Title
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Journal
Topics in antiviral medicine., 29(4)

ISSN
2161-5861

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Publication Date
2021

Peer reviewed

Invited Review

Challenges and Opportunities for Preexposure Prophylaxis

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Despite major advances in the HIV prevention toolbox in the past decade, there remain substantial social, economic, and structural barriers to access to preexposure prophylaxis (PrEP) that prevent a universal, population-level reduction in HIV incidence. Daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) has been the flagship PrEP regimen, and data support a pericoital/on-demand "2-1-1" dosing schedule for men who have sex with men. Daily oral PrEP with tenofovir alafenamide combined with emtricitabine (TAF/FTC) was approved by the US Food and Drug Administration (FDA) in 2019 for all routes of exposure other than vaginal exposures. The effectiveness of daily oral TDF/FTC has not been consistent in cisgender women outside of serodifferent couples, likely owing to differences in vaginal tissue penetration of PrEP agents resulting in less "forgiveness" of nonadherence. These observations have highlighted the need for additional choices of HIV prevention strategies. Injectable long-acting cabotegravir was recently shown to be superior to daily oral TDF/FTC across risk populations. PrEP studies of islatravir are underway for a monthly oral formulation and a drug-eluting subdermal implant. Lenacapavir, with a novel mechanism of action, is under investigation as a subcutaneous injection at 6-month intervals.

Keywords: HIV prevention, PrEP, long-acting PrEP, cabotegravir, injectable PrEP, islatravir, lenacapavir, dapivirine

Introduction

Despite major advances in HIV prevention in the past decade, and data supporting the extraordinary potential of preexposure prophylaxis (PrEP), many barriers remain that hamper the access and scale-up required to attain population-level benefits.[1] An estimated 1.7 million incident HIV infections every year worldwide[2] high-light the need for increased access and additional options for HIV prevention. To end the HIV epidemic globally, new PrEP formulations and delivery systems that increase acceptability, adherence, and persistence, while reducing stigma, costs, and barriers to use by all populations, will be required. Although the data to support oral tenofovir disoproxil fumarate (TDF)/emtricitabine (TDF/FTC) as PrEP revolutionized HIV chemoprophylaxis, the dapivirine vaginal ring (DPV-VR), tenofovir alafenamide (TAF)/emtricitabine (TAF/FTC), injectable long-acting cabotegravir (CAB-LA), monthly oral and subdermally implanted islatravir, and long-acting sub cutaneous lenacapavir are all currently under investigation as PrEP options (Table).

Oral Tenofovir Disoproxil Fumarate/Emtricitabine

In 2010, the iPrEx (Pre-Exposure Prophylaxis Initiative) study was the first phase III, double-blind, randomized control trial (RCT) to demonstrate the efficacy and safety of daily oral TDF/FTC for the prevention of HIV acquisition among cisgender men who have sex with men (MSM) and transgender women (TGW) who have sex with men.[3] Globally, 2499 HIV-negative participants were enrolled, and 100 participants acquired HIV during the study period: 36 versus 64 in the TDF/FTC versus placebo arm, respectively (hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.37-0.85; $P<.005$ in the modified intention-to-treat analysis). In a subanalysis, plasma and peripheral blood mononuclear cells (PBMCs) from active TDF/FTC-arm participants were tested for their metabolites and the study drug. Detectable study-drug concentrations were associated with a relative reduction in HIV risk by 92% (95% CI, 40-99; $P<.001$), underscoring the importance of study product use and highlighting the challenges of adhering to a daily oral PrEP regimen.

