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Invited Reviews

Topics in Antiviral Medicine™

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Invited Review

Prevention and Treatment of Cardiovascular Disease in HIV: Practical Insights in an Evolving Field

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Abstract: *People with HIV (PWH) are at higher risk for cardiovascular disease (CVD) than people without HIV. As antiretroviral therapy (ART) and the natural history of HIV have evolved, so have the pathogenesis and manifestations of HIV-associated CVD. Epidemiologic data from several cohorts demonstrate that PWH have an approximately 50% higher risk than people without HIV for CVD, including, but not limited to, myocardial infarction and heart failure. This elevated CVD risk is not universal among PWH; for instance, the risk is higher among individuals with a history of sustained unsuppressed viremia, diminished CD4+ cell count recovery, or hepatitis C virus coinfection. Specific antiretroviral drugs may also associate differently with CVD risk. Regarding management, the recent REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) study results demonstrated a 35% relative risk reduction in atherosclerotic CVD for PWH at low to moderate predicted risk taking pitavastatin; this is a larger reduction than for comparable moderate-intensity statins in the general population. Whether these higher-than-expected reductions in CVD risk among PWH also extend to higher-intensity statins and into secondary prevention settings for people with existing CVD merits further study. Nonlipid approaches to CVD risk reduction in PWH—ranging from antithrombotic therapy to inflammation-modulating therapy—remain under active investigation. Results of these studies will provide essential information to further guide CVD management in PWH.*

Keywords: atherosclerosis, antiretroviral therapy, ART, cardiovascular disease, CVD, heart failure, HIV, inflammation, myocardial infarction, statin

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Epidemiology of HIV-Associated Cardiovascular Disease (CVD): Evolving Phenotypes and Risks

Myocardial Infarction

Several epidemiologic studies over the past decade in distinct cohorts demonstrated that people with HIV (PWH) have significantly higher multivariable-adjusted risk for myocardial infarction (MI) than people without HIV.[1,2] Among PWH, those with detectable viremia have higher risks for MI than those without detectable viremia, with an underlying biologic gradient noted. PWH with an HIV RNA level below 500 copies/mL had a 1.39-fold higher risk for MI than PWH without detectable viremia; for PWH with an HIV RNA level above 500 copies/mL, this risk was 1.75-fold higher. Lower current or nadir CD4+ cell counts—markers of immunologic progression and incomplete recovery related to HIV, often in concert with histories of sustained viremia—have likewise been consistently associated with elevated MI risk among PWH.[1] In a more recent study, a large cohort of patients with HIV matched with people without HIV was followed up from 2005 to 2020. This study demonstrated that PWH had a 1.6-fold higher risk for MI than people without HIV, and that the cumulative incidence of MI increased from the period of 2005 to 2009 to the period of 2010 to 2017.[3]

Heart Failure, Arrhythmia, and Sudden Cardiac Death

HIV is likewise associated with a 1.5- to 2-fold elevated risk for heart failure, a complex clinical syndrome arising from heterogeneous pathophysiologic mechanisms (Figure 1).[4,5] Data are less consistent for HIV and atrial fibrillation. Analyses of data from MACS (Multicenter AIDS Cohort Study) and from within the Northwestern Medicine system observed no association between HIV and atrial fibrillation, whereas a study performed in a University of California San Francisco cohort observed an increased HIV-related risk for atrial fibrillation.[6-8]

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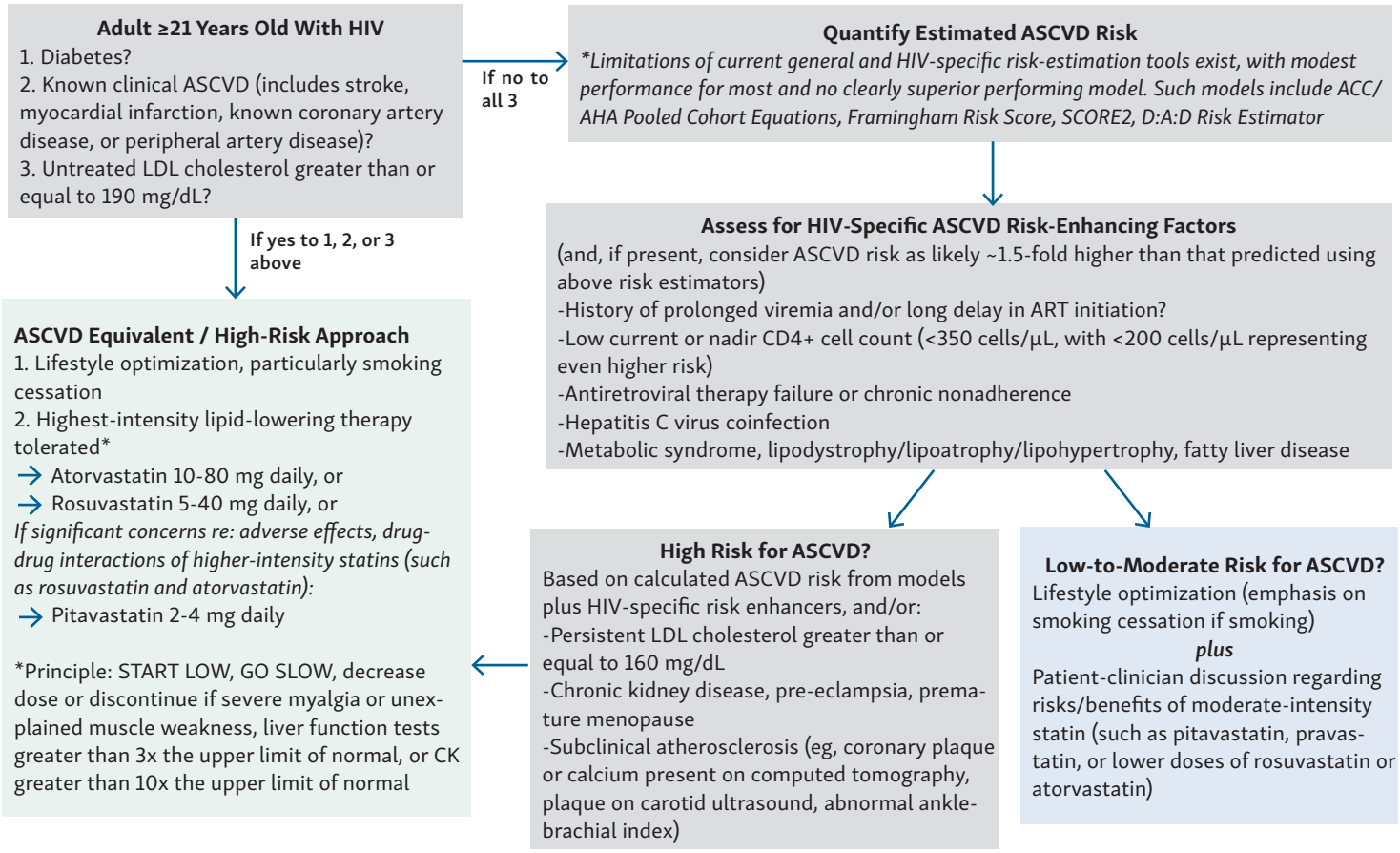

Figure 1. Approach to ASCVD Risk Assessment and Prevention for People with HIV. Adapted from Feinstein MJ, et al.[4] *Abbreviations: ACC/AHA = American College of Cardiology/American Heart Association; ART = antiretroviral therapy; ASCVD = atherosclerotic cardiovascular disease; CK = creatine kinase; LDL = low-density lipoprotein.*

Data on sudden cardiac death suggest a considerable HIV-associated increase in risk. In an autopsy study by the San Francisco medical examiner, PWH had nearly twice the incidence of sudden cardiac death as people without HIV.[9] Of those deaths among PWH, the mean CD4+ count was 475 cells/μL, and 79% were on antiretroviral therapy (ART), indicating that even in the setting of reasonable HIV control, underlying HIV-associated clinical factors or myocardial pathologies may confer particularly elevated sudden cardiac death risk.

The Role of Immune Dysregulation in HIV-Associated CVD

Innate and adaptive immune dysregulation resulting in persisting inflammation is a hallmark of HIV and is likewise implicated in the pathogenesis of an array of CVDs. In coronary artery disease, these inflammatory responses lead to plaque rupture, erosion, and eventual vasculopathies. In heart failure, they contribute to maladaptive responses to cell injury, microvascular dysfunction, and direct myocardial inflammatory infiltrates, each of which can contribute to systolic and diastolic dysfunction. This complex interplay between comorbidities, underlying immunologic abnormalities, and inflammatory bias can accelerate inflammation and ultimately result in CVD.[10-13] In homeostatic conditions, effectors of inflammation such as inflammatory monocytes and macrophages and inflammatory T-cell populations—initially activated in response to foreign antigens or neoantigens—are counterbalanced by immunoregulatory populations such as regulatory T cells and resident macrophages.[14] Over time, and in conditions of viral reactivation and persistence, "appropriate" inflammation transforms into a sustained inflammatory state, loss of self-tolerance, and amplified autoreactivity resulting in overt CVD; this is especially the case in HIV as a result of diminished regulatory immunity and vulnerability to additional pathogens due to microbial translocation and viral coinfection.[15] Persistent

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unresolving inflammation among PWH has also been associated with worse clinical outcomes. Indices of immune activation and elevated levels of inflammatory effectors, such as interleukin-6, soluble CD14, and chemokine C-X-C motif ligand 13, have been associated with decreased survival in PWH even with HIV control on ART.[16]

In addition to chronic inflammation, PWH have higher rates of traditional CVD risk factors, such as smoking, which is substantially more prevalent among PWH than among people without HIV. Dyslipidemia and metabolic dysfunction are also common in PWH as a result of complex factors ranging from viremia-associated inflammation to ART-associated lipid dysregulation.[17-20]

Heterogeneous Associations Between ART and CVD Risk

With the widespread adoption of ART, PWH have life expectancies similar to patients without HIV.[21] Given early concerns related to off-target ART effects, the SMART (Strategies for Management of Antiretroviral Therapy) study investigated HIV/AIDS-related endpoints, as well as non–AIDS-related endpoints, for PWH randomly assigned to either continuous or interrupted ART. Although continuous ART unsurprisingly reduced AIDS-related endpoints, it also conferred a lower risk for MI than interrupted ART.[22] This trial, coupled with subsequent trials such as START (Strategic Timing of Antiretroviral Treatment), helped confirm early and continuous ART as the standard of care for PWH.[23]

