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Invited Reviews CME

Perspective

Topics in Antiviral Medicine™

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Learning Objectives

On completion of this activity, which contains 3 articles, the learner will be able to:

- Describe additional choices of HIV prevention strategies beyond daily oral TDF/FTC
- Identify how to optimally predict, prevent, and treat cardiovascular diseases among individuals with HIV
- Describe the comorbidities that are of primary concern for older adults with HIV

Intended Audience

This enduring material is designed for physicians who are actively involved in the medical care of people with HIV and other viral infections.

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Invited Review

Challenges and Opportunities for Preexposure Prophylaxis

Mary Catherine Cambou, MD; Raphael J. Landovitz, MD, MSc

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

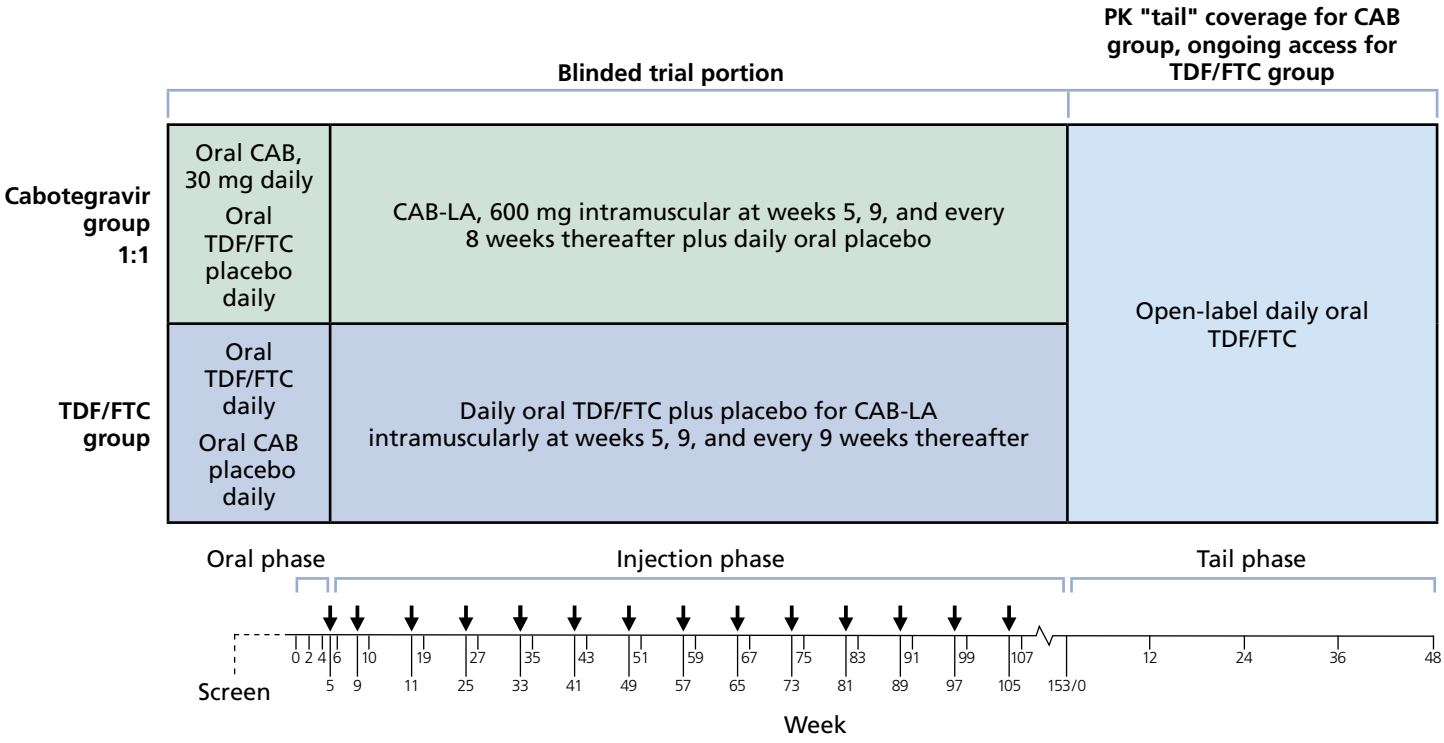

Figure 1. HIV Prevention Trials Network 083 trial design. Abbreviations: CAB, cabotegravir; CAB-LA, long-acting cabotegravir; PK, pharmacokinetic; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine. Adapted from Landovitz et al.[27]