In a separate analysis, PBMC tenofovir diphosphate concentrations from the active iPrEx-arm participants were compared with the concentrations from HIV-negative participants who were administered TDF/FTC in directly observed doses 2, 4, or 7 times per week.[4] Extrapolating those dosing concentrations to iPrEx participants in whom TDF/FTC achieved comparable concentrations, 7 doses per week was associated with a 99% risk reduction, with 96% and 76% risk reduction estimates for 4 and 2 doses per week, respectively, compared with placebo-arm risk. These results suggest a relatively high level of "forgiveness" to nonadherence for rectal exposures, with 4 or more doses per week still conferring high levels of protection. This observation was further supported by the iPrEx Open-Label Extension study, which also supported high levels of protection against rectal HIV acquisition with 4 or more doses per week on average, using intraerythrocytic tenofovir diphosphate

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Table. Comparison of Selected PrEP Agents

PrEP agent	Route of administration	Phase of development	FDA approved
TDF/FTC	Oral	III	Yes
On-demand TDF/FTC	Oral	III	No – recommended by IAS–USA[12] and the WHO[13] for use in cisgender MSM
TAF/FTC	Oral	III	Yes – in cisgender MSM and TGW
Dapivirine	Monthly vaginal ring	III	No – recommended by the EMA and WHO for use in cisgender women in high-prevalence regions
Cabotegravir	Intramuscular injection every 8 weeks	III	No – under review at the FDA for PrEP. Approved for treatment of HIV-1 infection in combination with rilpivirine in virologically suppressed patients
Islatravir	Oral, subdermal implant	III	No
Lenacapavir	Oral, subcutaneous injection every 6 months	III	No

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; IAS–USA, International Antiviral Society–USA; MSM, men who have sex with men; PrEP, preexposure prophylaxis; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; TGW, transgender women; WHO, World Health Organization.

levels measured in dried blood spots (DBSs).[5]

The following year, the results of the Partners PrEP Study demonstrated the safety and efficacy of daily oral TDF/FTC as PrEP among heterosexual, HIV-1 serodifferent couples in Uganda and Kenya.[6] The HIV-negative partner within each of 4747 couples was randomly assigned to TDF, TDF/FTC, or placebo. Over a 3-year period, 82 HIV-1 infections occurred among the participants: 17 in the TDF arm, 13 in the TDF/FTC arm, and 52 in the placebo arm, representing a 75% relative reduction of HIV-1 acquisition in the TDF/FTC arm (95% CI, 55%-87%, $P<.001$). In 2012, the US Food and Drug Administration (FDA) approved daily oral TDF/FTC for PrEP for HIV-negative adults at high risk of HIV-1 seroconversion, based largely on the results of the iPrEx, Partners PrEP,[6] and TDF2 (Botswana TDF/FTC Oral HIV Prophylaxis Trial)[7] studies.[8]

In 2015, the results of the IPERGAY (Intervention Préventive de l'Exposition aux Risques avec et pour les Gays) study were published; IPERGAY was a double-blind RCT designed to evaluate the efficacy of pericoital TDF/FTC versus placebo in MSM in France and Canada.[9] The study's dosing schedule generated the nickname for the regimen, 2-1-1, and consisted of a loading dose of 2 TDF/FTC tablets 2 to 24 hours prior to planned sex and 1 pill each at 24 and 48 hours after the first dose. Among 400 participants, the incidence of HIV-1 seroconversion was 0.91 per 100 person-years in the TDF/FTC arm (2 cases), compared with 6.6 per 100-person years in the placebo arm (14 cases), representing a risk reduction of 86% (95% CI, 40%-98%; $P=.002$). Participants in the TDF/FTC arm took a median of 15 pills per month (interquartile range [IQR], 11-21), consistent with the findings of the iPrEx and iPrEx Open-Label Extension studies, demonstrating that at least 4 daily doses of TDF/FTC per week was highly protective against HIV-1 seroconversion.[10] Follow-up analyses of IPERGAY participants with fewer median PrEP courses taken had consistent findings of high levels of HIV protection.[10,11] Although the FDA has not approved TDF/FTC for on-demand dosing, the International Antiviral Society–USA (IAS–USA)[12] and the World Health Organization (WHO)[13] recommend the on-demand 2-1-1 schedule as an alternative to daily oral TDF/FTC for MSM.

