HIV infections.

3 | PRE-EXPOSURE PROPHYLAXIS

3.1 | Review of data supporting individual PrEP options

3.1.1 | FTC/TDF

FTC/TDF is not only an important backbone in HIV treatment but was also the first regimen approved for PrEP in at-risk adults and adolescents weighing at least 35 kg.[10] TDF, a prodrug for the NRTI tenofovir, is active against hepatitis B virus (HBV) and HIV and is eliminated renally. If patients are HIV negative with an estimated creatinine clearance (CrCl) above 60 mL/min, they may initiate prophylaxis with oral FTC/TDF 200 mg/300 mg once daily. Patients with HBV infection should be counseled on the dangers of abruptly stopping therapy.[5] If the tablet is too large to swallow or the patient has gastrostomy tube access only, data support crushing the tablet.[28] The administration of FTC/TDF with food does not significantly impact absorption and therefore recommendations are to administer FTC/TDF with or without food.[10] Dosing recommendations and drug interactions with FTC/TDF are listed in Table 1.

PrEP for a person without HIV taking partial ARV regimens to prevent acquisition was first validated in the multinational

TABLE 1 Dosing and drug interactions of PrEP options.[5,10–13]

	Regimen	Indicated Population	Generic Available	Metabolism	Drug Interactions
FTC/TDF	One tablet (200 mg/300 mg) PO daily	Adult and adolescent MSM, TGW, cis-gender women, PWID	Yes	TDF: Substrate: P-gp, BCRP, OAT1/3, Inhibitor: MRP2	TDF: Potential for renal toxicity with high dose or prolonged NSAID utilization FTC: Low risk of DDIs
	EB-PrEP: Take two tablets 2–24 h before having sex. Then take one tablet 24 and 48 h after the pre-sex dose	Adult MSM			
FTC/TAF	One tablet (200 mg/25 mg) PO daily	Adult and adolescent MSM, TGW	No	TAF: Substrate: P-gp (major), BCRP (major), OAT1/3, CYP3A4 (minor) Inhibitor: MRP2	TAF: Strong P-gp inducers (e.g., anticonvulsants, rifamycin, St. John's wort) FTC: Low risk of DDIs
CAB-LA	Optional OLI: CAB 30 mg PO daily for 28 days IM: CAB 600 mg/3 mL IM monthly for 2 months, then 600 mg/3 mL IM every other month	Adult and adolescent MSM, TGW, cis-gender women, PWID	No	Substrate: UGT1A1, UGT1A9, P-gp (minor), BCRP, OAT3	Strong P-gp inducers (e.g., anticonvulsants, rifamycin, St. John's wort) Cation chelation of PO CAB
DPV-VR[a]	Insert vaginal ring (25 mg) every 28 days. Vaginal ring releases approximately 4 mg of DPV over 28 days	Cis-gender women	No	Substrate: CYP1A1, CYP3A4 Inhibitor: CYP1A1 (major), multiple CYP and UGT enzymes (moderate/weak)	Low plasma concentrations, therefore low risk of DDIs

Abbreviations: BCRP, breast cancer resistance protein; CAB, cabotegravir; CYP, cytochrome P450; DDI, drug–drug interaction; DPV-VR, dapivirine vaginal ring; EB, event-based; FDA, United States Food and Drug Administration; FTC, emtricitabine; IM, intramuscular; kg, kilograms; LA, long-acting; MRP, multidrug resistance-associated protein; MSM, men who have sex with men; NSAID, non-steroidal anti-inflammatory drugs; OAT, organic anion transporter; OLI, oral lead in; P-gp, P-glycoprotein; PO, by mouth; PrEP, pre-exposure prophylaxis; PWID, persons who inject drugs; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TGW, transgender women; UGT, UDP-glucuronosyltransferase enzymes.

[a]Not available or approved by FDA as new drug application was withdrawn.

pre-exposure prophylaxis initiative (iPrEX) trial evaluating its use in HIV-seronegative men or transgender women (TGW) with evidence of high-risk behavior for HIV infection, which demonstrated a 44% reduction in the risk of HIV infection in the FTC/TDF group compared with placebo.[29] A summary of landmark PrEP trials is available in Table 2. Expanded use within serodiscordant heterosexual couples in preventing HIV acquisition by the uninfected partner was supported by the partners PrEP trial, with a 67% and 75% reduction in risk of HIV infection in the TDF and FTC/TDF group, respectively, compared with placebo.[30] In both trials, post hoc case control analyses showed that risk reduction efficacy was strongly related to adherence.[29,30] In addition, the Bangkok Tenofovir Study (BTS) was the first and only clinical trial evaluating efficacy of PrEP in PWID and demonstrated a 49% reduction in risk of HIV infection in PWID taking oral TDF 300 mg daily.[31] In a separate analysis of participants known to be adherent through their participation in directly observed therapy, who took at least 5 doses per week and did not miss more than 2 consecutive days, the risk of HIV acquisition was reduced by 74%. Although TDF was used in the BTS, combination treatment with FTC/TDF is preferred due to TDF being somewhat less effective in persons with only sexual risk of HIV acquisition.[5] Because TDF is available in a co-formulated tablet with FTC and PWID may have both sexual and IDU risk factors for acquiring HIV, PWID should only be offered TDF-based PrEP in combination with FTC.