In this context, understanding the diverse cardiovascular effects of distinct antiretroviral drugs is of interest to aid in CVD risk stratification, prevention, and management among PWH. Protease inhibitors were originally associated with elevated MI risk,[24] although emerging data suggested against this being a class effect, but rather being related to more nuanced drug-specific effects. For instance, ritonavir-boosted darunavir is associated with elevated CVD risk among PWH, whereas ritonavir-boosted atazanavir may be associated with decreased CVD risk.[25,26]

The putative effects of nucleoside reverse transcriptase inhibitors (nRTIs) on CVD risk are likewise complex. Older nRTIs have been linked to mitochondrial damage leading to myopathy, neuropathy, and other subsequent toxic effects.[4,27] Regarding more contemporary nRTIs, tenofovir alafenamide (TAF) increased total cholesterol and low-density lipoprotein levels compared with tenofovir disoproxil fumarate (TDF), but no significant difference in overall CVD risk was observed between the 2 drugs.[28,29] In a separate analysis, switching from TDF to TAF led to marked weight gain, suggesting an independent effect of TAF on metabolic health. Yet, the net CVD effect largely remains uncertain.[30]

In longer-term follow-up cohort studies, abacavir increased risk for CVD overall, and some studies specifically showed increased MI risk compared with non-abacavir ART.[31,32] However, in shorter-term clinical trials, there was no observable effect on CVD risk.[33] This discrepancy may relate to the younger ages of patients in these clinical trials, precluding sufficiently high absolute event numbers to disentangle abacavir-associated CVD risk in younger, lower-risk cohorts.[21,31-33]

Although integrase strand transfer inhibitors (InSTIs) have a well-established risk of weight gain, the net effect on CVD is uncertain, and data regarding long-term CVD risk are limited—particularly compared with other ART regimens.[34,35]

CVD Risk Stratification and Treatment: Understanding Net Clinical Benefit

Although PWH have elevated overall CVD risk compared with those without HIV, these HIV-associated risks differ depending on the presence or absence of underlying HIV-associated risk enhancers, such as sustained viremia and low CD4+ cell count. Accordingly, it is important to avoid adopting a "one size fits all" model for PWH and CVD risk, and instead to incorporate HIV-specific risk enhancers in risk stratification and optimal CVD prevention strategies for PWH. As discussed above, variability in immune progression and degree of recovery, viremic exposure, ART (historic and current), along with traditional risk factors ranging from smoking to dyslipidemia are all associated with distinct CVD risk profiles among PWH.

It is important to avoid adopting a "one size fits all" model for PWH and CVD risk, and instead to incorporate HIV-specific risk enhancers in prevention strategies

A limited but growing body of literature exists to inform approaches to CVD prevention and treatment in

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PWH. In general, hydroxy-methyl-glutaryl coenzyme A reductase inhibitors (ie, statins) reduce atherosclerotic CVD (ASCVD) risk by 20% to 25%, but whether this risk reduction differs in PWH remained largely unknown until recently. The recently published results of the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) study of more than 7000 PWH with low to moderate risk for ASCVD demonstrated that the risk-reducing effects of statins in PWH may be even higher than in the general population.[36] In REPRIEVE, PWH randomly assigned to pitavastatin 4 mg daily compared with those assigned a placebo experienced a 35% relative reduction in risk for major adverse cardiovascular events (hazard ratio, 0.65; 95% CI, 0.48-0.90), with some increase in adverse events including muscle symptoms (2.3% of PWH on pitavastatin vs 1.4% on placebo) and diabetes mellitus (5.3% vs 4.0%, respectively).

Net Clinical Benefit and Risk-Informed Clinical Decision-Making

A crucial concept informing the benefits and risks of statin therapy in PWH, as in the general population, is net clinical benefit. Simply put, net clinical benefit reflects the absolute benefit minus absolute risk of a particular therapy or intervention.[37] Therefore, assuming somewhat similar relative risk reductions across clinical strata from statins,[38,39] higher absolute risk means higher potential benefit of therapy. Thus, if there is a uniform ~35% relative risk reduction from statins, a patient with a 50% CVD risk over 10 years would have a 17.5% absolute reduction in CVD risk by initiating a statin. Meanwhile, a patient with a 5% CVD risk over 10 years would experience a 1.75% absolute reduction in CVD risk by initiating a statin. Taking this into account, the benefit of therapy when weighed against potential harms is clearly favorable for the individual at high ASCVD risk, but less obviously favorable for the person with low ASCVD risk. Data from the REPRIEVE study suggest a somewhat higher than expected ASCVD risk reduction with a moderate-intensity statin in PWH, raising the possibility that the benefit/risk tradeoff of statins in PWH is more favorable than in the general population, supporting a somewhat lower threshold for statin initiation.

These considerations highlight the need to consider individual ASCVD risk when discussing ASCVD prevention approaches in PWH. Certainly, PWH with existing clinical ASCVD should be treated aggressively with lipid-lowering therapy as is done in the general population, particularly given higher HIV-associated ASCVD risks and emerging data suggesting PWH may derive greater than expected benefit from statin therapy. For those without preexisting ASCVD, a reasonable approach is to derive a CVD risk estimate—whether using the Framingham Risk Score, the ASCVD Pooled Cohort Equations, the Systematic Coronary Risk Evaluation Score 2 (SCORE2), or another tool—with the understanding that many such models tend to underpredict risk for PWH,[40-42] and that HIV-specific models do not yet dramatically improve discrimination or calibration.[43]

Following such an assessment of ASCVD risk, considering unique patient-level factors (eg, history of sustained viremia, low nadir CD4+ cell count, and coinfection with hepatitis C virus) is essential to inform clinical decision-making. In other words, if a person with HIV has a predicted 10% 10-year ASCVD risk based on the Pooled Cohort Equations but also a nadir CD4+ count below 200 cells/μL and evidence of incomplete immune recovery, this individual likely has a somewhat higher ASCVD risk than inferred by the risk prediction tool alone. In such cases, extrapolation of epidemiologic data, an inexact science but one that leverages what is currently available,[44] would suggest this 10% 10-year ASCVD risk may be closer to 15%.

Although clearly imperfect, such general risk assessments can inform patient-clinician discussions regarding how likely an individual patient is to benefit from, rather than be harmed by, a therapeutic intervention such as statin treatment. Alternatively, adjunctive CVD risk-reducing interventions such as smoking cessation and pursuing a heart-healthy diet have a high potential for impact without similar adverse effect profiles.

New Horizons in CVD Prevention and Therapy for PWH

In addition to lipid-lowering therapy, antiplatelet therapy is an essential component of secondary prevention of ASCVD events, such as MI, though the role of antiplatelet therapy in primary prevention is less clear.[45] Small mechanistic studies suggest that the most common antiplatelet therapy, aspirin, may have somewhat reduced therapeutic effects in PWH. In a randomized clinical trial comparing daily aspirin with placebo in PWH on ART, researchers found that aspirin did not impact markers of immune activation or endothelial dysfunction.[46] In another trial studying clopidogrel and aspirin, clopidogrel reduced platelet activation and platelet-induced endothelial inflammation, but aspirin did not.[47] More clinical data are needed to inform the risks and benefits of antiplatelet therapy for primary

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prevention in PWH. These results suggest clopidogrel may be a more desirable alternative for the secondary prevention of ASCVD in PWH; however, considerably more clinical data are needed to assess this.

Apart from lipid-lowering and antithrombotic therapy for ASCVD risk reduction, there is also considerable interest in modulation of inflammation to reduce risk for ASCVD among PWH. Complicating matters is the complex immunology of chronic HIV, whereby some

Small mechanistic studies suggest that the most common antiplatelet therapy, aspirin, may have somewhat reduced therapeutic effects in people with HIV

interventions (eg, the inhibition of monocyte activation and the myeloid inflammation common in treated PWH[48]) offer theoretical promise, and rigorous larger-scale studies are needed to evaluate various potential off-target effects. Likewise, inflammation-targeted therapies such as canakinumab have demonstrated a reduction of inflammation in PWH,[49] although the net clinical effects of such therapies for PWH remain unclear. Colchicine was recently approved by the US Food and Drug Administration for ASCVD risk reduction in the general population, but the potential role in PWH remains to be seen, given colchicine's effects as a substrate for cytochrome P450 3A4 (CYP3A4) with potentially serious drug-drug interactions, particularly in PWH on ART.

Future approaches will also need to consider the prevention and treatment of heart failure and arrhythmia, and the prevention of sudden cardiac death. Few data from large-scale clinical trials exist—apart from observational studies of incidence—to inform optimal approaches in PWH. In the interim, diagnosis and treatment paralleling that in the general population is reasonable, with a particular focus on underlying risk factors (eg, hypertension, metabolic dysregulation, and substance and stimulant use) for these conditions. In addition, practitioners are encouraged to maintain a high index of suspicion for early evidence of forms of CVD in their patients with HIV to ensure appropriate and prompt diagnosis, treatment, and referral to specialty care as needed.

Conclusion

PWH are at elevated risk for atherosclerotic disease, thrombosis, and cardiac dysfunction. HIV sequelae such as chronic inflammation and immune activation persist despite effective ART and appear to play a pivotal role in the pathogenesis of diverse forms of CVD in PWH. Recent results from the REPRIEVE trial indicate a potentially greater-than-expected benefit of statins in PWH. Nevertheless, considerably more mechanistic and clinical research is needed to optimize the prevention and treatment of CVD in PWH.

This article is based on a presentation by Dr Matthew J. Feinstein on May 5, 2023. The initial presentation is available as a webcast here: Managing Cardiovascular Disease in People With HIV.