Although TDF/FTC has performed consistently well as PrEP for MSM and serodifferent heterosexual couples, studies among cisgender women have been inconsistent. The FEM-PrEP (Adherence Patterns and Factors Associated With Adherence to a Daily Oral Study Product for Pre-Exposure Prophylaxis) study, a double-blind RCT among 2120 HIV-negative women in South Africa, Tanzania, and Kenya, found no significant difference between incidence rates in the TDF/FTC group and the placebo group (4.7 per 100 person-years vs 5.0 per 100 person-years; HR, 0.94; 95% CI, 0.59-1.52).[14] Fewer than 40% of participants in the TDF/FTC arm had plasma evidence of recent study product dosing, highlighting the lesser "forgiveness" of TDF/FTC PrEP to nonadherence in the setting of vaginal exposures. The VOICE (Vaginal and Oral Interventions to Control the Epidemic) study, a placebo-controlled, randomized trial to assess oral TDF/FTC, oral TDF, or 1% tenofovir vaginal gel as PrEP agents among 12,320 cisgender women in sub-Saharan Africa, found that none of the investigational regimens reduced the risk of HIV-1 acquisition compared with placebo.[15] It is challenging to distinguish how much of the reduced efficacy for vaginal sex is attributable to drug tissue levels and how much to differential adherence, but it is clear from the Partners PrEP study that high levels of protection are possible with rigorous adherence.[6] These findings, and the companion qualitative work,[16-18] suggest that risk perception, competing priorities, stigma, and fear of intimate partner violence may have compromised pill-taking (and gel use), encouraging ongoing research into additional PrEP agents and delivery systems that could minimize these concerns and support adherence.

Oral Tenofovir Alafenamide/Emtricitabine

Although generally very safe, concerns about potential renal toxicity and loss of bone mineral density on dual-energy X-ray absorptiometry (DEXA) scanning attributable to TDF-based PrEP inspired the DISCOVER (Study to Evaluate the

Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex With Men and Are At Risk of HIV-1 Infection) trial, a double-blind, phase III, noninferiority trial comparing TAF/FTC with TDF/FTC in cisgender MSM and TGW.[19] More than 5380 participants in the United States, Canada, and Europe were randomly assigned to daily oral TAF/FTC or TDF/FTC in a double-blinded RCT. In the primary analysis, there were 7 seroconversions in the TAF/FTC group (0.16 infections per 100 person-years) compared with 15 in the TDF/FTC group (0.34 infections per 100 person-years). The incidence rate ratio (IRR) of 0.47 (95% CI, 0.19-1.15) was consistent with a noninferiority statistical result. Although sensitive laboratory renal biomarkers and bone mineral density were better in the TAF/FTC group than in the TDF/FTC group, there were no significant differences in clinical outcomes between the 2 arms, though there was an average weight gain of 1 kg in the TAF/FTC group, and no net weight change in the TDF/FTC group. There was also a small (1 mg/dL) increase in fasting low-density lipoprotein cholesterol level in the TAF/FTC group, compared with a 6.5 mg/dL decrease in fasting low-density lipoprotein level in the TDF/FTC group.[19] The FDA approved TAF/FTC for PrEP in 2019, but it did not extend the approval to those who engage in receptive vaginal intercourse.[20]

Moving to Next-Generation PrEP or "PrEP 2.0"

Stigma around taking a daily medication associated with and potentially confused with HIV treatment has been cited as a potential barrier to PrEP adherence.[16-18] Discrete delivery mechanisms, including vaginal rings, injectable medications, and drug-eluting implants, are attractive contenders to expand PrEP options. There is additional ongoing interest in topical gels, foams, threads, and inserts for vaginal or rectal use, as well as microneedle patches to be administered topically.

Dapivirine Vaginal Ring

Vaginal rings have been used successfully for hormonal contraception, making them an appealing option for PrEP for individuals at risk by vaginal exposure, given the structural, social, and environmental barriers to adherence with daily oral TDF/FTC seen in the randomized trials. Dapivirine, a nonnucleoside reverse transcriptase inhibitor (NNRTI) not available as an oral preparation, was tested in a monthly vaginal ring in 2 major phase III, double-blind, randomized trials: the ASPIRE (A Study to Prevent Infection with a Ring for Extended Use)[21] and Ring (Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women)[22] studies. In the ASPIRE study, 2629 cisgender women in South Africa, Uganda, and Zimbabwe were randomly assigned to a 25 mg DPV-VR or placebo ring.[21] Over a median follow-up of 1.6 years (IQR, 1.1-2.3 years), monthly replacement of the DPV-VR compared with placebo reduced the incidence of HIV-1 infection by 27% ($P = .046$). In the post-hoc adherence analysis stratified by age, the DPV-VR reduced incidence in women over 21 years of age by 56% ($P < .001$). The results of the Ring study were published the same year, in 2016; among 1959 cisgender women randomly assigned in a 2:1 fashion to the DPV-VR or placebo, monthly use of the DPV-VR reduced the incidence of HIV-1 acquisition by 31% (HR, 0.69; 95% CI, 0.49-0.99; $P = .04$).