In PrEP trials, the most common adverse effects were headache and mild gastrointestinal symptoms, which were attributed to a "start-up syndrome" lasting only 1 to 3 months after initiation.[10,29] In a meta-analysis of randomized clinical trials of PrEP in 15,678 participants, there was no significant difference in risk of Grade 3 or 4 clinical adverse events or renal or bone adverse outcomes between FTC/TDF (or TDF) and control.[32]

The FDA and Centers for Disease Control and Prevention (CDC) supports daily administration of FTC/TDF due to the higher rates of risk reduction compared with 2 or 4 doses per week.[5,10] Adherence is vital for the effectiveness of long-term oral PrEP. Alternative dosing strategies to daily oral PrEP have been explored. Event-based PrEP (EB-PrEP), also known as "2-1-1" or "on-demand" PrEP have been evaluated in a small number of clinical and observational trials

TABLE 2 Summary of landmark phase 3 HIV pre-exposure prophylaxis trials.[29–31,37,38,43,44,47,48]

Participants	Study	Intervention (patients, *n*)	HIV incidence outcome	Effect – HR [efficacy estimate] (95% CI)
Cis-gender men who have sex with men and transgender women who have sex with men	iPrex[29]	Oral FTC/TDF (1251) vs. oral placebo (1248)	36 infections in FTC/TDF arm; 64 infections in placebo arm	0.56 [44%] (0.37–0.85)
	DISCOVER[37,38]	Oral FTC/TAF (2694) vs. oral FTC/TDF (2693)	7 infections in FTC/TAF arm; 15 infections in FTC/TDF arm	0.47 [−53%] (0.19–1.15)
	HPTN 083[43]	Injectable CAB (2282) vs. oral FTC/TDF (2284)	13 infections in CAB arm; 39 infections in FTC/TDF arm	0.34 [66%] (0.18–0.62)
Cis-gender heterosexual men and women	Partners PrEP[30]	Oral TDF (1589) or oral FTC/TDF (1583) vs. oral placebo (1586)	17 infections in TDF arm; 13 infections in FTC/TDF arm; 52 infections placebo arm	TDF 0.33 [67%] (0.19–0.56); FTC/TDF 0.25 [75%] (0.13–0.45)
Cis-gender women	HPTN 084[44]	Injectable CAB (1613) vs. oral FTC/TDF (1610)	4 infections in CAB arm; 34 infections in FTC/TDF arm	0.11 [88%] (0.04–0.32)
	HOPE[47]	Vaginal ring DPV (1456) vs. matched placebo group from the ASPIRE study	35 infections in DPV arm (2.7/100 person-years); expected incidence 4.4/100 person-years in placebo arm	[39%]
	DREAM[48]	Vaginal ring DPV (941) vs. matched placebo group from the RING study	18 infections in DPV arm (1.8/100 person-years); expected incidence 4.7/100 person-years in placebo arm	[62%]
People who inject drugs	BTS[31]	Oral TDF (1204) vs. oral placebo (1207)	17 infections in TDF arm; 33 infections in placebo arm	0.51 [49%] (9.6–72.2)

Abbreviations: CAB, cabotegravir; DPV, dapivirine; FTC, emtricitabine; HR, hazard ratio; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

as a non-daily dosing strategy for high-risk MSM with frequent sexual activity, defined as a median of 10 sex acts per month and eight partners every 2 months.[10,33] The IPERGAY clinical trial compared EB-PrEP dosing of TDF/FTC versus placebo in HIV-negative MSM at high risk for HIV acquisition and found an 86% risk reduction.[33] A follow-up larger prospective cohort, ANRS-PREVENIR, evaluated daily versus on-demand TDF/FTC administration in a primarily MSM, HIV-negative population.[34] HIV transmission was reported as extremely low and did not differ between groups with an overall HIV incidence of 1.1 case/1000 person-years. Current CDC guidelines provide clinical guidance for prescribers on EB-PrEP as an alternative to daily dosing in MSM who seek PrEP but are not regularly sexually active and desire reduced long-term drug exposure.[5]

3.1.2 | FTC/TAF

In 2019, FTC/TAF became the second FDA-approved oral option for the prevention of HIV transmission in at-risk adult and adolescent MSM and TGWSM weighing at least 35 kg.[11] Similar to TDF, TAF is a prodrug of tenofovir that has increased plasma stability compared with TDF.[35] The majority of TAF is transported intracellularly where hydrolysis to tenofovir and the subsequent phosphorylation to tenofovir diphosphate occurs, leading to increased activity and decreased toxicity of TAF versus TDF. If patients are HIV negative with an estimated CrCl above 30 mL/min, they may initiate prophylaxis with FTC/TAF 200 mg/25 mg once daily, which may allow an alternative to those HIV-seronegative MSM or TGWSM who may not qualify for FTC/TDF use based on renal function.[11] FTC/TAF is also active against HBV, so patients with HBV infection receiving FTC/TAF should be counseled on the dangers of abruptly stopping therapy.[5] If a patient has gastrostomy access only, crushing FTC/TAF tablets is not recommended, but there is a case report describing the successful administration of FTC/TAF crushed in a PWH with a gastrostomy tube.[36] The administration of FTC/TAF with food does not significantly impact absorption and therefore recommendations are to administer FTC/TAF with or without food.[11] Dosing recommendations and drug interactions with FTC/TAF are listed in Table 1. More drug–drug interactions are present with TAF compared with TDF because it is a minor substrate of CYP3A4.[11]