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Invited Review

Doxycycline Postexposure Prophylaxis for Prevention of Sexually Transmitted Infections

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Abstract: *Doxycycline postexposure prophylaxis (doxy-PEP) is a novel strategy now demonstrated in several clinical trials to dramatically reduce incidence rates of gonorrhea, chlamydia, and syphilis in some key populations at high risk of sexually transmitted infections. Even so, much remains unknown about the long-term consequences of doxy-PEP, and several concerns, including the potential for the development of antibiotic resistance and disturbances to the microbiome, balance the benefits. This review highlights the history of antibiotic prophylaxis for sexually transmitted infections, and the rationale, current evidence, and future directions for doxy-PEP.*

Keywords: STI, prevention, antibiotic, resistance, prophylaxis, doxy-PEP, sexual health, sexually transmitted infection, doxycycline

Introduction

More than 370 million curable bacterial sexually transmitted infections (STIs) were diagnosed globally in 2020, with increasing rates in many countries.[1,2] The Centers for Disease Control and Prevention (CDC) reported nearly 2 million cases of gonorrhea, chlamydia, and primary and secondary syphilis in 2021 in the US.[3] The health burden associated with bacterial STIs can be substantial, including reduced fertility in women, adverse perinatal outcomes, and increased risk of HIV acquisition. Complications of syphilis, particularly neurologic, otic, and ocular, may lead to irreversible organ damage and decreased quality of life. Even more concerning, the US and other countries have seen dramatic increases in the past several years in rates of syphilis in pregnancy and in rates of congenital syphilis, which are associated with the risk of stillbirth and severe neonatal morbidity, including congenital disabilities and developmental delays. Syphilis in pregnancy and congenital syphilis are preventable with timely diagnosis and treatment.

Men who have sex with men (MSM) and transgender women (TGW)—particularly those from minoritized racial or ethnic groups—experience the highest burden of STI diagnoses in the US, and syphilis cases are increasing among heterosexual cisgender women and men.[3] Campaigns to test, treat, and raise awareness of STIs have been a pillar of the public health response, but it remains unclear if these campaigns have substantially altered the trajectory of STI incidence over the past decade. The CDC and the US Department of Health and Human Services have collaborated to develop a multiyear federal plan for STI control that urgently calls for accelerated progress in STI research and innovation by 2025.[4]

Doxy-PEP is an evidence-based prevention intervention that involves a person at risk of bacterial STI (ie, gonorrhea, chlamydia, or syphilis) taking a single dose of doxycycline 200 mg after condomless sex to proactively prevent infection

Doxycycline postexposure prophylaxis (doxy-PEP) is an evidence-based prevention intervention that involves a person at risk of bacterial STI (ie, gonorrhea, chlamydia, or syphilis) taking a single dose of doxycycline 200 mg after condomless sex to proactively

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prevent infection. Doxy-PEP is an innovative intervention with high efficacy among MSM and TGW who have a history of STI in the past year, and implementation work is ongoing to learn how to deliver doxy-PEP as part of a comprehensive package of options for STI prevention. In this review, we discuss the history of prophylaxis for STIs, rationale, current evidence, known and unknown benefits and risks, and future directions for doxy-PEP.

History of Prophylaxis for STIs

Antimicrobial prophylaxis against bacterial STIs predates the advent of modern antibiotics, including doxycycline. During and shortly after World War I, military troops in Paris who visited local sex workers were mandated to attend treatment stations where attendants instilled silver proteinate suspensions into the urethra and bathed the genitals in a mercury chloride solution. The intervention was reported to be highly effective in those for whom treatment was verified, with an estimated 2571 cases of gonorrhea, chancroid, and syphilis prevented.[5] In the 1940s, soldiers receiving sulfathiazole as periexposure prophylaxis saw significant reductions in the incidence of gonorrhea and chancroid,[6] and penicillin proved effective for the prevention of gonorrhea.[7] By the next decade, penicillin prophylaxis was widely used in all US ship fleets stationed in the Pacific.[8] In the 1970s, minocycline—a longer-acting, second-generation tetracycline—provided partial prophylactic protection against gonorrhea for crew on US naval ships in the western Pacific.[9] However, there was concern at the time that the use of minocycline prophylaxis selected for resistant gonococci, which would substantially limit its broader effectiveness for STI control. Indeed, *Neisseria gonorrhoeae* developed resistance over time to several common oral antibiotics,[10] which in turn diminished enthusiasm for the prospect of antimicrobial prophylaxis for bacterial STIs.

Doxy-PEP for STIs is a user-driven intervention that may be acceptable and prioritized for persons who cannot or choose not to use condoms

However, as rates of all bacterial STIs began to rise in the mid-2010s, interest in the use of prophylaxis resurged because of the increasing utilization and success of antiretroviral therapy (ART) and preexposure prophylaxis (PrEP) for HIV prevention. Reports of condomless sex have increased over time for gay, bisexual, and other MSM, likely reflecting a greater temporal trend that preceded and now has continued during HIV PrEP rollout.[11,12]

Modern Doxy-PEP Studies

Doxy-PEP for STIs is a user-driven intervention that may be acceptable and prioritized for persons who cannot or choose not to use condoms. Table 1 details key findings from several seminal trials that have evaluated or proven that doxy-PEP substantially reduces risk of bacterial STIs in MSM and TGW.

An early pilot trial randomly assigned 30 MSM and TGW with HIV and a history of more than 1 episode of syphilis since their HIV diagnosis to use daily doxycycline prophylaxis or receive incentive payments for testing negative for STI at follow-up visits. Although the intervention was effective at reducing incidence of all 3 bacterial STIs (odds ratio [OR], 0.27; 95% CI, 0.09-0.83), the authors recognized that daily use of an antibiotic was unlikely to be feasible or desirable on a large scale.[13] Notwithstanding, doxycycline remained a candidate drug of interest, as it is commonly used, safe, well tolerated, and highly effective against *Chlamydia trachomatis* and *Treponema pallidum* subsp. *pallidum*, the causative agent of syphilis. To date, there has never been a report of doxycycline resistance in either bacterium. In contrast, doxycycline currently has variable activity against gonorrhea; intermediate and high-level resistance is widespread in sub-Saharan Africa, ranges from 20% to 25% in the US, and is greater than 50% in parts of Europe.[14-17]

Based on data from a proof-of-concept pilot in MSM and TGW with HIV, France's National Agency for Research on AIDS and Viral Hepatitis (ARNS) launched the first major trial to evaluate doxy-PEP within the parent IPERGAY (Intervention Préventive de l'Exposition aux Risques avec et pour les Gays) study, which sought to examine the use of event-driven PrEP among MSM who were HIV negative in France.[18] A total of 232 participants were randomly assigned 1:1 to receive either open-label doxy-PEP taken once orally as 200 mg within 24 to 72 hours after condomless sex (with a maximum of 3 doses per week) or no doxy-PEP. The participants used a median of 680 mg of doxycycline per month. Among participants in the intervention arm, use of doxy-PEP was associated with a 47% relative risk

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Table 1. Evidence From Randomized Clinical Trials for Doxy-PEP, 2015 to 2023

Study (location, date)	Participating population		STI rate or outcome		Relative risk reduction (95% CI or *P*)	Absolute risk reduction	Comments
			Doxy-PEP	No doxy-PEP			
IPERGAY* (France, 2015-2016)	232 MSM on HIV PrEP		37.7 per 100 person-years	69.7 per 100 person-years	47%* (15-67)	32 per 100 person-years	Signal toward reduction of gonorrhea incidence at anogenital sites
DoxyPEP (US, 2020-2022)	501 MSM and TGW with bacterial STIs in prior 12 months	PWH (n = 174)	11.8% per quarter	30.5% per quarter	62% (40-76)	18.7% per quarter	Risk reduction seen for all 3 bacterial STIs
		PrEP users (n = 327)	10.7% per quarter	31.9% per quarter	66% (54-76)	21.2% per quarter	
DOXYVAC* (France, 2021-2022)	502 MSM on HIV PrEP with a bacterial STI in prior 12 months		5.6 per 100 person-years	35.4 per 100 person-years	84% (70-92)	30 per 100 person-years	Effect for gonorrhea found to be independent of 4CMenB vaccine
dPEP (Kenya, 2020-2022)	449 cisgender women on PrEP		50 total chlamydia/ gonorrhea infections	59 total chlamydia/ gonorrhea infections	12% (*P* = .51)	9 total infections at 12 months	Noneficacy likely due to suboptimal adherence

Abbreviations: doxy-PEP, doxycycline postexposure prophylaxis; DoxyPEP, Evaluation of Doxycycline Post-Exposure Prophylaxis to Reduce Sexually Transmitted Infections in PrEP Users and HIV-infected Men Who Have Sex With Men; DOXYVAC, Combined Prevention of Sexually Transmitted Infections in Men Who Have Sex With Men and Using Oral Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Pre-Exposure Prophylaxis; dPEP (Kenya), doxycycline postexposure prophylaxis trial (Kenya), IPERGAY, Intervention Préventive de l'Exposition aux Risques avec et pour les Gays; MSM, men who have sex with men; PrEP, preexposure prophylaxis; PWH, people with HIV; STI, sexually transmitted infection; TGW, transgender women.

*Risk reduction estimate is for chlamydia and syphilis only.

reduction in time to first incident STI (syphilis or chlamydia), and an estimated absolute risk reduction (ARR) of 0.3 STI episodes per person-year. Efficacy was similar for reductions in the occurrence of a first episode of chlamydia (hazard ratio [HR], 0.30; 95% CI, 0.13-0.70; *P* = .006) and of syphilis (HR, 0.27; 95% CI, 0.07-0.98; *P* = .047). There was no significant difference between groups in time to first episode of gonorrhea (HR, 0.83; 95% CI, 0.47-1.47; *P* = .52). Although doxy-PEP did not significantly reduce overall gonorrhea incidence, there was a trend toward efficacy for anogenital gonorrhea; among doxy-PEP users, fewer polymerase chain reaction (PCR) tests were positive for gonorrhea from urine and anal swabs than from pharyngeal swabs.

Based on the promising findings of this IPERGAY substudy, investigators in Seattle and San Francisco initiated a larger randomized clinical trial called DoxyPEP (Evaluation of Doxycycline Post-Exposure Prophylaxis to Reduce Sexually Transmitted Infections in PrEP Users and HIV-Infected Men Who Have Sex With Men) to understand if taking doxy-PEP would decrease bacterial STI incidence in US-based populations of persons without HIV who typically use daily PrEP and of persons with HIV (PWH), as a potential HIV status-neutral approach for STI prevention.[16] An important objective was to explore the impact of intermittent doxycycline use on antibiotic resistance in the bacteria that cause STIs and other infections. The DoxyPEP trial recruited persons assigned male sex at birth (MSM or TGW) with a history of a bacterial STI and condomless sex with a man in the past year. Investigators designed the study to have sufficient statistical power to assess efficacy separately in the 2 cohorts of PWH and those taking PrEP.