The open-label extensions of the ASPIRE and Ring studies have suggested higher levels of efficacy with more consistent use of the DPV-VR. The MTN (Microbicide Trials Network)-025/HOPE (HIV Open-label Prevention Extension) study was a phase IIIb open-label extension of the ASPIRE trial; HIV-negative participants in the original ASPIRE trial were offered 12 months of open-label DPV-VR to evaluate real-world uptake, consistent use, and acceptance outside of an RCT setting.[23] A total of 1456 women were enrolled, and 92.2% of study participants agreed to use the DPV-VR. Most participants reported acceptance of the DPV-VR at each visit, and 89.3% of the rings returned and tested for dapivirine release were consistent with use during the month. The HIV-1 incidence rate was 2.7 per 100 person-years, less than the placebo rate of 4.4 per 100 person-years. Similar results were reported by the DREAM (Determined, Resilient, Empowered, AIDS-free, Mentored and Safe) study, an open-label extension of the Ring study; the residual amount of dapivirine in returned rings was significantly lower in the DREAM study than in the Ring study (suggestive of more consistent use), and the HIV incidence of 1.8 per 100 person years was 62% lower than the simulated placebo rate.[24] The European Medicines Agency (EMA) and WHO recommend the DPV-VR for HIV prevention among cisgender women in high-prevalence regions.[25] The DPV-VR is currently under review by the FDA for use as a PrEP agent in the United States. Additionally, the DELIVER (Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral TDF/FTC in Pregnancy) study, an extension of ASPIRE, is an open-label phase IIIb study to evaluate the safety and efficacy of the DPV-VR in HIV-negative pregnant women compared with daily TDF/FTC PrEP.[26] The study will provide safety data in pregnancy, and is currently enrolling.

Injectable Cabotegravir

CAB-LA, a novel integrase strand transfer inhibitor (InSTI) administered as an intramuscular gluteal injection every 8 weeks, is an attractive PrEP option for high-risk individuals unable to adhere to a daily oral PrEP formulation, or who may prefer injections to tablets for a variety of reasons, including discretion and convenience. Cabotegravir has been evaluated in 2 phase III clinical trials and is currently pending regulatory review in the United States.

The HIV Prevention Trials Network (HPTN) 083 trial is a double-blind, phase III, noninferiority RCT designed to compare the efficacy and safety profile of CAB-LA with daily oral TDF/FTC in cisgender MSM and TGW.[27] EligibleHIV-negative participants were recruited from sites in Africa, Asia, Latin