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

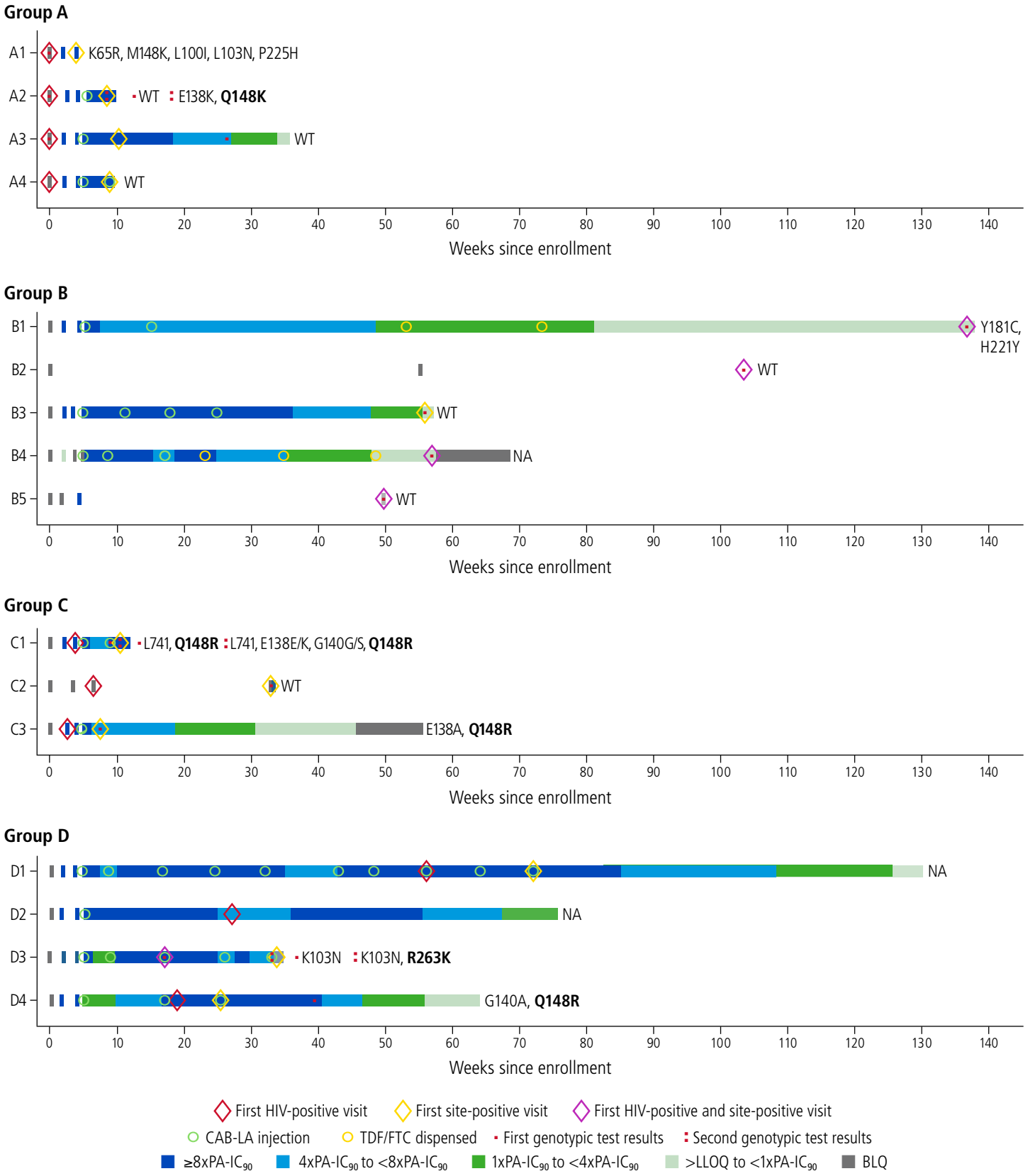

Figure 2. Pharmacologic and virologic data for HIV breakthrough cases in the cabotegravir group from the HIV Prevention Trials Network 083 study. study. Bold mutations are major mutations in the International Antiviral Society-USA resistance guidelines. See text on page 4 for more context. Abbreviations: 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.

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Invited Review

HIV and Cardiovascular Disease: From Insights to Interventions

Matthew J. Feinstein, MD, MSc

Individuals with HIV have elevated risks for cardiovascular diseases (CVDs) ranging from myocardial infarction to heart failure. Our understanding of this heightened HIV-associated cardiovascular risk has evolved over the past 2 decades. In the early era of antiretroviral therapy (ART), concern existed that ART was the primary driver of cardiovascular risk. However, it has become increasingly apparent that HIV-related viremia, immune dysregulation, and inflammation are primary drivers of HIV-associated cardiovascular risk, along with traditional cardiovascular risk factors such as tobacco smoking. Indeed, early and effective ART blunts risk for CVDs among individuals with HIV. Despite these improvements in HIV-associated cardiovascular risk, questions remain regarding how to optimally predict, prevent, and treat CVDs among individuals with HIV. Efforts are underway to define more precisely which diagnostic and therapeutic strategies will be most effective in curbing HIV-associated CVDs.