Published clinical trials evaluating FTC/TAF in PrEP are limited primarily to the 48- and 96-week results of the DISCOVER trial, which compared FTC/TAF with FTC/TDF as PrEP in cis-gender MSM and TGWSM considered to be at high risk for HIV acquisition.[37,38] At the 48- and 96-week analyses, FTC/TAF was non-inferior to FTC/TDF for HIV prevention in cis-gender MSM and TGWSM. Current FDA approval excludes individuals at risk for HIV acquisition via receptive vaginal sex as studies evaluating FTC/TAF in this population are ongoing. Evaluation of the distribution of TAF and the active moiety, tenofovir diphosphate, into mucosal tissue is limited. A phase I, prospective, multi-site study evaluating the multi-compartmental pharmacokinetics of FTC/TDF and FTC/TAF in cis-gender, HIV-uninfected women demonstrated higher tenofovir diphosphate concentrations in peripheral blood mononuclear

cells (PBMCs) and similar or higher concentrations in female genital tract tissues for FTC/TAF versus FTC/TDF.[35] Authors concluded FTC/TAF should be protective against vaginal acquisition of HIV to a similar or even greater degree than FTC/TDF, but more data are needed to recommend use in cis-gender women. A study assessing the safety and efficacy of FTC/TAF for PrEP in adolescent girls and women at risk for HIV is underway.[39]

FTC/TAF was well-tolerated in clinical trials and real-world experience, with the most common adverse effects involving headache, nausea, and diarrhea. In the 96-week analysis of the DISCOVER trial, the mean glomerular filtration rate (GFR) significantly declined by 0.6 mL/min in the FTC/TAF group compared with 4.1 mL/min in the FTC/TDF group.[38] Of note, baseline GFR was greater than 120 mL/min in both study arms, so the greater reduction in GFR in the FTC/TDF arm may not be clinically significant. Conversely, the FTC/TDF arm had favorable outcomes related to weight and lipids, with less weight gain compared with FTC/TAF (median weight gain of 0.05 kg for FTC/TDF vs. 1.7 kg for FTC/TAF), along with improvements in the lipid profile.

3.1.3 | CAB-LA

In December 2021, the FDA-approved CAB-LA for use as PrEP becoming the first and, to date, only long-acting agent approved for PrEP.[12] It is indicated for all at-risk adults and adolescents who weigh at least 35 kg to decrease the risk of sexually acquired HIV infection. CAB is a potent integrase strand transfer inhibitor (INSTI) that works by blocking the viral integrase enzyme, preventing replication of HIV.[40] As an analog of DTG, it is expected to have a high barrier to resistance but the risk of integrase mutations is two times higher with CAB compared with DTG, and with extensive cross-resistance.[41] CAB is approximately 99.8% protein bound and exhibits a prolonged half-life of approximately 40 days due to slow absorption from the site of injection, which allows it to be administered every 2 months.[40,41] The resulting long-acting formulations allow for infrequent dosing, which may help with adherence in some individuals. If patients are HBV and HIV negative, they may initiate prophylaxis with CAB-LA.[12] Dosing adjustments are not required for renal or hepatic impairment. Caution should be taken in patients with BMI ≥30 kg/m^2 as CAB-LA must be administered into muscle, therefore a longer needle (i.e., 2 inches) may be needed to reach the gluteal muscle.[42] CAB-LA has not been studied in pregnant or lactating women and should therefore be avoided in these populations. Dosing recommendations and drug interactions of CAB-LA are described in Table 1. When beginning CAB-LA for PrEP, an optional oral lead-in can be administered as CAB 30 mg orally once daily for 28 days to assess drug tolerability prior to beginning the injectable CAB-LA. The injections can be administered 7 days before or after the scheduled date of the injection. CAB-LA should only be administered in the gluteus muscle, with the ventrogluteal site recommended and the dorsogluteal site as an alternative.

The Phase III trials that brought CAB-LA to the market are known as the HIV Prevention Trials Network (HPTN) 083 and 084 trials, which compared CAB-LA to FTC/TDF[43,44] HPTN 083 compared CAB-LA and FTC/TDF in cis-gender men and TGW considered to be at high risk for HIV acquisition.[43] Adherence to CAB-LA, defined as injections within 2 weeks of a target date, was high with 91.5% person-years receiving on-time injections compared with 74.2% in the FTC/TDF arm with an optimal tenofovir plasma concentration. During a median follow-up of 1.4 years, a total of 13 HIV infections occurred in the CAB-LA group (0.41/100 person-years) compared with 39 HIV infections in the FTC/TDF group (1.22/100 person-years), resulting in a 66% lower risk of acquiring HIV infection with CAB-LA compared with FTC/TDF ($p < 0.001$). HPTN 084, conducted in Sub-Saharan Africa, compared CAB-LA and FTC/TDF in cis-gender women considered to be at high risk for HIV acquisition.[44] During a median follow-up of 1.2 years, a total of four HIV infections occurred in the CAB-LA group (0.2/100 person-years) compared with 36 HIV infections in the FTC/TDF group (1.85/100 person-years), resulting in an 88% lower risk of acquiring HIV infection with CAB-LA compared with FTC/TDF ($p < 0.0001$). Adherence to CAB-LA was high with 89% receiving on-time injections compared with 46% in the FTC/TDF arm with an optimal tenofovir plasma concentration. It is important to note that both the HPTN 083/084 trials were stopped at the first preplanned interim end point analysis on the recommendation of the Data Safety Monitoring Board because of the superiority of CAB-LA over FTC/TDF.[43,44]

The most common adverse effects are injection site reactions (ISRs). In HPTN 083, ISRs, which lasted a median of 4 days, were seen in 81.4% of participants, versus in HPTN 084, ISRs, which lasted a median of 8 days, occurred in 38% of participants.[43,44] It is unclear why the rate of ISRs in this trial was considerably lower. It is important to note that, in all trials, ISRs decreased in frequency over time and very few participants discontinued the trials due to ISRs. Other than ISRs, CAB-LA appears to be well-tolerated. There is increasing evidence that INSTIs may be associated with weight gain.[45] At Week 96 in HPTN 083 and HPTN 084, those who received CAB-LA had gained a median of 2.1 and 4 kg, respectively, compared with 1 and 3 kg, respectively, for those who received FTC/TDF.[43,44] The clinical significance of this weight gain is unclear, and there is less data with CAB-LA compared with other INSTIs, but clinicians and patients should be aware of the potential for weight gain.