Participants were randomly assigned to receive open-label doxy-PEP (doxycycline 200 mg once by mouth within 24-72 hours after condomless sex, and up to a maximum of 1 dose per day) or standard of care (quarterly STI testing with treatment per existing clinical protocols).[16] Over the course of the study, STI incidence in the control group reached 30% per quarter, which was substantially higher than the anticipated 10%. There was a single efficacy review by the data and safety monitoring board after a median of 9 months of follow-up, and further enrollment into the standard-of-care arm was halted early for high efficacy based on exceeding the prespecified interim efficacy bounds. In primary analyses, the researchers found that doxy-PEP led to a significant 65% relative risk reduction for all 3 bacterial STIs at 12 months, including symptomatic and asymptomatic infections. The relative risk

reduction differed slightly between the cohorts on PrEP and PWH for gonorrhea (55% vs 57%, respectively), chlamydia (88% vs 74%, respectively), and syphilis (87% vs 77%, respectively). In contrast to the earlier French study, the DoxyPEP trial saw an absolute risk reduction in STI of approximately 20% per quarter.

The ARNS followed the IPERGAY substudy with DOXYVAC (Combined Prevention of Sexually Transmitted Infections [STIs] in Men Who Have Sex With Men and Using Oral Tenofovir Disoproxil Fumarate/Emtricitabine [TDF/FTC] for HIV Pre-Exposure Prophylaxis [PrEP]), a trial that used a factorial design to randomly assign MSM on PrEP for at least 6 months with a history of bacterial STI in the prior year to receive open-label doxy-PEP or no doxycycline in combination with the meningococcal type B (4CMenB) vaccine or no vaccine (as a preventive intervention for gonorrhea).[19] After results from the DoxyPEP trial were released, the data and safety monitoring board conducted an interim review of the results, and this trial was also halted early for efficacy. Despite baseline gonococcal resistance to tetracyclines being greater than 50% in France and the research team not expecting to find a significant effect on gonorrhea based on the IPERGAY substudy results, the DOXYVAC interim review found reductions in gonorrhea (51% risk reduction; 95% CI, 0.32-0.76; P = .001) and in chlamydia and syphilis (84% relative risk reduction; 95% CI, 0.08-0.30; P < .0001).[19] Similar to the initial substudy, use of doxy-PEP was associated with an approximate ARR of 0.3 bacterial STI episodes per person-year. The findings about borderline efficacy of the 4CMenB vaccine, which were presented at the Conference on Retroviruses and Opportunistic Infections (CROI) in 2023, have been retracted and are being audited; the final results are pending.

The dPEP Kenya (doxy-PEP Kenya) study randomly assigned cisgender women taking PrEP to receive open-label doxycycline or standard of care (quarterly STI testing and treatment).[20] The primary study outcome was a reduction in chlamydia incidence given that nearly 100% of *Neisseria gonorrhoeae* isolates in Kenya harbor the tet(M) plasmid that confers high-level tetracycline resistance, and that syphilis is rare in Kenya, so achieving enough syphilis endpoints for analysis was not feasible. Despite an overall STI incidence of 27 per 100 person-years, the study found no statistical difference in chlamydia incidence between the 2 groups. Results did not change for STI incidence when analyzed among subgroups stratified by age, hormonal contraception use, transactional sex, and whether an STI was present at baseline. When preliminary results were presented at the 2023 CROI meeting, the study investigators noted that there were no new cases of HIV diagnosed in the trial, suggesting at least moderate adherence to PrEP and presumably also to doxy-PEP.[20] However, at the 2023 STI & HIV World Congress, investigators presented new information on the question of behavior versus biology as a primary contributor to the negative study results.[21] Among a random subset of 50 participants in the doxy-PEP arm, only 56% (28 of 50) had doxycycline levels detected in hair at least once, and only 29% (58 of 200) of all quarterly visits had detectable drug levels in hair.[21] This strongly suggests that low adherence to doxy-PEP was the most likely cause of the null effect seen for STI prevention in the dPEP Kenya trial.

Although yet unproven, it is plausible that the risk reduction from doxy-PEP also has the potential to decrease STI rates at the population level

Haaland et al show that doxycycline levels in vaginal secretions reach levels 5- to 20-times higher than the minimum inhibitory concentration (MIC) for *Treponema pallidum*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* after a single oral dose, and that these levels persist above the MIC at which 90% of the isolates for the species were inhibited for 48 hours for *Neisseria gonorrhoeae*, for 72 hours for *Treponema pallidum*, and for 96 hours for *Chlamydia trachomatis*.[22] Thus, the pharmacokinetic-pharmacodynamic study establishes biologic plausibility, supporting that doxy-PEP may still be a useful intervention for cisgender women. Future studies will need to corroborate efficacy in this key population and may explore whether adherence could improve with different regimens, such as 2 fixed doses of doxycycline per week.

Taken together, the 3 trials (IPERGAY, DoxyPEP, and DOXYVAC) have provided consistent and robust evidence of the efficacy of doxy-PEP. Its primary benefit is a substantial reduction in risk of bacterial STIs in certain MSM and TGW, regardless of HIV status, who are at high risk of repeat infection based on their history of a recent STI. The number needed to treat to prevent 1 STI from the US DoxyPEP trial was approximately 5. Although yet unproven, it is plausible that the risk reduction

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from doxy-PEP also has the potential to decrease STI rates at the population level. Although doxy-PEP was not found to be efficacious in cisgender women in the dPEP Kenya study, efficacy seems to be tied to adherence, which was also the case with other prevention interventions like PrEP. If we can better understand how to support adherence, doxy-PEP may be useful for cisgender women in the future.

Beyond the established benefit of STI risk reduction, qualitative data from the DoxyPEP trial suggest that doxy-PEP is associated with increased sexual pleasure and peace of mind, decreased stigma about receiving and disclosing STI diagnoses, and the facilitation of positive discussions about sexual health with partners.[23] Doxycycline is an inexpensive, safe, and well-tolerated medication, and acceptability and adherence were high in clinical trials.[16,18-20] Ceftriaxone use was reduced by 50%,[16] and doxy-PEP as a strategy is associated with much lower use of antibiotics than daily oral tenofovir-based PrEP for HIV prevention (~50 days vs 365 days, respectively). Based on data from the trials, the average doxy-PEP user might take an approximate 43 extra days of antibiotics over 12 months to avert 1.4 STI episodes per year; of these averted infections, 50% are expected to be gonorrhea, 43% chlamydia, and 7% syphilis.[24] For these and other reasons, interest and demand for doxy-PEP in real-world settings are high.[25-27]

Evaluating Doxy-PEP Efficacy

The benefits of doxy-PEP must be balanced with several potential risks and unknowns. First, most STIs prevented in the clinical trials were asymptomatic. It is still uncertain whether doxy-PEP as an intervention will prevent morbidity from STIs. Of the 3 bacterial STIs that were reduced by doxy-PEP, syphilis has the highest risk of complications in MSM and TGW. The efficacy of doxy-PEP was very high against syphilis, as evidenced by the fact that very few incident diagnoses were observed in the doxy-PEP arms; it is anticipated that doxy-PEP would reduce syphilis morbidity, but the trials were stopped after a median of 9 months, limiting the opportunity to explore this further. It remains unknown if doxy-PEP will reduce the incidence of infectious or complicated syphilis, gonorrhea, or chlamydia at a population level. A recent analysis of doxy-PEP implementation scenarios at the Fenway Clinic in Boston, Massachusetts, demonstrated the efficiencies and trade-offs of different eligibility criteria, estimating that 39% of bacterial STIs could be averted if MSM and TGW with a history of recent STI were offered doxy-PEP.[28] If supplied with local and regional STI incidence data from sites implementing doxy-PEP, mathematical models could estimate its broader impact and inform how use in populations could maximize efficiencies while minimizing unnecessary antibiotic exposure. Implementation studies are being planned to examine the real-world uptake of doxy-PEP and will be crucial in helping define its impact on STI incidence within geographic areas and key populations.

One potential tradeoff of doxy-PEP use is the emergence of resistance in STI pathogens. *Neisseria gonorrhoeae* develops resistance to tetracyclines through numerous mechanisms, including efflux pumps and ribosomal subunit binding. If doxy-PEP uptake increases such that use becomes widespread, its effectiveness for gonorrhea prevention could diminish quickly as tetracycline-resistant strains predominate within the population. Mathematical modeling suggests this could occur within 10 years depending on the level of doxy-PEP uptake and coverage, and tetracycline resistance in *Neisseria gonorrhoeae* within the populations that use it.[29] Although tetracycline resistance (and by extension resistance to doxycycline) in *Chlamydia trachomatis* and *Treponema pallidum* subsp *pallidum* has never been reported and is thought to be highly unlikely to occur, it is theoretically possible. A single point mutation produced widespread macrolide resistance in *Treponema pallidum* subsp *pallidum*,[30] and some *Chlamydia suis* strains in animals are resistant to tetracycline, raising concern for possible horizontal transfer into species that affect humans.[31] It remains to be seen how or if intermittent doxycycline use will impact our ability to diagnose *Treponema pallidum* subsp *pallidum* using current serologic tests, as doxy-PEP could be considered subtherapeutic treatment for both infections.