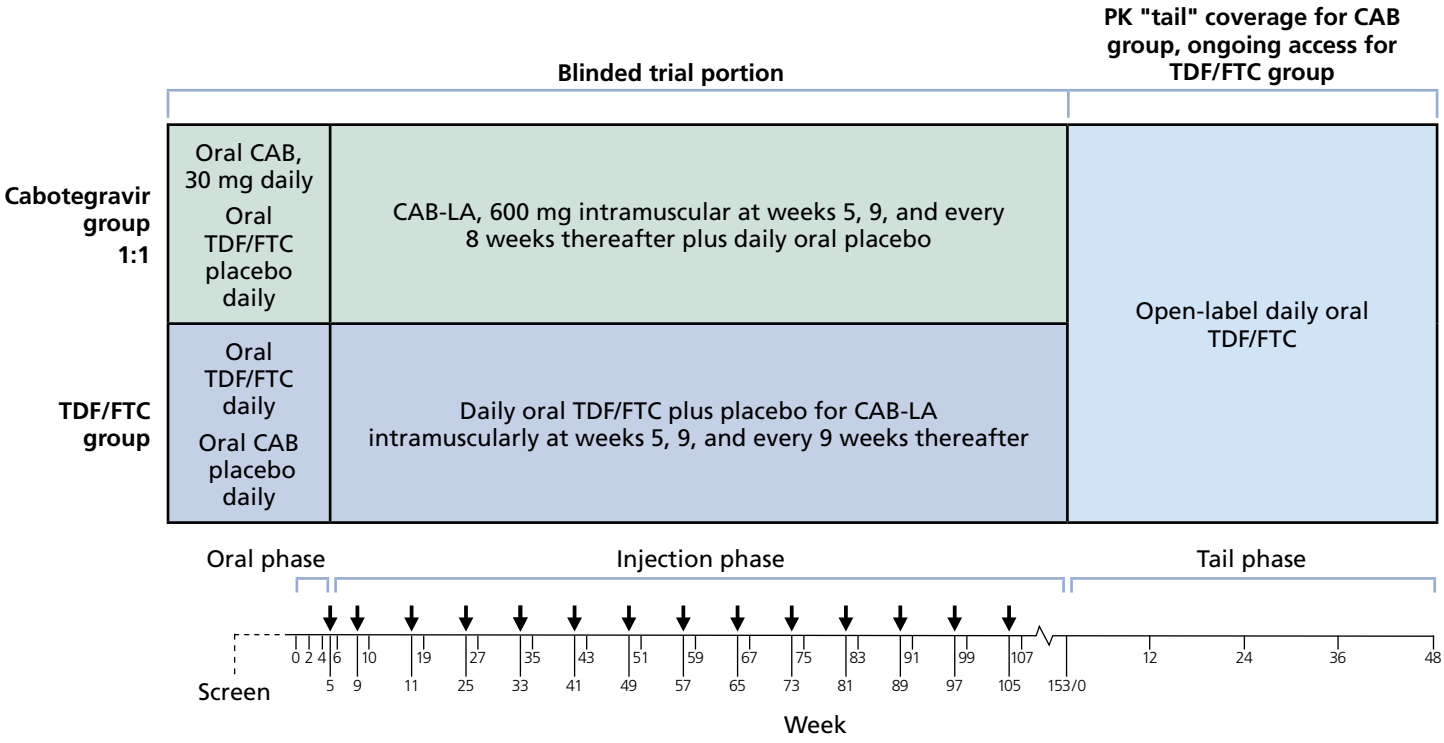

Figure 1. HIV Prevention Trials Network 083 trial design. Abbreviations: CAB, cabotegravir; CAB-LA, long-acting cabotegravir; PK, pharmacokinetic; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine. Adapted from Landovitz et al.[27]

America, and the United States. Participants were randomly assigned 1:1 to the CAB-LA arm or the TDF/FTC arm. The protocol consisted of 3 phases: 1) a lead-in phase with oral tablets lasting 5 weeks, 2) an injection phase, and 3) a "tail" phase (Figure 1).[27] As the study was double-blinded, participants assigned to the CAB-LA arm received 30 mg daily oral cabotegravir tablets for 5 weeks, followed by 600 mg CAB-LA injections every 8 weeks (after a 4-week interval separating the first 2 injections), as well as a daily oral placebo tablet throughout the entirety of the blinded portion of the study. Participants in the TDF/FTC arm received an active daily oral TDF/FTC pill, and a cabotegravir placebo oral tablet for 5 weeks, followed by placebo intramuscular injections in the gluteal muscle on the same injection schedule as the active CAB-LA arm above. Participants in either arm who stopped the injections early received 48 weeks of open-label TDF/FTC for PrEP, to provide ongoing standard-of-care biomedical HIV prevention as the prolonged pharmacokinetic (PK) "tail" of cabotegravir washed out of their systems.