3.1.4 | DPV-VR

In January 2021, the WHO endorsed the use of DPV-VR for PrEP, which led to both the Medicines Control Authority of Zimbabwe and the South African Health Products Regulatory Authority approval of the vaginal ring for use in their countries.[46] DPV is an NNRTI that works by blocking viral reverse transcriptase enzyme, preventing replication of HIV.[13] If patients are HIV negative, they may initiate prophylaxis with monthly DPV-VR 25 mg (releasing 4 mg of dapivirine over 28 days), which may allow an alternative to those HIV-seronegative cis-gender women who may not qualify for FTC/TDF use based on renal function, or who desire a different delivery

option that does not require daily pills or injection visits. Dosing adjustments are not required for renal or hepatic impairment. Dosing recommendations and drug interactions of DPV-VR are described in Table 1. The DPV-VR is inserted into the vagina and kept in until replaced each month with a new ring. The most common adverse effects reported in clinical trials are urinary tract infection (15.2%), vaginal discharge (7.1%), vulvovaginal pruritus (6.5%), vulvovaginitis (6.4%), and pelvic pain (6.2%).

The phase III trials that brought DAP-VR to the international market are known as the HOPE and DREAM trials, which were open-label extension trials of ASPIRE and The Ring Study, respectively.[47,48] The HOPE study evaluated DPV-VR in HIV uninfected women in Malawi, South Africa, Uganda, and Zimbabwe.[47] The women chose whether or not to accept the offer of the ring at each study visit. Adherence to DPV-VR was measured by residual DPV levels in returned rings, and 89% of returned rings had levels consistent with some use during the prior month. A total of 35 HIV infections occurred in the DPV-VR group (2.7/100 person-years) compared with an expected incidence of 4.4 per 100 person-years among a matched placebo group from ASPIRE, resulting in a 39% lower risk of acquiring HIV infection with DPV-VR. The DREAM study evaluated DPV-VR in HIV uninfected women in South Africa and Uganda.[48] All participants received the DVR for insertion at the enrollment visit. Adherence to DPV-VR was also measured by residual DPV levels in returned rings, and most participants had ring residual amounts consistent with at least some use. A total of 18 HIV infections occurred in the DPV-VR group (1.8/100 person-years) compared with an expected incidence of 4.7 per 100 person-years among a matched placebo group from The Ring Study, resulting in a 62% lower risk of acquiring HIV infection with DPV-VR. Efficacy in these studies was highly associated with age and adherence, with increased protection observed in women over 25 years of age and greater adherence, defined as a ring residual value of less than 23.5 mg of DPV.[47,48] Despite the WHO endorsement of DPV-VR, the New Drug Application (NDA) was voluntarily withdrawn in the United States in late 2021 based on HIV epidemiology and the prevention landscape for women in the United States at the time.[46]

3.2 | Investigational PrEP

The lessons learned from existing HIV prevention strategies suggest that the most successful HIV prevention modalities will need to be both varied and flexible, giving users options that will best fit their needs, lifestyles, and preferences. To that end, the pipeline of products in development for HIV prevention consists of modalities with increased convenience in the form of long-acting formulations as well as multipurpose prevention technologies (e.g., HIV prevention combined with contraceptive). Investigational PrEP options and their delivery methods are summarized in Table 3.[49]

A long-acting injectable, lenacapavir (LEN), is a first-in-class capsid inhibitor, which inhibits multiple steps of the viral life cycle including a capsid-mediated nuclear update of HIV pro-viral DNA, virus assembly and release, and capsid core formation.[50] Its unique mechanism of action means it has no cross-resistance to any existing drug classes, making it an attractive option for HIV prevention. Its high potency and slow clearance have made it amenable to long-acting administration. An oral formulation has been evaluated at both daily and weekly administration and a subcutaneous formulation is under investigation for dosing every 6 months. PURPOSE 1 and PURPOSE 2 are Phase III randomized trials assessing PrEP efficacy of subcutaneous lenacapavir in young women or MSM, transgender men who have sex with men (TGMSM), TGWSM, and gender non-binary (GNB) individuals who have sex with men.[39,51] Results for these trials are expected in 2027.

Implants, films, and vaginal rings provide additional novel delivery options for HIV prevention. A subdermal implant, islatravir (MK-8591), is novel HIV nucleoside reverse transcriptase translocation inhibitor (NRTTI), making it the first-in-class translocation inhibitor.[52] It has high

TABLE 3 Summary of select investigational products for HIV pre-exposure prophylaxis.[49]

Delivery Method	Agent	Class	Current stage of development
Implant	Islatravir	Nucleoside reverse transcriptase translocation inhibitor	N/A; development discontinued by manufacturer
	Tenofovir alafenamide	Nucleotide reverse transcriptase inhibitor	Phase I
Subcutaneous injectable with oral lead-in	Lenacapavir	Capsid inhibitor	Phase III
Intravaginal ring (multipurpose prevention technology)	Dapivirine + levonorgestrel	Non-nucleoside reverse transcriptase inhibitor + progestin	Phase I
	Tenofovir + levonorgestrel	Nucleotide reverse transcriptase inhibitor + progestin	Phase II
Intravaginal film	MK-2048	Integrase inhibitor	Phase I
Antibody infusion	VRC01	Broadly neutralizing HIV-1 monoclonal antibody	N/A; VRC01 did not significantly reduce overall risk of HIV infection
Oral	Islatravir	Nucleoside reverse transcriptase translocation inhibitor	N/A; development discontinued by manufacturer

Abbreviations: HIV, human immunodeficiency virus; N/A, not available.