Keywords: HIV, cardiovascular disease, CVD, inflammation, atherosclerosis, heart failure, myocardial infarction

Individuals with HIV have higher risks for cardiovascular diseases (CVDs), including myocardial infarction (MI), heart failure, and pulmonary hypertension, than individuals without HIV.[1-5] As life expectancy has increased for individuals with HIV as a result of effective antiretroviral therapy (ART), the burden of diseases of aging, including CVDs, has increased among individuals with HIV.[6-8]

There are several reasons for elevated CVD risk among people with HIV that reflect the diverse pathophysiologies of CVDs. Diseases of the vasculature, such as MI, occur as a result of a combination of atherosclerosis and thrombosis. Meanwhile, heart failure reflects a final common pathway of different and often overlapping pathophysiologies, ranging from the sequelae of MI to the toxic effects of drugs on the myocardium. Our understanding of HIV-associated CVD risks has improved greatly over the past decade and a half due to seminal epidemiologic and mechanistic studies.

Epidemiology of HIV-Associated Cardiovascular Diseases

Studies in large cohorts comparing individuals with HIV with individuals without HIV have demonstrated approximately 50% higher risk for MI among individuals with HIV.[3,9,10] This elevated risk remained after accounting for demographic and clinical confounding variables. Likewise, studies investigating heart failure have demonstrated 50% or higher increased risk among individuals with HIV than among individuals without HIV, even after adjustment for key confounding variables.[2,4] Studies also suggest a mildly increased risk for stroke among individuals with HIV[11] and a dramatically increased risk for pulmonary hypertension.[12]

In the early ART era, prolonged exposure to ART was hypothesized as a primary contributor to HIV-associated CVD risks. Indeed, there is some variability in the putative effects of individual antiretroviral drugs on CVD outcomes, including a potential modest effect of abacavir on increasing MI risk.[13,14] Nevertheless, more recent data suggest that the effects of ART on CVD are relatively small,[15] particularly compared with the problematic effects of uncontrolled HIV. Several studies from large cohorts indicate that HIV viremia and lower CD4+ cell counts are strongly associated with MI and heart failure risk.[1-4] Taken together, along with clinical data suggesting that immediate (vs deferred) ART protects against MI,[16,17] these data tilt the balance in favor of a net-cardioprotective effect of immediate and continuous ART.[1] Of course, immediate and continuous ART remains the cornerstone of HIV therapy. Therefore, from both a CVD prevention standpoint and an overall HIV care standpoint, it is clear that early and continuous ART is essential to optimizing health outcomes for individuals with HIV.

In addition to poor HIV control (ie, with HIV viremia) and immunologic progression (marked by decreasing CD4+ cell count), there are other factors that may increase risk of CVD among in dividuals with HIV. Metabolic abnormalities, including atherogenic dyslipidemia and body composition changes, are common among individuals with HIV. In the current era, increases in dysfunctional subcutaneous fat and visceral fat have been observed among people with HIV; these changes, in turn, are associated with atherosclerotic plaque.[18] Coinfection with hepatitis C virus or cytomegalovirus (CMV) reactivation may also contribute to HIV-associated CVD risk. Individuals with HIV smoke at a significantly higher rate than uninfected individuals; the MI attributable to smoking is considerably higher for

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individuals infected with HIV than those without.[19] Finally, hypertension and high alcohol use may also contribute disproportionately to HIV-associated CVD risk.[1]

Mediators of Atherosclerosis and Thrombosis in HIV

Atherosclerosis and thrombosis play central roles in the development of vascular diseases and their clinical manifestations, including MI and stroke. Classically, MIs occur when lipid-rich, inflammatory plaque ruptures or erodes acutely, triggering overlying thrombus and vessel occlusion. In addition to these classic type I MIs, individuals with HIV are at heightened risk for type II MIs, in which myocardial oxygen supply is inadequate relative to demand, triggering myocardial injury.

In this setting, investigators in several studies have observed increased levels of systemic and vascular inflammation, as well as increased platelet activation or aggregation, in individuals with HIV. A common finding across studies of individuals with HIV, as well as monkey models of HIV pathogenesis, is the centrality of inflammation and immune activation to HIV-related CVD risk. Individuals infected with HIV have heightened levels of systemic inflammation and more subclinical atherosclerosis than uninfected individuals.[1] These include elevated levels of soluble CD163 and CD14, as well as common CVD-associated inflammatory markers such as interleukin-6, which are in turn associated with atherosclerosis and mortality. Treatment with ART reduces the levels of several of these markers, but some remain elevated despite ART. Likewise, individuals with HIV have elevated levels of coagulation markers and tissue factor-expressing inflammatory monocytes, creating a functionally procoagulant state that has been associated with clinical thrombosis in HIV.[20]