A total of 4566 participants were included in the modified intention-to-treat analysis. The study population was diverse; the median age was 26 years, 49.8% of US participants identified as Black, and 12.5% of all participants were TGW. An independent data safety monitoring board (DSMB) recommended that the study be unblinded in May 2020 based on an early efficacy finding: In the cabotegravir arm, there were 13 incident infections (incidence, 0.41 per 100 person-years), and in the TDF/FTC arm, there were 39 incident infections (incidence, 1.22 per 100 person-years), representing a 66% reduction in HIV-1 acquisition (HR, 0.34; 95% CI, 0.18-0.62) for cabotegravir compared with TDF/FTC, meeting statistical superiority.[27]

In the case of cabotegravir PrEP breakthrough infections, the potent antiviral properties of cabotegravir were found to suppress viremia and delay antibody detection, thus delaying the time to reactivity of conventional, largely antibody-based, diagnostics. Qualitative and quantitative RNA testing were found to be more sensitive than traditional antigen and antibody assays, and such post-hoc testing resulted in a reanalysis of the HPTN 083 primary results to instead contain 12 incident infections in the CAB-LA arm, and an unchanged number (39) in the TDF/FTC arm.

Of the 16 total infections in the CAB-LA arm, 4 were prevalent/baseline (ie, within the window period at enrollment into the study by conventional algorithmic HIV testing), and 12 were incident. These 16 were classified by the investigators into 4 groups: 4 infections occurred prior to enrollment (group A), 5 occurred without recent exposure to CAB-LA (group B), 3 occurred prior to a CAB-LA injection (ie, during the oral lead-in, group C), and 4 infections occurred with expected plasma CAB-LA concentrations based on the timing of the injections (group D). InSTI resistance mutations were detected in 1 group A case, 2 group C cases, and 2 group D cases (Figure 2). In the cases of HIV acquisition during the "tail" phase, resistance was not identified (all were wild type). The 4 group D infections remain incompletely explained; hypotheses for the breakthrough cases include possible lower plasma levels