ARV potency, a unique mechanism of action, and a prolonged plasma half-life of 48–64 h, making it an ideal option for treatment and prevention. Islatravir was being investigated as an oral once-monthly tablet and long-acting implant for HIV treatment and prevention. In September 2022, Merck reported they will discontinue the development of once-monthly oral islatravir for PrEP, after the FDA placed a clinical hold on all islatravir formulations in development in response to observations of reductions in total lymphocytes and in CD4+ cells in clinical study participants receiving islatravir.[53] It is not clear when or if development of the long-acting implant will be resumed. A second subdermal implant, sustained-release TAF, is being evaluated in CAPRISA-018, which is a phase I/II study assessing the pharmacokinetics as well as safety, acceptability, and tolerability of a subdermal implant designed to release 0.25 mg/day of TAF for HIV prevention in women.[54] The phase I trial will determine the dosing, implant location, and implant replacement interval for the phase II trial. Vaginal rings represent an opportunity to co-formulate HIV prevention and contraception. MTN-044/IPM 053 evaluated the pharmacokinetics, safety, and bleeding patterns associated with a silicone elastomer vaginal matrix ring containing both dapivirine and levonorgestrel and concluded that the formulation was well tolerated and achieved concentrations in vaginal fluid previously associated with protection when the ring was used continuously or cyclically for 90 days.[55] CONRAD evaluated another co-formulated vaginal ring with tenofovir and levonorgestrel every 90 days in a phase I pharmacokinetic study in healthy women which demonstrated the formulation caused changes in cervical mucus, sperm penetration, and ovulation compatible with contraceptive efficacy.[56] A vaginal film is being evaluated in FAME103, which is a phase I randomized trial assessing the safety, acceptability, and pharmacokinetics of two formulations of a novel INSTI-based vaginal film, MK-2048.[57] A critical end point of this study will be to see whether this delivery system can deliver sustained drug for at least 7 days, which may inform the utility of this route for this and other future PrEP options.

Lastly, broadly neutralizing antibodies (bnAb) are antibodies that develop naturally in some PWH and have been identified for their potential in HIV treatment and prevention.[58] Two parallel phase IIb, multicenter, randomized, double-blind, placebo-controlled, proof-of-concept trials evaluated the preventative efficacy of the bnAb VRC01 administered every 2 months in MSM and TGWSM and heterosexual women. These studies demonstrated no overall reduction in HIV acquisition but observed reduced infections from strains that were neutralized by the VRC01 antibody, demonstrating proof-of-concept for bnAbs having a potential role in HIV prevention. Future studies are needed with broader, more potent bnAbs, and potentially in combination with other ARVs.

3.3 | Personalizing PrEP in key populations

3.3.1 | Personalizing PrEP: PWID

As mentioned, all sexually active adults and adolescents should be offered PrEP, but key populations have been identified by UNAIDS to guide countries closer to reaching HIV prevention targets by 2025.[1] Within the United States, more than 106,000 drug overdose deaths occurred in the 12 months ending in February 2022, the highest number of overdose deaths ever recorded in a 12-month period.[59] New HIV infections in PWID have declined in the United States in recent years, but account for 7% of estimated incident infections annually.[4] SSPs, which provide access to sterile injection equipment and other healthcare services, have been identified as playing a key role in the reduction of new HIV infections. SSPs not only reduce HIV and viral hepatitis infections but also help improve rates of HIV testing, PrEP awareness, linkage to HIV care, outbreak response, and access to medication for opioid use disorder (MOUD).[60] Although beneficial, legislative barriers and bans on funding for sterile syringes make SSPs difficult to implement in the United States. As mentioned, BTS is the only clinical trial evaluating efficacy of PrEP in this high-risk population.[31] In the open-label extension, study investigators evaluated patient characteristics and risk behaviors associated with uptake and adherence to PrEP.[61] Patients who were 30 years of age and older, injected heroin, or had been in prison were more likely to initiate PrEP, suggesting that patients based their decision to take PrEP on their perceived risk for acquiring HIV. Despite limited data, the CDC guidelines recommend FTC/TDF for oral PrEP in PWID or CAB-LA for injectable PrEP in PWID who are also sexually active.[5]

3.3.2 | Personalizing PrEP: cis-gender men and TGW

Despite various efforts to increase PrEP utilization in the United States, PrEP still remains underutilized with only about 18% of the 1.2 million people who have an indication for PrEP receiving PrEP.[4] Males, including transgender people based on sex at birth, accounted for 81% (30,691 out of 37,968) of new HIV diagnoses in 2018 where 86% of these diagnoses were in gay, bisexual, and other MSM.[62] Meanwhile, as reported by the CDC, approximately 2% of transgender females were diagnosed with HIV in 2018.[4] Although PrEP is three times more likely to be prescribed in males (28%) compared with females (10%), there remains extraordinary gaps in the utility and uptake of PrEP services.[63] A survey conducted by the CDC revealed only 32% of HIV-negative TGW used PrEP although 92% were aware of the medication. Despite the awareness surrounding PrEP and its benefits, PrEP uptake remains very low among TGW. PrEP providers experienced in transgender health offering PrEP services may help resolve barriers to care in TGW through improved patient-provider relationships.[64] While daily oral options for PrEP using FTC/TAF or FTC/TDF and every 2-month dosing of injectable CAB-LA remain options in cis-gender males and TGW, only EB-PrEP dosing of FTC/TDF remains an option for cis-gender MSM.[5]

3.3.3 | Personalizing PrEP: cis-gender women

Among women, HIV diagnoses are on the decline in the United States; however, cis-gender women continue to comprise approximately