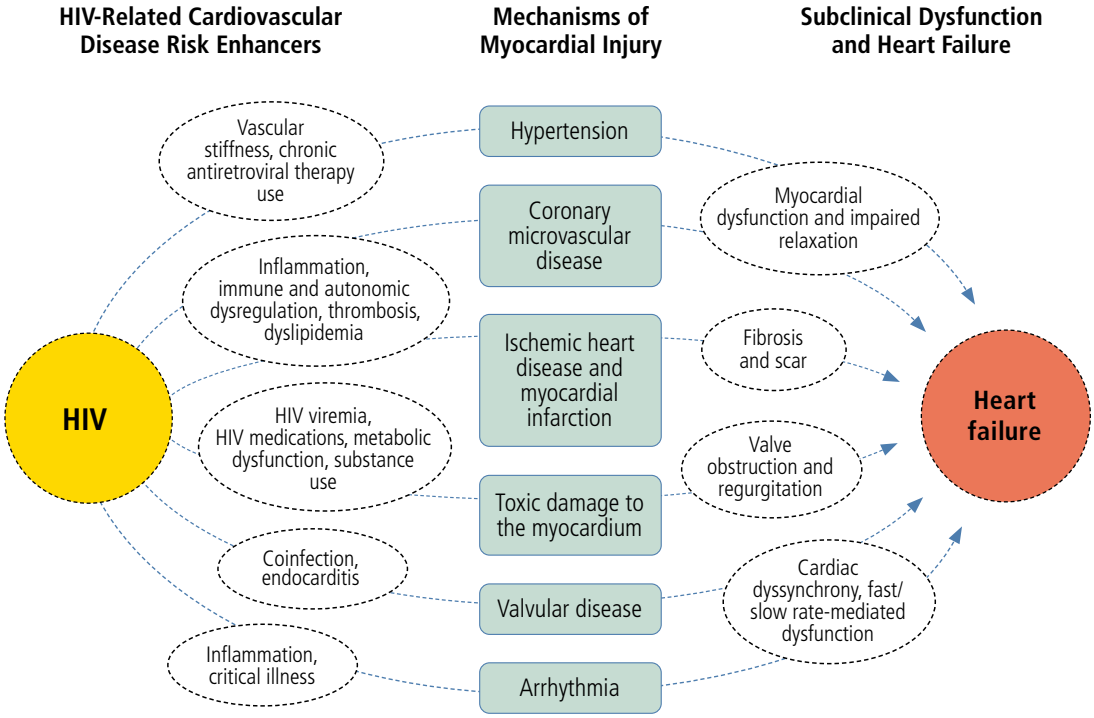

Figure 1. Conceptual model of the proposed mechanisms of heart failure in HIV. Adapted from Feinstein et al.[1]

Mechanisms and Presentation of HIV-Associated Heart Failure

Causes and presentations of heart failure are heterogeneous in the general population and for individuals with HIV. In the pre-ART era, heart failure was a recognized complication of advanced HIV and marked by viremia and progressive immune compromise, along with global myocardial dysfunction and often inflammation. With widespread uptake of ART, the causes and manifestations of heart failure in individuals with HIV have likewise expanded (Figure 1).

Individuals with persistent HIV viremia, immune progression, and opportunistic infections may still experience HIV-associated cardiomyopathy marked by severe systolic dysfunction in the absence of obstructive coronary artery disease. Furthermore, viremia and immune progression still play a role in less overt cardiomyopathy and heart failure, as each are associated with diastolic dysfunction among individuals with HIV. Yet, with the increasing burden of coronary artery disease and MI among individuals with HIV, ischemic etiologies of heart failure, driven by post-MI myocardial scarring and potential microvascular dysfunction, have become increasingly common. Toxic etiologies of myocardial dysfunction and heart failure also play an outsized role in HIV-related heart failure given the higher rates of myocardial-toxic drug use (eg, methamphetamines) among individuals with HIV.

More subtle manifestations of heart failure in the absence of systolic dysfunction also occur in HIV, as individuals with HIV have higher risks for heart failure with preserved ejection fraction than individuals without HIV. This is likely due to a combination of factors, including but not limited to myocardial inflammation, fibrosis, microvascular ischemia, and myopericardial fat deposition. Indeed, several studies using cardiac magnetic resonance imaging, computed tomography, and positron emission tomography have demonstrated that individuals with HIV have more myocardial inflammation, fibrosis, and steatosis than matched control individuals without HIV.[1] These subclinical changes in cardiac tissues are known to be associated with myocardial injury and dysfunction.