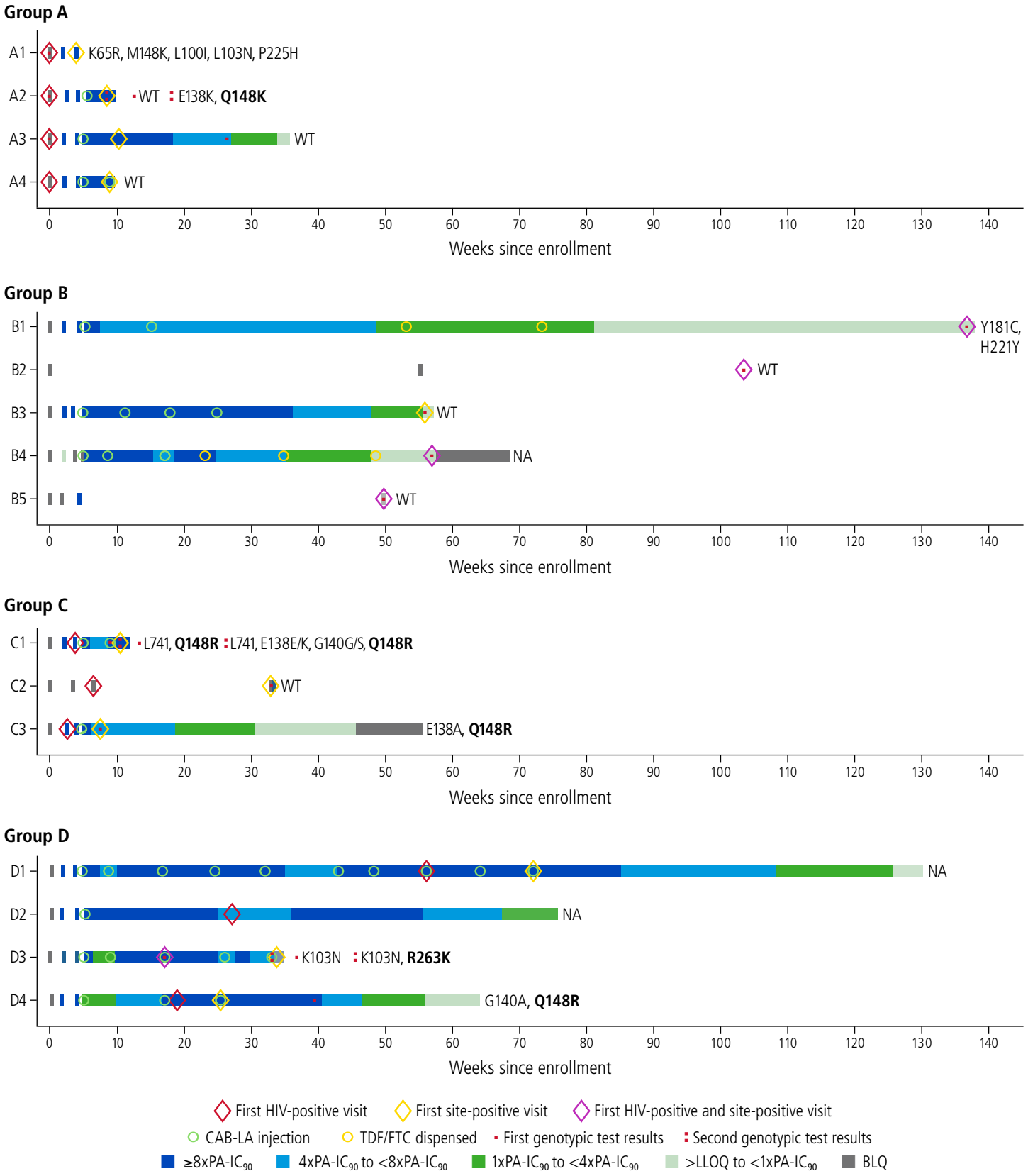

Figure 2. Pharmacologic and virologic data for HIV breakthrough cases in the cabotegravir group from the HIV Prevention Trials Network 083 study. study. Bold mutations are major mutations in the International Antiviral Society-USA resistance guidelines. See text on page 4 for more context. Abbreviations: BLQ, below the limit of quantification; CAB-LA, long-acting cabotegravir; LLOQ, lower limit of quantitation; PA-IC_{90}, protein-adjusted 90% inhibitory concentration; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine. Adapted from Landovitz et al.[27]

between the 2 initial injections, low cabotegravir partitioning into rectal tissue, or concomitant rectal inflammation.[27] High-sensitivity assays, such as nucleic-acid–based viral load testing to detect HIV breakthrough as early as possible, are currently being evaluated in an open-label extension to the parent study. These viral load tests would be useful if earlier detection can reduce the probability of InSTI resistance, but would pose additional implementation and scale-up challenges.

In the HPTN 083 trial, CAB-LA was generally well tolerated. Most participants in the CAB-LA group (83%) reported an injection site reaction, although most of these were mild or moderate and declined over time with serial injections. Only 2.2% of participants reported a sufficiently severe injection-related event to lead to injection discontinuation. In addition, CAB-LA was associated with an average weight increase of 1.3 kg per year compared with 0.3 kg per year in the TDF/FTC arm.

HPTN 084 is the sister study of HPTN 083; it was a similarly designed double-blind phase III RCT that compared the efficacy of CAB-LA with daily oral TDF/FTC in more than 3200 cisgender women in sub-Saharan Africa.[28] The DSMB also halted the blinded comparison of the HPTN 084 trial early, in November 2020, for CAB-LA's superiority to daily oral TDF/FTC; there were 4 incident HIV infections in the CAB-LA group (incidence rate, 0.21%) compared with 34 infections in the TDF/FTC group (incidence rate, 1.79%), representing an 89% risk reduction (HR, 0.11; 95% CI, 0.04%-0.32%). Bridging safety, tolerability, and acceptability studies in adolescents are ongoing, as are designated studies for pregnant and breastfeeding people. Cabotegravir as a PrEP agent is currently under review by the FDA.