Based on in vitro experiments and observational data, many experts have raised concerns that doxy-PEP could also increase the risk of resistance in bystander bacteria like *Staphylococcus aureus*, *Streptococcus pneumoniae*, and gram-negative bacteria in the gut. This could result in the development of tetracycline-resistant bacterial strains that cause severe infections with fewer ambulatory treatment options. Investigators attempted to monitor for antimicrobial resistance (AMR) in 2 of the doxy-PEP trials. Among DOXYVAC participants, there was a slight absolute increase in methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from pharyngeal swabs at month 12 compared with baseline in the doxy-PEP and the control arms (8.1% and 3.9%, respectively).[19] The DoxyPEP trial found a 14% absolute

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decrease ($P < .01$) in *Staphylococcus aureus* colonization in the doxy-PEP arm;[32] among those colonized with *Staphylococcus aureus* in the doxy-PEP arm, there was an 8% absolute increase in doxycycline resistance compared with baseline.[16]

To examine potential effects on the gut microbiome, the DOXYVAC trial collected serial anal swabs to test for extended-spectrum beta-lactamase *Escherichia coli* and found that rates for the doxy-PEP and control arms increased from 31.4% to 40% and from 32.1% to 35.6%, respectively, at month 12.[19] Characterizing and quantifying the breadth and extent of potential changes in the microbiome among doxy-PEP users and in the general population will be complex and challenging; however, this will be a crucial area of interest for future implementation studies.

Epidemiologic (epi) treatment or preemptive treatment of persons exposed to bacterial STIs is common practice in the US, and the CDC estimates that epi treatment could represent nearly 5% of all doses of overused antibiotics nationwide.[33] One study that sought to quantify the proportion of MSM who are overtreated after contact with gonorrhea or chlamydia found that 65% of contacts ultimately test negative after an exposure and thus receive empiric antibiotics unnecessarily.[34] Thus, if we take the fact that only one-third of MSM who are exposed to gonorrhea or chlamydia will test positive and combine this with the relative risk reduction for gonorrhea (56%) and chlamydia (81%) from the US Doxy-PEP trial, it can be estimated that for persons taking doxy-PEP as directed, the likelihood of testing positive is approximately 15% after an exposure to gonorrhea (ie, 0.33 x 0.44) and 6.5% after an exposure to chlamydia (ie, 0.33 x 0.12). These estimates would suggest that, for asymptomatic persons who are adherent to highly effective doxy-PEP and who have known gonorrhea or chlamydia exposures, the most prudent approach from an antimicrobial stewardship perspective may be to test only and to defer empiric treatment. Current standards of care are unlikely to change for the management of contacts to syphilis, who should continue to be tested and to be empirically treated due to risk of forward transmission and the potential lag in diagnosis associated with current serologic tests.

Implementation of Doxy-PEP

Implementation of doxy-PEP in communities began shortly after initial results from the DoxyPEP study were reported at the 2022 International AIDS Conference, followed by the DOXYVAC study at CROI 2023. The San Francisco Department of Public Health was the first to release recommendations in October 2022, and since then, more than 2500 early adopters have been initiated on doxy-PEP (H. Scott, MD, MPH, email, August 8, 2023). A retrospective analysis of 828 patients initiated on doxy-PEP at the San Francisco City Clinic between November 2022 and June 2023 found that uptake among MSM and TGW was 74% for those with 1 or more STI and 1 or more partner in the past year, and 60% for those with 2 or more partners but no STIs in the past year.[35] The main predictor of doxy-PEP uptake was having a higher number of sex partners, suggesting the intervention can successfully be targeted to those who might most benefit from it.

The choice to prescribe doxy-PEP should result from a shared decision-making process between the health care practitioner and the patient

Other public health jurisdictions in the US have now released guidelines, including several counties in California, the California Department of Public Health, and Public Health Seattle & King County in Washington.[24,36] Most jurisdictions have focused their guidance on the populations studied in the clinical trials, and others have elected to expand their recommendations more broadly. Outside of these local provisional recommendations, official guidelines from national health organizations remain limited. The CDC recently released a set of guidelines that underwent a 45-day period of public review (ending November 16, 2023)[37,38] and the Australasian Society for HIV, Viral Hepatitis, and Sexual Health Medicine have acknowledged doxy-PEP,[39] and their guidelines based on expert consensus and review of current evidence are forthcoming. The International Antiviral Society–USA recommends considering doxy-PEP on a case-by-case basis.[40] Public Health England and the British Association for Sexual Health and HIV currently do not endorse doxy-PEP due to concerns about AMR,[41] but there may be an updated statement to come. The Australian Sexual Health Medicine Association recently published a consensus statement about the evidence for and implementation of doxy-PEP for MSM with an emphasis on offering it to MSM with recent syphilis or

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Table 2. Number and Frequency of Reported Laboratory Abnormalities, Adverse Events, and Other Outcomes From Clinical Doxy-PEP Trials

Randomized clinical trial	Laboratory abnormalities	Adverse events	Discontinuations	Other outcomes
IPERGAY	Grade 4 transaminitis due to acute hepatitis C infection (n = 3)	Drug-related gastrointestinal adverse events (n = 29); more common in PEP group (*P* = .03)	29 (26%) for all reasons; 8 (7%) due to drug-related adverse events	No difference between groups in serious adverse events
DoxyPEP	Grade 2 transaminitis (n = 1)	Grade 3 diarrhea or headache (n = 5)	2%	No weight gain compared to standard of care
DOXYVAC	None as of July 2023	Gastrointestinal adverse events (n = 2)	3 (0.9%) due to gastrointestinal adverse events or fear of adverse events	Further data pending final review
dPEP (Kenya)	Not collected	7% (gastrointestinal side effects)	5%	Social harms related to PEP use among 3 participants

Abbreviations: DoxyPEP, Evaluation of Doxycycline Post-Exposure Prophylaxis to Reduce Sexually Transmitted Infections in PrEP Users and HIV-Infected Men Who Have Sex With Men; DOXYVAC, Combined Prevention of Sexually Transmitted Infections in Men Who Have Sex With Men and Using Oral Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Pre-Exposure Prophylaxis; dPEP (Kenya), doxycycline postexposure prophylaxis trial (Kenya); IPERGAY, Intervention Préventive de l'Exposition aux Risques avec et pour les Gays; PEP, postexposure prophylaxis.

Note: Data obtained and compiled from Molina,[18] Luetkemeyer et al,[16] Molina,[19] and Stewart[20] (Jean-Michel Molina, MD, PhD, email, August 26, 2023; Jenell Stewart, DO, MPH, email, August 8, 2023).

numerous STIs.[42] Clinicians interested in offering doxy-PEP to their patients may consider adapting existing guidelines from US public health departments to their local context or choose to await official guidelines from the CDC or the World Health Organization, which are in developmental phases.

The choice to prescribe doxy-PEP should result from a shared decision-making process between the health care practitioner and the patient. Known benefits and risks should be reviewed at each discussion about initiation, as should the potential unknowns, including the possibility of emerging resistance in STI pathogens, bystander bacteria, and changes to the individual and population-level microbiome that could have future adverse health effects. The specific number of pills and refills to prescribe depends on the user's number of reported and anticipated sexual exposures. Based on the US DoxyPEP trial data, King County's guidelines recommend that for most persons 30 pills with 1 refill may be a reasonable quantity for an initial prescription.[24] Laboratory monitoring during doxy-PEP is likely not necessary given that adverse events and discontinuations were uncommon in all 3 trials (Table 2).

As doxy-PEP implementation begins to roll out in the US and other countries, clear guidance and data are needed to inform several remaining areas of clinical uncertainty. These areas include how to counsel and manage the use of doxy-PEP in populations that were not yet studied in clinical trials (eg, cisgender men who have sex with women), what the optimal intervals are for STI screening, whether a maximum number of uses of doxy-PEP per week or month should be recommended, and how to manage contacts of individuals with STIs who are taking doxy-PEP. Other key areas to explore are whether existing surveillance systems can be leveraged to monitor for the possibility of emergent resistance in *Chlamydia trachomatis* and *Treponema pallidum*, and the role of molecular resistance testing for incident STIs.

It is now time to proactively design and monitor doxy-PEP implementation using an equity lens. Previous studies have shown that the majority of STI burden falls on a small proportion of MSM.[43,44] It will be imperative to identify which key populations might benefit most from doxy-PEP while balancing the risk of excess antibiotic exposure. We must strive to avoid perpetuating the sort of disparities for doxy-PEP access and uptake that persist for HIV PrEP. Future implementation and demonstration projects may be useful in providing data on uptake and real-world use, STI incidence estimates for mathematical modeling, early signals of adverse impacts, and progress on equitable use in communities at risk. Additionally, for some persons who have very frequent sex and who would use doxy-PEP nearly daily, lower-dose doxy-PrEP may be a more appropriate option. Doxy-PrEP, in which doxycycline is taken daily rather than specifically after condomless sex, is currently being studied in clinical trials in Australia

and Canada,[45-47] and the same implementation and AMR concerns will need to be thoroughly evaluated for this strategy.

Conclusion

Doxy-PEP is an exciting new intervention that may become an important component in our arsenal of STI prevention tools. Evidence from 3 randomized trials has shown that use of doxy-PEP within 24 to 72 hours after condomless sex dramatically reduces the risk of gonorrhea, chlamydia, and syphilis in MSM and TGW with a history of an STI in the prior year. Having access to doxy-PEP may increase sexual pleasure and decrease stigma associated with STI. For persons who cannot or choose not to use condoms, doxy-PEP may be a preferred STI prevention option. The choice to prescribe or use doxy-PEP should result from a shared decision-making process during which the benefits of doxy-PEP are considered along with its numerous potential risks and concerns. These include eventual loss of efficacy against *Neisseria gonorrhoeae* if tetracycline-resistant strains predominate within affected communities, the potential for the emergence of resistance in STI pathogens and in important bystander bacteria such as *Staphylococcus aureus*, and possible alterations in the gut microbiome that may have adverse health impacts in the months and years after intermittent doxycycline exposure. Clinical trial data will eventually provide information about the relative efficacy and AMR associated with doxy-PrEP compared with doxy-PEP, and the aforementioned considerations will remain germane for both strategies. Much needs to be learned about the long-term effects of biomedical STI prophylaxis on individual and population levels, and real-world implementation data with monitoring of uptake, impact on AMR, and population-level STI rates may provide answers to these important questions in the future.

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Invited Review

2023 Updated Guidelines on Infant Feeding and HIV in the United States: What Are They and Why Have Recommendations Changed?