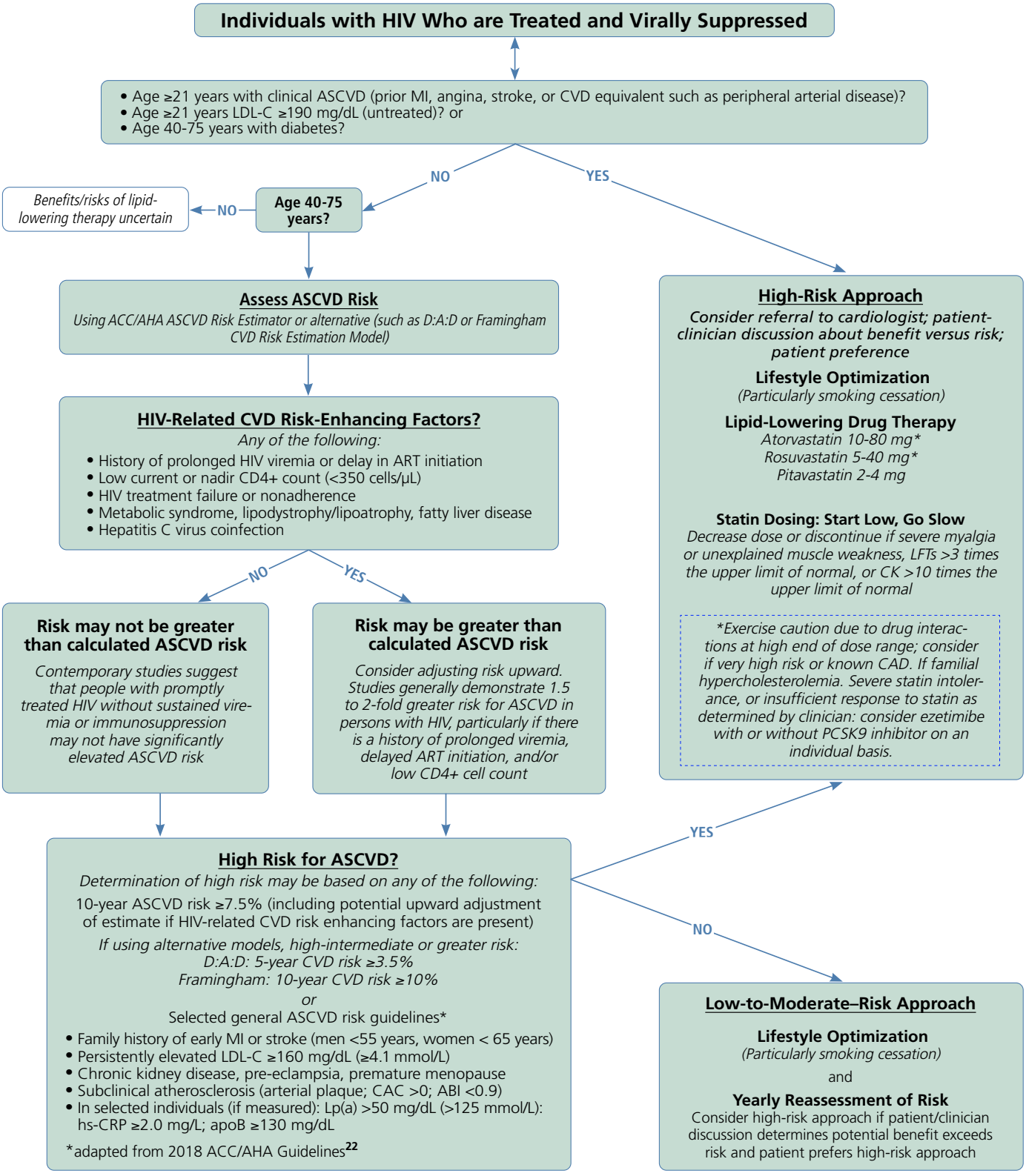

Figure 2. A pragmatic approach to atherosclerotic CVD risk stratification, prevention, and therapy for individuals with HIV. Adapted from Feinstein et al[1] and 2018 ACC/AHA guidelines.[22] Abbreviations: ABI, ankle brachial index; ACC, American College of Cardiology; AHA, American Heart Association; apoB, apolipoprotein B-100; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CK, creatine kinase; CVD, cardiovascular disease; D:A:D, Data collection on Adverse events of anti-HIV Drugs; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LFT, liver function test; Lp(a), lipoprotein (a); MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9.

Cardiovascular Disease Risk Stratification, Prevention, and Therapy for Individuals with HIV

Epidemiologic and mechanistic studies have advanced our knowledge of the scope and causes of CVDs in individuals with HIV. However, there are relatively sparse data to practically guide cardiovascular risk stratification, prevention, and treatment for individuals with HIV who are effectively treated with ART. Despite the limitations of these data and absent large-scale trial data for CVD prevention and treatment during effective ART, there are certain consistent findings on HIV-associated CVD risk that may help inform practical approaches..

The clinical data on CVD-preventive stratagies among individuals with HIV are relevant in this regard. Over the past 2 decades, numerous small studies have evaluated the effects of statin use on various subclinical markers of inflammation and atherosclerosis for individuals with HIV.[21,22] Results of these studies on arterial inflammation have not been consistent, although statins do appear to reduce select inflammatory markers and, as expected, reduce atherogenic lipid levels (eg, low density lipoprotein cholesterol) in individuals with HIV. Questions related to the efficacy of statins in preventing hard atherosclerotic coronary artery disease endpoints in individuals with HIV will be answered with more clarity by the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) study. REPRIEVE randomly assigned individuals with HIV at low to moderate risk for atherosclerotic CVD to pitavastatin or placebo. Enrollment of more than 7500 individuals with HIV is complete and follow-up is ongoing.