20% of new diagnoses, with Black and Hispanic or Latina women accounting for most diagnoses.[4] PrEP represents an effective intervention to reduce transmission in women but remains underutilized for a variety of reasons including low awareness of PrEP, low perceived risk of infection, competing priorities, need for adherence if taking oral PrEP, perceived complexity of PrEP monitoring and follow-up, distrust of the medical system, and concerns about adverse effects, drug interactions, disclosure, stigma, and financial challenges.[65] Daily oral FTC/TDF and CAB-LA remain the only PrEP options for cis-gender women that are FDA-approved and guideline recommended.[5] EB-PrEP oral dosing of FTC/TDF is not recommended due to lower concentrations in the female genital tract.[66] As mentioned previously, cis-gender women were not included in the PrEP clinical trials for daily oral FTC/TAF and it is not FDA-approved to protect against HIV transmission during vaginal sex, but studies are underway.[39] Long-acting PrEP also has the potential to improve PrEP uptake for those who prefer not to take a daily pill or have difficulty doing so. HIV acquisition during pregnancy presents a serious threat to maternal and child health, therefore it is recommended that women of childbearing potential who take PrEP and do not desire pregnancy are referred for effective contraception.[5] The CDC recommended PrEP regimen for women during periconception, pregnancy, and breastfeeding is FTC/TDF. Studies have demonstrated both the safety and efficacy of FTC/TDF PrEP during the prenatal, pregnancy, and post-partum periods.[67]

3.3.4 | Personalizing PrEP: adolescents

Adolescents are another key population at increased risk of acquiring HIV, especially young women.[1] UNAIDS has associated their risk with incomplete knowledge about PrEP, fear of stigma, concern for side effects, fewer protections under law, and less social power. Globally, many countries continue to have age-of-consent laws preventing young people from accessing HIV testing and prevention. In a survey of adolescents aged 10–16 in Malawi, 80% reported willingness to take daily oral PrEP but had a preference for injections, and 87% of caregivers reported they would want their child to take PrEP.[68] A study evaluating uptake of and adherence to PrEP in adolescent girls and young women in Africa highlighted the importance of integrating PrEP into reproductive health services including contraception and sexually transmitted infection (STI) treatment as well as to provide repeated counseling on importance of adherence, as a substantial portion of young women do not persist with PrEP.[69] Cis-gender male adolescents reported a preference for long-acting (once yearly) options with high efficacy and limited side effects, and reported frequent clinic visits (i.e., 6 times/year) and privacy as barriers to access.[70] To address known barriers in adolescents (e.g., transportation, privacy, and lack of independent access to providers), electronic PrEP (ePrEP) is being tested using smart phones to provide access to PrEP providers who can provide access to testing and medication without needing to leave home.[71] The disparity in developmental maturity when compared with adults not only impacts adolescents' outcomes in HIV treatment but may also influence PrEP uptake.[17] The National Survey of Family Growth data shows that American youths are less likely to receive STI and pregnancy prevention education than they were 25 years ago.[72] To meet the needs of PrEP education, teaching outside of the clinical setting will be necessary through efforts in improving sexuality education preparation standards, expanding federal programs, and novel education programs such as peer- and community-led PrEP interventions.[73,74] In clinical studies, young men and women under 25 years of age demonstrated lower adherence and lower efficacy for oral tenofovir-based PrEP compared with older adults.[29] Young men and women were included in HPTN083 and HPTN084, but data in adolescents are limited to extrapolations from the MOCHA trial evaluating pharmacokinetics and safety of CAB/RPV-LA in adolescents 12 years of age and older weighing at least 35 kg.[43,44,75] Oral FTC/TDF and FTC/TAF are also indicated in adolescents 12 years of age and older weighing at least 35 kg, with the exception of FTC/TAF in adolescents at risk for HIV acquisition via receptive vaginal sex.[10,11]

3.3.5 | Personalizing PrEP: racial and ethnic minorities

In 2018, Black persons accounted for 42% and Hispanic or Latinx persons accounted for 27% of new HIV diagnoses, however only 6% and 10% with indications for PrEP had received prescriptions, respectively.[4] The low utilization of PrEP among racial and ethnic minorities contributes to overall disparities, and improving uptake of PrEP in these populations is important.[1] Knowledge of PrEP, medication cost, medical mistrust, skepticism, and stigma have been identified as barriers to PrEP, specifically within the Black community.[76] Disclosure of same-sex behaviors is also less likely in Black MSM, possibly due to experiences of provider biases, stereotyping, or perceived homonegativity.[77] Together, these may reduce the knowledge of PrEP and reduce promotion or limit conversations about PrEP by providers. In a telephone survey completed in the United States, African Americans, and Latinos reported they perceive racism in the healthcare system and are more satisfied with their care when their own physicians match their own race or ethnicity.[78] Additionally, relatable healthcare providers who use non-stigmatizing language when talking about PrEP have been reported as ways to increase uptake of PrEP among Black MSM.[79] Therefore, efforts should be made to personalize PrEP providers to patients' racial and ethnic preferences. With regard to inclusion of racial minorities in prevention studies, the key PrEP clinical trial, iPrEX, studying daily FTC/TDF, included a large proportion of participants identifying as non-white (9%, 5%, 72%, and 68% self-identified as Black, Asian, Hispanic, or Latinx and mixed race or other, respectively).[29] More recently, in a clinical trial comparing CAB-LA with FTC/TDF for HIV prevention, 49.8% of participants in the United States identified as Black and 17.8% as Hispanic or Latinx.[43] Personalizing PrEP in racial minorities is critical and requires clinicians to develop trusting relationships and provide education to patients regarding eligibility for and benefits of PrEP.