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The US Department of Health and Human Services guidelines on infant feeding among people with HIV have changed in response to (1) evidence of low risk of transmission via breast milk among individuals with consistent viral suppression, (2) considerations of equity and cultural norms, and (3) community desires. The 2023 guidelines recommend patient-centered shared decision-making. Individuals with HIV who are receiving antiretroviral therapy (ART) and have consistent viral suppression should be counseled on the options of formula feeding, feeding with banked donor milk, or breast (or chest) feeding, and nonjudgmentally supported in their decision. Individuals who choose to breastfeed should be counseled on and supported in adherence to ART, viral suppression, and engagement in postpartum care for themselves and their babies. Exclusive breastfeeding is recommended, with the understanding that brief periods of replacement feeding may be necessary. Data are lacking on ideal infant prophylaxis regimens.

Keywords: breastfeeding, infant, human milk, HIV, guidelines

Background

Counseling about infant feeding is an integral component of care for pregnant and postpartum people with HIV. The American Academy of Pediatrics recommends exclusive breastfeeding/chestfeeding (herein breastfeeding [see Authors' Note]) for 6 months for most babies. They cite the unique composition of human milk and numerous health benefits for the baby and the lactating parent.[1] For decades, women and other birthing people with HIV in the US and other high-income countries were told that formula feeding was the only safe option available to them. In recent years, this guidance has shifted as a result of advocacy from community members and people with lived experience, accumulating data showing that the risk of HIV transmission through breast milk among individuals with viral suppression is very low, and the recognition that restricting breastfeeding might increase the inequities that already exist for many birthing people with HIV. In January 2023, US guidelines were substantially revised, supporting shared decision-making for people with HIV who are receiving antiretroviral therapy (ART) and have consistent viral suppression. This article reviews the considerations that led to this change, infant feeding considerations for people with HIV, and best practices in counseling and treatment of people with HIV who choose to breastfeed their infants.

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History of Reproductive Coercion and HIV

People with HIV have long had to fight for reproductive freedom. Ronald Bayer wrote about this history in 1990.[2] In the setting of many unknowns, in 1985 the then Centers for Disease Control (now the Centers for Disease Control and Prevention [CDC]) published its first *Morbidity and Mortality Weekly Report* on the prevention of perinatal transmission of the virus that would come to be known as HIV. This report contains the statement that "infected women should be advised to consider delaying pregnancy until more is known about perinatal transmission of the virus."[3] A CDC

Authors' Note
Breastfeeding and chestfeeding are both terms used to describe feeding a baby one's own human milk. Not everyone who gives birth or lactates identifies as a woman and some transgender men and gender-diverse individuals may prefer the terms "chestfeeding" or "bodyfeeding" over "breastfeeding."

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official wrote in 1987 that women and their sexual partners would have to "suppress often strong desires to bear children,"[4] acknowledging the coercion implied by this recommendation. Other agencies echoed the CDC guidance and at times went even further, from stating that women with HIV should be "advised to postpone pregnancy" to the overtly directive language that women with HIV should be "strongly encouraged not to become pregnant."[5,6] In his article, Bayer points out that the directive counseling adopted toward women with HIV was very different from the nondirective posture prioritized in genetic counseling for pregnant people and potential parents: "... the disquiet provoked by pediatric AIDS had elicited a willingness to embrace ... clinical practices that deviated from the conventions of nondirective counseling."[2]

Early policies designed to limit the birth of infants with HIV contributed to long-lasting stigma against women with HIV and a climate of intolerance for the reproductive freedom of people with HIV

There have always been vocal proponents of a nondirective, noncoercive approach to reproductive health and decision-making for people with HIV, including Janet Mitchell, a former chair of the obstetrics and gynecology department at Harlem Hospital, who was a forceful critic of the public health posture on HIV infection and pregnancy.[2] It was not lost on Dr Mitchell and many others that women with and at risk for HIV were disproportionately Black, Latinx, and poor, and were often injection drug users. Recommendations were not culturally responsive to the meaning of childbearing for these women: "we must ensure that counseling is as nonjudgmental, culturally sensitive, and ethnic specific as possible. Otherwise we run the risk of further alienating populations we have historically had little success in reaching."[7]

Breastfeeding Guidelines in the US

Early policies designed to limit the birth of infants with HIV contributed to long-lasting stigma against women with HIV and a climate of intolerance for the reproductive freedom of people with HIV,[8,9] even with the availability of interventions to reduce or even eliminate the risk of perinatal transmission of HIV. However, the CDC and other federal agencies have moved away from official policies of discouraging pregnancy and have embraced the use of HIV preexposure prophylaxis, universal HIV testing, ART, and viral suppression for pregnant people with HIV, and antiretroviral prophylaxis for babies exposed to HIV, to reduce and eventually eliminate perinatal transmission of HIV.[10-13]

Until 2023, part of this package of preventive measures was a fairly absolute prohibition on breastfeeding for people with HIV. The Department of Health and Human Services (DHHS) Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States (hereafter referred to as the "DHHS Perinatal HIV Guidelines") evolved over time to support counseling and harm-reduction measures for people with HIV "who choose to breastfeed despite intensive counseling," but maintained a stance that breastfeeding is not recommended for people with HIV.[10] The CDC consistent statement was that "in the United States, to prevent HIV transmission, it is recommended that mothers living with HIV not breastfeed their infants."[14] In 2023, the DHHS Perinatal HIV Guidelines were revised to include a greater focus on shared decision-making.

Change in Guidelines

On January 31, 2023, the DHHS Perinatal HIV Guidelines were updated with a greatly revised section on "Infant Feeding for People With HIV in the United States." This section states: "People with HIV should receive evidence-based, patient-centered counseling to support shared decision-making about infant feeding.... For people with HIV who are not on ART and/or do not have a suppressed viral load at delivery, replacement feeding with formula or banked pasteurized donor human milk is recommended to eliminate the risk of HIV transmission... Individuals with HIV on ART with a consistently suppressed viral load during pregnancy (at a minimum during the third trimester) and at the time of delivery should be counseled on the options of formula feeding, banked donor milk, or breastfeeding."[10] In another substantial change, the CDC archived its document on breastfeeding and HIV and chose to instead reference the DHHS Perinatal HIV Guidelines and the American Academy of Pediatrics' recommendations.[15]

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Table 1. Infant Feeding Considerations for People With HIV

Risk of HIV transmission	• Postexposure prophylaxis should be offered as soon as possible, within 72 hours, to all individuals who have sustained a mucosal or parenteral exposure to HIV. • Cases have been reported of HIV transmission when maternal HIV RNA level was less than 50 copies/mL leading up to and close to the time of transmission. • Fully suppressive antiretroviral therapy during pregnancy and breastfeeding decreases transmission risk to less than 1%, but not zero.
Bodily autonomy and reproductive justice	• Having support to choose how to feed one's baby is important for bodily autonomy and making decisions about what is best for oneself and one's family. • Directive counseling can feel degrading and harmful and strip an individual of agency.
Cultural considerations	• Sense that there are environmental, social, familial, and personal pressures to consider breastfeeding. • Fear that not breastfeeding would lead to disclosure of their HIV status.
Health benefits of breastfeeding	• Infant: lower risk of asthma, obesity, type 1 diabetes, severe lower respiratory disease, otitis media, sudden infant death syndrome, gastrointestinal infections, and necrotizing enterocolitis. • Lactating parent: lower risk of hypertension, type 2 diabetes, and breast and ovarian cancers.
Health equity	• Black women are disproportionately affected by HIV. • People of color experience a greater burden of many health conditions that may be alleviated by breastfeeding.

Infant Feeding Considerations for People With HIV

Even before the change in federal guidelines, there were people with HIV in the US who expressed interest in breastfeeding and who successfully breastfed their babies, sometimes with the help and support of medical practitioners and sometimes surreptitiously. In a survey published in 2019, among 93 clinicians who provided specialty care to women with HIV, 29% were aware that women in their care had breastfed.[16] In a similar 2021 survey, 42% had cared for a person with HIV who breastfed.[17] If there is a risk of HIV transmission from breastfeeding and if formula feeding in the US is supposed to be acceptable, feasible, affordable, sustainable, and safe (AFASS, in the vernacular of the World Health Organization), why do so many parents choose to breastfeed? Beyond reducing the risk of HIV transmission to their baby, people with HIV may be thinking about the stigma and lack of privacy they face when they do not breastfeed, the health benefits of breastfeeding, and the goal of having the same choices and health outcomes as people without HIV. A summary of infant feeding considerations for people with HIV appears in Table 1.

Low Risk of Transmission

Without the use of ART, the estimated rate of breast milk transmission of HIV is about 16% over 2 years.[18] No systematic studies have been reported that indicate the risk of HIV transmission through human milk when the lactating person with HIV is started on ART before pregnancy or in the first trimester. The existing data come from studies in low- and middle-income countries, with ART started at varying time points during pregnancy. A systematic review and meta-analysis published in 2017 identified 6 studies with ART started at some point during pregnancy and continued for at least 6 months postpartum that provided estimates of postnatal transmission rates, excluding peripartum infections diagnosed before 6 weeks of age. The pooled postnatal transmission rate at 6 months was 1.1% (95% CI, 0.32%-1.85%), with substantial heterogeneity. Transmission rates in included studies ranged from 0.2% to 3.1%.[19]

The largest study to date on the use of antiretroviral medications to reduce the risk of lactational HIV transmission was the PROMISE (Promoting Maternal and Infant Survival Everywhere Study) trial, which included more than 2400 women with CD4+ counts 350 cells/μL and higher and compared the efficacy of prolonged infant nevirapine (NVP) prophylaxis with maternal ART. Both treatments continued through the cessation of breastfeeding or 18 months postpartum, whichever came first. This study showed estimated transmission rates of 0.3% at 6 months and 0.6% at 12 months in both arms.[20] Maternal plasma HIV RNA level and maternal HIV drug resistance were each independently associated with HIV transmission via breast milk.[21] Overall, out of 1220 mother-infant pairs in the maternal ART arm, there were 7 cases of HIV transmission. Two infants in the maternal ART arm acquired HIV despite a maternal plasma HIV RNA level

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measured as not detected or detected but less than 40 copies/mL on the date that the infants' first samples tested positive for HIV RNA. In both cases, maternal HIV RNA was detectable at delivery and in subsequent testing, which makes it challenging to extrapolate the findings to patients with longer and more consistent viral suppression.[22]