Compared with statins, even less clarity exists regarding other potential CVD preventive stratagies for individuals with HIV. Ongoing studies (not yet powered for clinical endpoints) are evaluating the role of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors for individuals with HIV. More data are likewise needed related to antithrombotic therapy among individuals with HIV, who have elevated risks for thrombosis. Mechanistic and biomarker studies suggest that aspirin may not be as effective an antiplatelet agent for individuals with HIV than for uninfected individuals, but further study and clinical correlations related to aspirin and other antithrombotic therapies in HIV are needed.

Other anti-inflammatory therapies for individuals with HIV are also of interest. These include therapies that target the gut to reduce microbial translocation and gut inflammation, which have not consistently affected biomarkers of inflammation among individuals with HIV. Other therapies tested include canakinumab, an interleukin-1-beta antagonist that reduced inflammatory markers and reduced arterial and bone marrow inflammation in a small study of individuals with HIV, and methotrexate, which did not affect inflammatory markers but modestly reduced CD8+ T-cell counts in individuals with HIV. The efficacy and ultimate clinical applicability of these options remain under investigation.

In the absence of large-scale clinical trial data powered for hard CVD endpoints, interim guidance related to CVD risk stratification, prevention, and treatment for individuals with HIV is based on extrapolation of clinical and mechanistic data. Regarding risk stratification, several studies indicate that traditional CVD risk estimation tools consistently underestimate CVD risk among individuals with HIV. This heightened risk is largely attributable to HIV-related CVD risk-enhancing factors such as prolonged HIV viremia, low current or nadir CD4+ cell count, coinfection (eg, with hepatitis C virus), and the presence of lipid distribution abnormalities. However, for those who are treated promptly and who do not experience these HIV-related risk enhancers, HIV-related increases in CVD risk are modest. Accordingly, the American Heart Association's scientific statement on HIV-1 recommended adjusting predicted CVD risk upwards by 1.5-fold to 2-fold for individuals with HIV who have HIV-related risk enhancers (Figure 2). In the absence of compelling data otherwise, risk-based approaches to CVD-preventive therapy for individuals with HIV is recommended, with the understanding that as CVD risk increases, the absolute and net benefit of statin therapy for CVD prevention likewise increases.

Conclusion

As life expectancy among individuals with HIV has increased, noncommunicable conditions such as CVDs have become more common for individuals aging with HIV. Several HIV-related factors increase CVD risk, with chronic inflammation and immune dysregulation playing a key role. Limited large-scale clinical trial data exist to guide HIV-specific CVD prevention and therapy, highlighting the importance of further clinical and mechanistic study in this area.

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Perspective

Primary Care Concerns for the Aging Population With HIV

Because individuals with HIV are living longer, comorbidities are moving to the forefront of HIV patient care. People with HIV have a higher risk for HIV-related and non–HIV-related cancers than the general population, making cancer screening vital for this population. Immunizations are another important element of primary care for older adults with HIV, including a COVID-19 vaccine, about which data continue to evolve. This article summarizes a presentation by Steven C. Johnson, MD, at the International Antiviral Society–USA (IAS–USA) virtual HIV course Aging and HIV: Issues, Screening, and Management in Individuals with HIV as They Age *in June 2021.*

Keywords: HIV, aging, primary care, cancer screening, vaccine, immunization, COVID-19, mortality

Antiretroviral therapy (ART) has improved outcomes for individuals with HIV, and HIV-related deaths have continued to decline (Figure 1).[1] In the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study, a reduction in AIDS-related deaths was observed along with improved CD4+ cell counts from 1999 to 2011, although deaths due to non–AIDS-related cancers increased during this period.[2] In a study from the Kaiser Permanente group, life expectancy from 2000 to 2016 among individuals with HIV approached that of individuals without HIV; however, those with HIV continued to experience more comorbidities than those who did not have HIV.[3] As people with HIV age, primary care becomes an increasingly important element of their care.

Understanding the causes of morbidity and mortality in older people with HIV is central to HIV primary care. Common comorbidities of HIV infection are listed in Table 1. It is incumbent on infectious diseases programs and HIV clinics to develop protocols for screening for common comorbidities in patients with HIV. The US Preventive Services Task Force (USPSTF) and the Infectious Diseases Society of America (IDSA) each provide detailed guidance on screening for people with HIV,[4,5] including for various cancers, osteoporosis, and prevention of falls.

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Cancer Screening

People with HIV have a higher risk for HIV-related and non–HIV-related cancers than the general population.[6] In a study that compared individuals with HIV from 2 separate cohorts with individuals from the Surveillance, Epidemiology, and End Results (SEER) Program from the National Cancer Institute, individuals with HIV had statistically higher levels of various cancers (Table 2).[7] Strategies that HIV care clinicians can implement for cancer screening in their patients are shown in Table 3.