3.3.6 | Personalizing PrEP: serodiscordant couples

Upwards of 87% of partnerships affected by HIV are serodiscordant, though this varies greatly based on local prevalence.[80] Transmission between partners within a serodiscordant couple may lead to as many as two-thirds of new transmissions, with increased risk for transmission when the partner with HIV is not virologically suppressed.[81] Frequent HIV testing, counseling with both partners, and condom use have been associated with reduced transmission of HIV in serodiscordant couples.[82] As mentioned previously, U=U supports the use of TasP, but successful TasP relies on retention in care, sustained adherence, and consistently undetectable viral loads. PrEP in combination with TasP should not be necessary and should not further reduce the risk of HIV acquisition. However, PrEP may be particularly useful in serologic discordant relationships when virologic suppression is unknown or not consistently achieved due to adherence, drug interactions, or ineffective therapy, or if there are multiple partners. PrEP could also serve as a temporary option for patients awaiting their partner with HIV to achieve virologic suppression.[83] Studies of patient perceptions describe couples finding it easier to adhere to medication, which is critical to PrEP efficacy, when one partner was taking ART and the other was taking PrEP and were able to help remind each other.[84] In addition, pharmacotherapeutic options including TasP, PrEP, or combining TasP and PrEP, have been considered as an alternative to other high-cost assisted reproductive technologies among serodiscordant couples desiring to conceive.[85]

3.4 | Access to PrEP

The 2021 update to the US Public Health Service and Centers for Disease Control and Prevention (CDC) guidelines on PrEP recommends informing all sexually active adults and adolescents about PrEP and simplifies the indication for PrEP to all sexually active persons.[5] As more effective and convenient options become available and indications for PrEP continue to expand, financial and sociopolitical barriers continue to impact access. In the United States, financial concerns and social stigma are reported as barriers across all key populations, although improvements in PrEP coverage and ePrEP may help to overcome these barriers.[86] Globally, the cost of PrEP varies drastically across different countries.[87] In the United States, the Affordable Care Act mandates that PrEP medications, laboratories, and clinic visits must be free under almost all health insurance plans, although individual states may rule the mandatory coverage as a violation of religious freedoms, further restricting access.[88,89] To address barriers to medication access, medication assistance programs and state PrEP assistance programs, like the National Alliance of State and Territorial AIDS Directions (NASTAD), help provide medication and copay assistance, and in some cases clinical visit and lab test assistance when coverage is limited or lacking.[90] In addition to financial barriers, patient knowledge about HIV and PrEP and privacy barriers should also be addressed though novel interventions including community-based interventions, ePrEP, long-acting and well-tolerated formulations, and embedding PrEP into routine care.[1] Pharmacists play an important role in increasing access to PrEP and have been associated with increased PrEP uptake when they are involved in screening and treatment.

4 | POST-EXPOSURE PROPHYLAXIS

4.1 | Review of data supporting PEP

PEP involves taking ARV medications to prevent HIV infection after a potential exposure to the virus, and was first utilized in the late 1980s. PEP is based on the idea that receipt of antiretroviral chemoprophylaxis during the "window of opportunity" will impair initial HIV replication thereby preventing systemic infection and allow the host immunologic response to eradicate HIV.[91] In the early 1990s, the CDC recommended AZT monotherapy as PEP following occupational exposures based on HIV treatment safety and efficacy data as well as limited animal and human data.[92] This recommendation was further validated after a multinational case–control study published in 1997 found an 81% reduction in the risk of seroconversion among healthcare workers who received AZT within 4 h following a needle stick injury.[93] PEP should be initiated within 72 h of the suspected/confirmed exposure. If given within 72 h, current guidelines suggest efficacy that approaches 100% (5.2 transmissions/1000 PEP users).[94] If given beyond this window, PEP is unlikely to be effective. Only one confirmed case of occupationally acquired HIV has been reported since 1999.[95] Although no randomized controlled trials have evaluated occupational PEP, observational animal and human studies, in addition to the rare occurrence of occupationally acquired HIV, support the use of PEP in healthcare personnel exposed to HIV.[94] Data from animal transmission models, perinatal prevention studies, and case reports along with occupational PEP efficacy has supported CDC recommendations on the use of PEP to reduce the risk of HIV transmission after sexual, injection drug use, or other non-occupational exposures to HIV.[96]

4.2 | Guideline recommendations for PEP

The CDC provides guidance on how to manage patients who have been exposed to HIV through occupational exposures (oPEP) and non-occupational exposures (nPEP).[94,96] Every effort should be made to determine the HIV status of the exposure source, if possible, to guide the need for oPEP. Whenever a potential exposure to HIV occurs in the occupational setting, such as a needle stick injury, and the source is known to be HIV-positive, oPEP is recommended.[94] However, this may not always be feasible, and PEP should be started as soon as possible and within 72 h of the exposure in order to be effective. Therapy should begin as soon as possible with at least a 3-drug regimen and continued for 28 days. Currently, guidelines recommend the combination of FTC/TDF plus raltegravir (RAL) as a

preferred regimen for oPEP based on potency, tolerability, and few drug–drug interactions.[94] Testing for HIV should occur at baseline and then at 6 weeks, 12 weeks, and 6 months after exposure.