There have been at least 5 additional reported cases of HIV transmission in which the maternal viral load was less than 50 HIV RNA copies/mL close to the time of transmission.[23-25] Two cases were from an observational study in Malawi. In the first case, ART was started 8 weeks before delivery and maternal plasma HIV RNA level was less than 37 copies/mL at 1 month, 3 months, 6 months, and 12 months postpartum. The baby was breastfed until 9 months of age and tested positive for HIV at 12 months of age, after testing negative at months 1, 3, and 6. HIV RNA level measured in the breast milk was 293 copies/mL at 1 month postpartum and less than 37 copies/mL at months 3 and 6. In the second case, ART was started 14 weeks before delivery and maternal plasma HIV RNA level was less than 37 copies/mL at 1 month and 3 months postpartum. The baby tested positive for HIV at 3 months of age, after testing negative at 1 month. HIV RNA level measured in the breast milk was less than 37 copies/mL at 1 month postpartum and 90 copies/mL at 3 months.[24]

The Mma Bana study in Botswana compared triple nucleoside analogue reverse transcriptase inhibitor (nRTI) therapy with protease inhibitor-based therapy (lopinavir/ritonavir). Triple nRTI therapy is no longer recommended as a complete regimen for HIV treatment for pregnant or nonpregnant individuals, as these regimens are inferior to currently recommended combination antiretroviral regimens.[26] There were 2 cases of lactational transmission in which maternal plasma and breast milk HIV RNA levels were less than 50 copies/mL at 1 and 3 months postpartum, both in the nRTI arm. In one case, ART was started 4 weeks before delivery and viral load was elevated at delivery; the baby tested positive for HIV at 94 days of life after testing negative at 28 days. In the other case, ART was started 14 weeks before delivery and HIV RNA level was less than 50 copies/mL at delivery, although there were reported issues with adherence; the baby tested positive for HIV at 91 days of life after testing negative at 21 days.[25]

In DolPHIN-2 (Dolutegravir in Pregnant HIV Mothers and Their Neonates), which compared dolutegravir- versus efavirenz-based ART started in the third trimester, out of 268 mother-infant pairs, there was 1 case of breastfeeding-related HIV transmission. It was in the efavirenz group; the baby tested positive for HIV at 72 weeks of age (16 months), and maternal viral load was less than 50 copies/mL at 12 weeks, 24 weeks, 48 weeks, and 72 weeks postpartum.[23]

Where does this leave us in terms of the risk of HIV transmission through breastfeeding in the context of ART? The risk is less than 1%, but not zero, at least with ART started in the third trimester or at delivery. In high-income countries, case series have been reported in which ART was started before pregnancy or in the first trimester, with no cases of transmission.[27-34] However, the overall numbers were small. Thirteen women, described in a prospective study conducted in Italy, had no instances of transmission of HIV through breastfeeding.[31] In Germany, among 30 women with HIV who breastfed, there were no cases of transmission of HIV, although only 25 women had optimal viral suppression.[28,34] Four of the 5 women not considered to have optimal suppression had viral loads of 50 copies/mL to 70 copies/mL at some point postpartum, and 2 had had a detectable viral load early in pregnancy. A retrospective multisite study conducted in the US and Canada involved 72 cases of breastfeeding among people with HIV.[32] Of the 72 individuals, 86% were receiving ART before pregnancy, 85% had a viral load of less than 40 copies/mL at initiation of prenatal care, and 90% had a viral load of less than 40 copies/mL close to delivery (the viral load was >40 copies/mL in 1 case and unknown in 6 cases). There were no cases of HIV transmission, although 4 infants were lost to follow-up. Twenty-one of these cases had been reported previously in separate publications.[29,30,33]

The largest study to date on the use of ART to reduce the risk of lactational HIV transmission was the PROMISE trial, which showed estimated transmission rates via breastfeeding of 0.3% at 6 months and 0.6% at 12 months

Bodily Autonomy and Reproductive Justice

Many activists in the HIV community have framed the issue of choice in infant feeding within the concept of reproductive justice.[35] Reproductive justice is

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a movement started and led by Black women that focuses on reproductive liberty, which is understood to include but go beyond the right to choose abortion. Rather, the movement examines the structures and oppressive societal forces that affect all aspects of reproduction. SisterSong, a national membership organization devoted to improvement of the reproductive lives of marginalized communities, defines reproductive justice as "the human right to maintain personal bodily autonomy, have children, not have children, and parent the children we have in safe and sustainable communities."[36] For many people with HIV, receiving support to choose how they want to feed their baby is an important step in maintaining or regaining bodily autonomy and claiming their right to parent in safe and sustainable communities, "building upon a trust that they will make the best decisions for themselves and their families when equipped with comprehensive information and adequate resources and support," free from policing and undue surveillance.[35]

Qualitative research in the United Kingdom, Canada, and the US has elucidated the many considerations that people with HIV weigh when they choose an option for infant feeding or are told that formula feeding is the only option.[37-39] In the pre-2023 era when formula feeding was recommended for all people with HIV—without much consideration of the social, cultural, and emotional aspects of infant feeding—counseling was generally directive, sometimes to the point of being coercive.[39] Even for those who ultimately chose to feed their baby formula, this directive counseling could feel degrading and harmful and strip an individual of agency: "I was always told, since my first pregnancy, that I could ONLY formula feed ... when I continued to inquire about it my nurse said to me, 'Do you want to give your child HIV?? Then you can't breastfeed.' I was so hurt by this response I haven't inquired since. Even after multiple children."[39]

Cultural Considerations

For some people, breastfeeding is part of the cultural expectation of motherhood, and not having this option is associated with a steep emotional cost. Participants in these studies described feelings of guilt and loss of an anticipated maternal experience. As one individual put it, "I just accept it but in my heart it pains me because as a woman you have to breastfeed your baby."[37]

Because breastfeeding is such a deeply ingrained expectation of new motherhood, people with HIV report having to explain themselves over and over again and make up excuses for not breastfeeding: "It was difficult, I mean, I had so much company coming over here when I first had the baby and they all asked me why I wasn't breastfeeding, every single person."[38] Particular importance is placed on breastfeeding among many migrant women from countries in sub-Saharan Africa, where breastfeeding is the cultural norm and a decision to bottle-feed may signal a mother's HIV-positive status. One study participant said, "It's so sad because most people, like most Africans, they know that the moms who do not breastfeed are moms who has [sic] HIV. They know about that, so sometimes if they come to your apartment, they'll be watching to see if you're gonna give the baby milk."[38]

For some people, breastfeeding is part of the cultural expectation of motherhood, and not having this option is associated with a steep emotional cost

Health Benefits of Breastfeeding

The American Academy of Pediatrics recommends exclusive breastfeeding for approximately 6 months after birth and supports continued breastfeeding—along with appropriate complementary foods introduced at about 6 months—as long as mutually desired by parent and child, for up to 2 years or beyond. These recommendations are consistent with those of the World Health Organization.[1] Breastfeeding is associated with improved neonatal immune status and a lower risk of asthma, obesity, type 1 diabetes, severe lower respiratory disease, otitis media, sudden infant death syndrome, gastrointestinal infections, and necrotizing enterocolitis. In addition to bonding with their infant and avoiding the monetary costs of formula, benefits to the lactating parent include decreased risk of hypertension, type 2 diabetes, and breast and ovarian cancers.[1]

People with HIV are exposed to the same "breast is best" messaging as the general population. One study participant said they wanted to breastfeed because from what they read in all the books, breast milk was the best, so they wanted to give that to their baby.[37]

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Table 2. Components of Counseling on Infant Feeding Options for People With HIV

The infant feeding options that eliminate the risk of HIV transmission are formula and pasteurized donor human milk.
Fully suppressive antiretroviral therapy during pregnancy and breastfeeding decreases breastfeeding transmission risk to less than 1%, but not zero.
If breastfeeding is chosen, exclusive breastfeeding up to 6 months of age is recommended over mixed feeding (ie, breast milk and formula), with the understanding that intermittent formula feeding may be necessary, such as in cases of infant weight loss, a not-yet-established milk supply, or the mother not having enough stored milk. Solids should be introduced as recommended at 6 months of age, but not before.
The postpartum period, which can be difficult for all parents, can present several challenges to medication adherence and engagement in care. Ensuring that parents have access to both a supportive clinical team and peer support in the postpartum period is beneficial in promoting medication adherence and viral load monitoring.
Access to a lactation consultant or lactation support provider with expertise in supporting breastfeeding by individuals with HIV is beneficial.
As most studies of breastfeeding in people with HIV were conducted in resource-limited settings, more information is needed about the risk of HIV transmission through breastfeeding in high-resource settings and when individuals are adherent to antiretroviral therapy with sustained viral suppression starting early in pregnancy.
Breastfeeding provides numerous health benefits to both the infant (eg, reduction in risk of asthma, gastroenteritis, and otitis media) and the parent (eg, reduction in risk of hypertension, type 2 diabetes, and breast and ovarian cancers).

Adapted from the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission.[10]

Others felt that, although not breastfeeding made them feel "guilty" and "inadequate," the health risks of breastfeeding while infected with HIV outweighed the benefits: "I felt comfortable with the decision I made and felt I personally had no choice but to bottle feed if my babies' well-being was my greatest concern."[39] With the evidence supporting the low risk of HIV transmission in the setting of ART and consistent viral suppression starting before pregnancy or early in the pregnancy, and the different ways that each individual weighs the benefits of breastfeeding, experts have argued that breastfeeding by people with effectively treated HIV infection is an "equipoise option" and that it should be up to the patient, not the medical team, to decide which option is best.[40]

Health Equity

An additional important consideration in the discussion about infant feeding for people with HIV is that of health equity. Black women and birthing people in the US are disproportionately vulnerable to HIV and perinatal morbidity and mortality while simultaneously experiencing several barriers to successful breastfeeding, even when they do not have HIV.[41-44] People with limited access to social and health resources are the most affected by HIV, primarily owing to the effects of structural racism, and also experience a greater burden of health conditions that may be attenuated by breastfeeding. Prohibiting breastfeeding may inadvertently exacerbate these health inequities.[45]

Even in the US, some people have limited access to safe water or difficulty obtaining formula. In 2022, reports of contaminated formula, increasing costs of formula, and formula shortages revealed flaws in the formula production and distribution system, leaving many of the country's most vulnerable families struggling to feed their babies.[46] In addition to the widely publicized water crisis in Flint, Michigan, it is estimated that millions of Americans have incomplete indoor plumbing or poor water quality, making them reliant on expensive bottled water or forced to use potentially unsafe tap or well water to prepare formula.[47] Giving parents with HIV the option to breastfeed their babies does not fix these problems—all families deserve access to clean water and safe and affordable formula—but these inequities and health disparities should be considered as part of counseling and support for infant feeding decisions for people with HIV in the US.