Colorectal Cancer

The USPSTF recommends colorectal screening for all adults aged 50 to 75 years (grade A recommendation), as well as for those aged 45 to 49 years (grade B recommendation) and for selected individuals aged 76 to 85 years based on overall health, prior screening, and preferences (grade C recommendation).[8] Suggested screening methods include stool-based tests (eg, fetal occult blood or fecal immunochemical test) or direct visualization (eg, computed tomography [CT] colonography, flexible sigmoidoscopy, or colonoscopy).

Lung Cancer

Lung cancer is more common in people with HIV when compared with the general population (Table 2), so adherence to screening guidelines is important. The USPSTF recommends lung cancer screening annually in all adults aged 50 to 80 years with a 20 pack-year history of smoking who are current or former (within 15 years) smokers.[9] Screening is performed via a low-dose CT scan of the chest. The USPSTF recommends that screening be discontinued after 15 years without smoking, or if the individual develops a health problem that substantially limits life expectancy or the ability and willingness to have curative lung surgery.

Breast and Cervical Cancers

The IDSA recommends breast cancer screening at least every 2 years for individuals with HIV aged 50 to 75 years. They also recommend cervical cancer screening beginning at age 30 years, with a Papanicolaou (Pap)

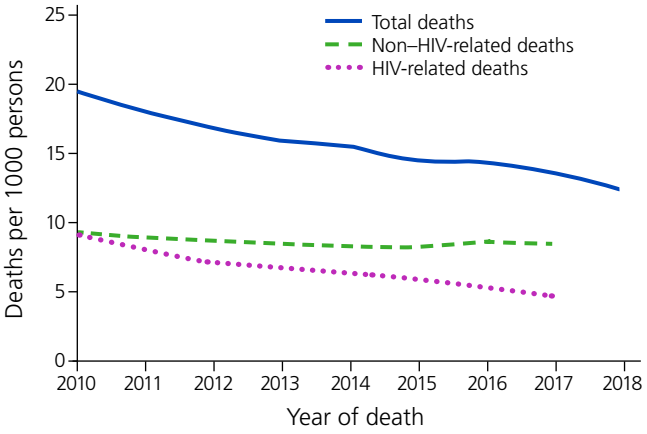

Figure 1. Age-adjusted rates of total, HIV-related, and non–HIV-related deaths among individuals aged 13 years and older with HIV from 2010 to 2018. Adapted from Bosh et al.[1]

Table 1. Common Comorbidities in Older Individuals With HIV

- Alcohol use
- Bipolar disorder
- Depression
- Diabetes
- Drug use
- Heart disease
- Hepatitis B
- Hepatitis C
- Human papillomavirus infection, syphilis, and other sexually transmitted infections
- Hyperlipidemia
- Hypertension
- Non–AIDS-related cancers
- Osteoporosis
- Tobacco use
- Tuberculosis

test at the time of HIV diagnosis and repeated annually, and then every 3 years if results are normal for 3 years consecutively.

Anal Cancer

People with HIV also have a markedly increased risk of anal cancer. This has led to many programs performing anal cytologic screening and high resolution anoscopy to treat anal dysplasia in an attempt to reduce the incidence of anal cancer. This approach has been recently validated with the results from the ANCHOR (Anal Cancer/HSIL Outcomes Research) study, which is funded by the National Institutes of Health (NIH) and is awaiting publication. This study will likely lead to stronger recommendations regarding anal cytologic screening.

Table 2. Relative Risk of Cancer in Individuals With HIV Compared With the General Population

Type of cancer	Standardized rate ratio (95% confidence interval)
Anal cancer	42.9 (34.1 – 53.3)
Vaginal cancer	21 (11.2 – 35.9)
Hodgkin lymphoma	14.7 (11.6 – 18.2)
Liver cancer	7.7 (5.7 – 10.1)
Lung cancer	3.3 (2.8 – 3.9)
Melanoma	2.6 (1.9 – 3.6)
Oropharyngeal cancer	2.6 (1.9 – 3.4)
Leukemia	2.5 (1.6 – 3.8)
Colorectal cancer	2.3 (1.8 – 2.9)
Renal cancer	1.8 (0.4 – 0.8)

Adapted from Patel et al.[7]

Table 3. Strategies for Cancer Screening and Prevention in an HIV Program

Type of cancer	Prevention strategy
Lung	Tobacco counseling, low-dose chest computed tomography scanning
Oral	Oral exam
Anal	Rectal exam, anal cytology
Prostate	Rectal exam, prostate-specific antigen testing discussion
Cervical	Pelvic exam, cervical cytology, human papillomavirus testing
Colorectal	Rectal exam, fecal occult blood testing, colonoscopy
Melanoma	Periodic skin exam, sun exposure counseling
Liver	Hepatitis B vaccine, hepatitis B and C treatment if applicable, abdominal ultrasound, computed tomography scan for surveillance

Immunizations

Immunizations are an important part of primary care for older adults with HIV. The Centers for Disease Control and Prevention (CDC) and the US Department of Health and Human Services provide guidance on appropriate dosing and frequency of available vaccines for individuals with HIV.[10,11] An immunization schedule by vaccine type and age group is provided in Table 4.