Examples of non-occupational HIV exposures are injection drug use or sexual exposure.[96] Similar to oPEP, any person requiring nPEP should initiate therapy as soon as possible and within 72 h after the exposure. It should be initiated when the exposure source is known to be HIV-positive, and the reported exposure presents a substantial risk for transmission of HIV. In scenarios where the HIV status of the source exposure is unknown, use of nPEP must be determined on a case-by-case basis. Recommended nPEP regimens are similar to oPEP regimens, with RAL + FTC/TDF for 28 days being preferred. The nPEP guidelines were published more recently, and also recommend DTG in place of RAL. PEP should only be used for emergency situations and does not take the place of other HIV prevention measures, such as PrEP and the use of condoms. Testing for HIV should occur at baseline and then at 6 weeks, 12 weeks, and 6 months after exposure.

4.3 | Updated PEP regimens

Newer ARVs are often more tolerable and are associated with fewer side effects than early ARVs. Additionally, adherence rates to PEP regimens range from 40.2% in sexual assault-related nPEP and 65.6% in oPEP, highlighting the need for more convenient and well-tolerated PEP regimens.[96] In the MiPEP trial comparing maraviroc (MVC) + FTC/TDF to LPV/r + FTC/TDF for 28 days of PEP, there was no difference in overall completion rates but significantly fewer adverse events in the MVC arm.[97] Similarly, the STR elvitegravir/cobicistat/FTC/TAF (EVG/c/FTC/TAF) has been associated with improved tolerability compared with traditional PEP regimens, in addition to improved adherence and completion rates and is listed as an alternative option in international guidelines, however, drug interactions may limit its use.[98] High levels of adherence and completion have also been observed with RPV/FTC/TDF PEP with similar reductions in adverse effect rates compared with traditional regimens; however, regional RPV resistance rates may limit use. The STR bictegravir/FTC/TAF (BIC/FTC/TAF) may represent the best of all these options as it is well-tolerated, has minimal drug interactions, and a high barrier to resistance. The potential efficacy of BIC/FTC/TAF for PEP was first demonstrated in animal studies, and results from a single-center study confirmed its overall safety and tolerability.[99] The authors noted, however, that several thousands of patients would be required to have a sufficient event rate to evaluate the efficacy of one PEP regimen against another. The data to support expansion of these newer treatment agents to PEP have increased over time and select STRs have already been incorporated into treatment guidelines in other countries.[98] Finally, future long-acting ARVs could also play a role in improved adherence to HIV PEP, with an early study showing potential benefit in combination with oral therapy for 28 days.[100] Future long-acting injectables with the capability to provide one injection for the entirety of PEP therapy should be explored to further enhance adherence.

4.4 | Personalizing PEP in key populations

4.4.1 | Personalizing PEP: incarcerated individuals

Multiple factors may influence selection of PEP regimens, especially in key populations such as incarcerated individuals.[101] The 2016 nPEP guidelines recommend establishment of HIV prevention programs in prisons to alleviate legal, emotional, and medical issues following exposure to HIV.[96] These programs should include HIV education, risk reduction services, mechanisms to identify potential exposures, and confidential and voluntary HIV testing in addition to confidential evaluations for nPEP medication. Although the Federal Bureau of Prisons recommends each facility establish their own protocol, decisions regarding nPEP should follow CDC guidance. Incarceration and imprisonment represent a unique syndemic which facilitates disease transmission, whereby incarcerated individuals are at five times greater risk of HIV acquisition compared with unincarcerated individuals.[1] This is compounded by the prevalence of high-risk groups such as MSM and PWID in incarcerated populations. Tracking HIV transmission in this patient population is also equally challenging due to poor reporting and frequent inmate turnover.[102] Data on use of PEP in prisoners are scant but has been described, albeit with the use of antiquated ART.[103] From an epidemiologic standpoint, prevention of disease via PEP becomes paramount in those who are later released from prison.

4.4.2 | Personalizing PEP: adolescents

Exposure to HIV in adolescents is often due to accident, sexual abuse, or assault.[101] Local regulations and institutional policies dictate which services (i.e., HIV testing, access to contraceptives) are available without parental or guardian consent, but nPEP is seldom offered even when indicated.[104] Though expert consultation is often necessary, the 2016 nPEP guidelines provide recommendations for preferred regimens in children aged 4 weeks to 12 years.[96]

4.5 | Access to PEP

While oPEP is viewed as an emergent medical issue, numerous barriers exist preventing access to nPEP despite the substantial benefits to prevent acquisition of HIV. US federal law mandates employers cover all costs associated with an exposure, including oPEP medications, but nPEP may represent a financial stressor if medications and testing are not covered by insurance plans.[105] Medication assistance programs and federally funded victim's compensation programs can be urgently accessed to provide financial assistance.[101] However, awareness of nPEP remains low among both providers and patients and nPEP remains underutilized due to medical mistrust, HIV stigma, racism, homophobia, and transphobia, all of which may decrease likelihood of patients accessing care within 72 h of potential exposure.[106] Additionally, healthcare personnel, especially trainees, may

have limited knowledge on the transmissibility of blood borne pathogens leading to delays or avoidance of accessing oPEP.[107]

5 | CONCLUSION

TasP, PrEP, and PEP collectively play a role in reducing new HIV infections globally. With progress toward ending the HIV epidemic stalled, it is vital to increase access to prevention. Key populations have been identified by UNAIDS to prevent continued HIV acquisition. Selecting optimal PrEP in these populations must take into consideration clinical data, medication access and cost considerations, and patient factors such as renal function, co-infection status, and concomitant medications and disease states. In order to increase the rates of PrEP uptake, PrEP should be routinely offered by providers regardless of clinical setting and should not be reliant on patient inquiry. Providers should personalize PrEP to individual preferences to improve access, retention in care, and adherence to prevention. Pharmacist expertise and accessibility are keys to addressing health disparities and increasing access to HIV prevention services. With multiple HIV prevention methods available and in the pipeline, personalizing prevention to the patient can further address disparities in new HIV infections and help end the HIV epidemic.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

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