Islatravir

Islatravir is an investigational first-in-class nucleoside reverse transcriptase translocation inhibitor (NRTTI) that inhibits translocation and results in early chain termination of the viral reverse transcriptase DNA product.[29] PK studies of the oral formulation of islatravir and drug-eluting subdermal implants have demonstrated prolonged plasma and intracellular half-lives and excellent antiviral potency.[29]

There are 2 ongoing phase III blinded RCTs that will evaluate the efficacy and safety of once-monthly oral tablets of islatravir as PrEP: the Impower-022 study among cisgender women at high risk of HIV-1 acquisition in sub-Saharan Africa and the United States,[30] and the Impower-024 study among cisgender MSM and TGW in the United States, France, Japan, and Europe.[31] Both studies started enrollment in early 2021 and are actively recruiting participants. The results of a phase I study to evaluate the islatravir implant were presented at CROI 2021. A total of 36 participants were randomly assigned to a placebo implant or varying doses of the islatravir implant for 3 months.[32] The intracellular half-life was 198 hours following removal of the implant, suggesting maintenance of target concentrations up until 1 year postimplantation, based on triangulation of a macaque challenge model and therapeutic efficacy targets.[32] The majority of participants reported mild adverse effects, although half of the placebo implant group did as well. There were no serious adverse effects requiring discontinuation of the implant. A phase II study to test the highest dose implant formulation is currently underway.

Lenacapavir

Previously known as GS-6207, lenacapavir is an investigational first-in-class, long-acting HIV capsid inhibitor available as an oral formulation and as a subcutaneous injection administered every 6 months.[33] Subcutaneous lenacapavir has shown high metabolic stability and antiviral potency in a phase II/III trial of heavily treatment-experienced people with HIV; the addition of lenacapavir to a failing antiretroviral (ARV) regimen among 24 participants resulted in a 1.93 $\log_{10}$ copies/mL decline in HIV-1 RNA at day 15, compared with a 0.29 $\log_{10}$ copy/mL decline in the placebo group of 12 participants ($P < .0001$).[34] There were no serious adverse events leading to discontinuation of lenacapavir, and injection site adverse effects were generally mild. The efficacy and safety profile of long-acting lenacapavir make it an attractive option for PrEP as monotherapy. There are currently 2 planned phase III randomized trials to evaluate the efficacy and safety of lenacapavir for PrEP compared with a counterfactual placebo: PURPOSE 1 (Study to Assess Safety and Efficacy of Lenacapavir and Emtricitabine/Tenofovir Alafenamide for Pre-Exposure Prophylaxis in Adolescent Girls and Young Women at Risk of HIV Infection) among adolescent girls and young cisgender women at high risk of HIV-1 acquisition,[35] and PURPOSE 2 (Study to Assess the Effectiveness and Safety of Lenacapavir for Human Immunodeficiency Virus Pre-Exposure Prophylaxis) among MSM, TGW, and gender nonbinary people who have condomless receptive anal intercourse.[36] Both studies are open and actively recruiting participants.

Conclusion

Novel PrEP formulations and alternative modes of delivery are needed to expand PrEP options for at-risk populations. Drawing from family planning literature, more choices will provide more options that will be acceptable and congruent with the lives of more at-risk individuals. Daily oral TDF/FTC is FDA-approved for PrEP in the United States across risk-populations and in many other countries globally, and TAF/FTC was recently approved in the United States for all routes of exposure except vaginal intercourse. The DVP-VR shows use-dependent results in cisgender women, but it may be acceptable to women who will not or cannot use pill-based HIV prevention strategies; a phase III clinical trial in pregnant people is actively recruiting participants in sub-Saharan Africa. CAB-LA was found to be superior for prevention of HIV-1 acquisition to daily oral TDF/FTC in the HPTN 083 and HPTN 084 trials. Clinical trials of a monthly oral islatravir tablet and a long-acting drug-eluting islatravir

implant are currently underway. The addition of long-acting lenacapavir monotherapy to failing ART regimens in heavily treatment-experienced people with HIV resulted in a clinically significant and rapid decline in HIV-1 RNA, making it an attractive option for PrEP in at-risk populations.

This article was based, in part, on a webcast presented by Dr Raphael J. Landovitz in May 2021: https://youtu.be/xji7c9pRag0. This article was prepared by Dr Cambou and Dr Landovitz in August 2021.

Financial affiliations with ineligible companies (formerly named "commercial interests" by the ACCME) in the past 24 months: Dr Cambou has no relevant financial affiliations to disclose. (Updated November 15, 2021) Dr Landovitz received honoraria and travel support from Gilead Sciences, Merck & Co., Inc, and Roche. (Updated November 15, 2021)

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