Influenza Vaccine

The high-dose influenza vaccine is more immunogenic in individuals aged 65 years and older[12] and in individuals with HIV.[13] Additionally, the high-dose influenza vaccine has been shown to provide better protection against laboratory-confirmed influenza than the standard-dose vaccine.[14] In a study that compared the effectiveness of the high-dose inluenza vaccine and the standard-dose vaccine in preventing death, the high-dose vaccine was more effective during the 2012 to 2013 influenza season; however, it was not more effective during the 2013 to 2014 season.[15]

COVID-19 Vaccine

Large cohort studies have reported a higher risk of mortality in people with HIV who develop COVID-19.[16-21] People with HIV often have other comorbidities associated with risk for severe COVID-19, including older age, obesity, cardiovascular disease, lung disease, hypertension, diabetes, and cancer. The CDC has recognized HIV infection as one of the medical conditions that increase risk for severe illness with COVID-19, and in 2021 the organization added a recommendation that everyone who is aged 12 years and older should receive the COVID-19 vaccine.[10] Recent CDC data in the general population indicated the Moderna vaccine to be better than the Pfizer vaccine, which is considered better than Johnson & Johnson, although we do not have comparative data in people with HIV.[22] Of note, people taking ART with well-controlled HIV were included in the phase III trials of the Moderna, Pfizer, and Johnson & Johnson vaccines, but complete data from these trials on immunogenicity, efficacy, and safety in people with HIV are not yet available. Although none of the COVID-19 vaccines currently available are live vaccines, people with HIV who

Table 4. HIV Adult Immunization Schedule by Vaccine and Age Group, December 2021*

Vaccine	Age			
	19-26 years	27-59 years	60-64 years	≥65 years
Influenza	1 dose annually			Consider high dose
Tetanus-diphtheria (Td)/ Tetanus, diphtheria, pertussis (Tdap)	Substitute Tdap for Td once, then Td booster every 10 years			
Varicella	2 doses 3 months apart (if CD4+ cell count ≥200/µL and no immunity to varicella)			
Human papillomavirus vaccine	3 doses (0, 2, and 6 months)	27-45 years: Discuss with patient		
Zoster recombinant	2 doses at 0 and 2-6 months			
Measles, mumps, and rubella (MMR)	1 or 2 doses (if CD4+ cell count ≥200/µL and no immunity)			
Pneumococcal conjugate vaccine 13 (PCV-13)	1 dose, preferably prior to pneumococcal polysaccharide vaccine 23 (PPSV-23)			
PPSV-23	2 doses 5 years apart, at least 8 weeks after PCV-13 vaccine			1 dose
Hepatitis A	2 or 3 doses, depending on the vaccine (0 months and at 6-18 months). Check hepatitis A virus antibodies after vaccination			
Hepatitis B	2 or 3 doses depending on the vaccine. Check hepatitis B surface antibodies after vaccination			
Meningococcal conjugate	If no prior vaccine, 2 doses of either MenACWY-D or MenACWY-CRM 8-12 weeks apart. Boost every 5 years			
COVID-19 vaccine	2-3 does of Pfizer, 2-3 doses of Moderna, or 1 dose of Johnson & Johnson followed by a homologous or heterologous booster at 6 months for mRNA vaccines and 2 months for Johnson & Johnson			

*After assessing age, presence of immunity, and CD4+ cell count, high-dose influenza vaccine is the author's recommendation. Live vaccines (eg, MMR, varicella, yellow fever) should not be given if CD4+ count is less than 200 cells/µL. The oral typhoid and live influenza vaccines are contraindicated in those with HIV.

Abbreviations: MenACWY, meningococcal serogroups A, C, W, Y.

Adapted, in part, from the Centers for Disease Control and Prevention.[10]

are taking ART and have CD4+ cell counts in normal ranges respond well to live vaccines, so there is potential for this to hold true with COVID-19 vaccines in the future.[11] People with HIV who have advanced disease and are immunocompromised may have a reduced response to vaccines but are also at greater risk for severe COVID-19. For patients with advanced HIV infection (eg, CD4<200 cells/µL) or untreated HIV infection, a third dose of the mRNA vaccine is recommended at least 28 days after the receipt of the first 2 doses of either of the mRNA vaccines. People with HIV are now eligible for boosters of the COVID-19 vaccine 6 months after the primary series of the mRNA vaccines or 2 months after the primary immunization with the Johnson & Johnson vaccine. The booster can either be the same vaccine previously received (a homologous booster) or a different COVID-19 vaccine (a heterologous booster).

Summary

Life expectancy continues to improve for people with HIV, but comorbidities continue to play a large role in morbidity and mortality, making primary care crucial for this population. Many of the USPSTF recommendations are particularly important for older people with HIV, including updated guidelines for lung and colorectal cancer screening. Immunizations are also important in older people with HIV, with the role of COVID-19 vaccination continuing to evolve as more data become available.

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