Counseling and Management

The DHHS Perinatal HIV Guidelines state that individuals with HIV who are receiving ART and have consistent viral suppression during pregnancy (at least during the third trimester) and at the time of delivery should be counseled on the options of formula feeding, feeding with banked donor milk, or breastfeeding. This counseling should begin before conception or as early in pregnancy as possible, and plans for infant feeding

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Table 3. Components of Management for People With HIV Who Choose to Breastfeed

Support the parent's antiretroviral therapy adherence and engagement in care throughout pregnancy and infant feeding	• Provide case management and/or social work support from individual(s) with perinatal support experience. • Provide early active referral to a supportive lactation consultant knowledgeable about concerns regarding HIV transmission and situations in which to consider stopping or temporarily interrupting breastfeeding. • Screen and provide support for postpartum depression and other mental health conditions that are highly prevalent among new parents and may affect antiretroviral therapy adherence. Postpartum depression occurs more frequently in individuals with HIV than in those without HIV.
Document sustained viral suppression before delivery and throughout breastfeeding	• No data exist to inform the appropriate frequency of viral load testing for the breastfeeding parent. One approach is to monitor the plasma viral load of the parent every 1 to 2 months during breastfeeding. • Decide which clinician (eg, prenatal care clinician or primary care HIV clinician) is responsible for monitoring viral loads of the parent postpartum and continuing counseling/education around infant feeding. • If the parent's viral load becomes detectable, consult an expert in breastfeeding and HIV immediately and consider options for temporarily or permanently discontinuing breastfeeding. • Recommend exclusive breastfeeding in the first 6 months of life, followed by the introduction of complementary foods with continued breastfeeding, if desired. Some people may choose to breastfeed for less than 6 months. • In pre–antiretroviral therapy studies, exclusive breastfeeding was associated with lower rates of HIV transmission than mixed feeding (a term used to describe feeding of breast milk plus other liquid or solid foods, including formula). The highest risk in these studies was from very early introduction of solids (before 2 months of age). • In the context of parental antiretroviral therapy and viral suppression, it is not known whether formula supplementation increases the risk of HIV acquisition in the breastfed infant.
Administer appropriate antiretroviral prophylaxis starting at birth	Options include the following: • zidovudine for 2 weeks, if otherwise eligible • zidovudine for 4 to 6 weeks • nevirapine for 6 weeks • nevirapine continued throughout breastfeeding
Provide guidance on good breast care	• Include strategies to avoid and promptly resolve overproduction of breast milk, milk stasis, and breast engorgement, which can lead to sore nipples, mastitis, or abscess. • Promptly identify and treat mastitis, thrush, and cracked or bleeding nipples. These conditions may increase the risk of HIV transmission through breastfeeding, although the impact of these conditions in the context of antiretroviral therapy and viral suppression is unknown.
Develop a joint plan for weaning with family and clinicians	• Because very rapid weaning was associated with increased risk of HIV shedding into breast milk and risk of transmission in the pre–antiretroviral therapy era, weaning over a 2- to 4-week period might be safer, with special attention paid to good breast care and avoidance of breast engorgement and milk stasis.
Monitor for infant HIV acquisition with periodic virologic diagnostic testing	For infants with perinatal HIV exposure who are being breastfed, virologic diagnostic testing is recommended at the following times: • birth • 14 to 21 days • 1 to 2 months • 4 to 6 months An additional test should be performed between the 1- to 2-month and 4- to 6-month time points if the gap between tests is greater than 3 months. Testing should continue every 3 months for the duration of breastfeeding. Testing should also be performed at 4 to 6 weeks, 3 months, and 6 months after cessation of breastfeeding.

Adapted from the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission.[10]

should be nonjudgmentally reviewed throughout pregnancy and again after delivery.[10] A summary of the components of counseling can be found in Table 2. If a parent decides to breastfeed, counseling should include the importance of adherence to ART, viral suppression during pregnancy and breastfeeding, and engagement in postpartum care for both the lactating parent and the infant.[10] A summary of the components of management can be found in Table 3.

The DHHS Perinatal HIV Guidelines explicitly state

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that referral to child protective services (CPS) or similar family welfare agencies is not an appropriate response to someone's asking about breastfeeding or choosing to breastfeed. There are many heartbreaking stories of health care practitioners threatening to call or calling CPS and refusing to provide care to people with HIV who choose to breastfeed, often in an attempt to intimidate and coerce them into not breastfeeding.[17,48] Calling CPS or refusing to provide care shuts down conversation, furthers HIV stigma, pushes people out of care, harms families, and fits into a pattern of biased policing and application of policies that lead to the most marginalized people—particularly Black and Indigenous communities—being unjustly surveilled and punished for reproduction-related health decisions.[49]

Infant Prophylaxis

There is no consensus on the appropriate management of antiretroviral prophylaxis for infants of individuals with sustained viral suppression who are breastfed. The DHHS Perinatal HIV Guidelines give several options: most panel members agree that low-risk infants who otherwise qualify for only 2 weeks of infant zidovudine (ZDV) do not need any additional prophylaxis; several panel members prefer to extend the duration of ZDV prophylaxis to 4 to 6 weeks; some panel members recommend 6 weeks of NVP; and others opt to continue NVP throughout breastfeeding. Daily lamivudine and daily lopinavir/ritonavir are alternatives for infants who cannot tolerate ZDV or NVP.

It is important to note that no trials have been conducted to evaluate or compare different agents for postnatal prophylaxis among breastfeeding infants of people receiving ART. In a post hoc analysis of the HPTN (HIV Prevention Trials Network) 046 study, which showed a less than 1% risk of postnatal HIV transmission in the extended NVP and the placebo arms, the addition of infant prophylaxis did not further reduce breastfeeding transmission in mothers who were receiving ART.[50] In the absence of data or consensus, practitioners may choose to include parents or caregivers in the decision about how long to continue infant prophylaxis. The primary focus should be on ART adherence and support for the lactating person with HIV.

Formula

In pre–ART studies, exclusive breastfeeding was associated with lower rates of HIV transmission than mixed feeding (ie, feeding of infants with breast milk plus other liquid or solid foods, including formula).[51,52] The highest risk in these studies was from the very early introduction of solids (before 2 months of age).[53,54] In the context of parental ART and viral suppression, it is not known whether formula supplementation increases the risk of HIV acquisition in breastfed infants. As is the case with all individuals who choose to breastfeed, exclusive human milk feeding is recommended for the first 6 months of life, followed by the introduction of complementary foods with continued breastfeeding, if desired, with the understanding that intermittent formula feeding may be necessary, such as in cases of infant weight loss, a not-yet-established milk supply, mastitis, or bleeding nipples.[1]

Detectable Viral Load

In the case of a detectable viral load in a lactating parent, the DHHS Perinatal HIV Guidelines recommend that breastfeeding be temporarily stopped while viral load testing is repeated.[10] The following options may be considered in the interim: (1) giving previously expressed and stored milk from a date when the person had viral suppression, (2) pumping and flash heating expressed milk before feeding it to the baby, or (3) providing replacement feeding with formula or pasteurized donor human milk. If repeated testing shows a viral load below the level of detection, breastfeeding may resume.

Exclusive breastfeeding is recommended for the first 6 months of life, with the understanding that intermittent formula feeding may be necessary, such as in cases of infant weight loss, a not-yet-established milk supply, mastitis, or bleeding nipples

This situation also presents an opportunity to provide positive feedback and review the risks and benefits of continued breastfeeding, adherence strategies, and other considerations. If the repeated testing shows a detectable viral load, the guidelines advise immediate cessation of breastfeeding; this guidance is more directive than counseling for individuals receiving suppressive ART because of the increased risk of

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HIV transmission.[10] Given the sensitivity of HIV RNA assays, the level of detectable viral load above which breastfeeding should be stopped and additional infant antiretroviral prophylaxis should be started is a matter of clinical judgment and review of viral load trends. Consultation with an expert or the national perinatal HIV/AIDS hotline (888-448-8765) is recommended.

Conclusion

Women and other birthing people with HIV want to have happy, healthy, thriving children and families. HIV transmission is not the only factor parents might be weighing when they think about how best to support the health and well-being of their baby and their family. Support for informed choice of infant feeding options for people with HIV is a major shift in the care of women and other birthing people with HIV toward bodily autonomy and reproductive justice. This shift is due in large part to the advocacy of community members and organizations that have been pushing for years for parents with HIV to have access to the information, support, and tools necessary to make informed decisions about infant feeding.[35]

More data are needed on the risk of HIV transmission from a lactating parent with HIV who is receiving ART and has achieved and maintained viral suppression starting before pregnancy or early in pregnancy. Future work may lead to the ability to equate "undetectable" with "untransmittable," but, unfortunately, we are not there yet in this setting. Also needed is more research on the optimal antiretroviral prophylaxis regimen for breastfed infants and the impact of mixed feeding on HIV transmission risk in the context of viral suppression. Several institutions have published information on protocols for managing breastfeeding in people with HIV and their babies.[29,55,56] As more institutions and practitioners develop and refine protocols, materials, and best practices related to HIV and infant feeding, ideally in collaboration with patients and others with expertise that comes from lived experience, we hope these can be shared and disseminated.

Not everyone with HIV who is receiving ART with a viral load below the level of detection and gives birth is going to choose to feed their baby their own milk. Many, when given information about the nonzero risk of HIV transmission, will choose formula. Some may have access to banked human milk and will choose that for a certain period before switching to formula. Some may start off breastfeeding and then decide that it is not the right decision and switch to formula. In addition to providing supportive wraparound care for those who choose to breastfeed, we need to continue to push for universal access to high-quality, safe, and affordable formula as well as better lactation support and accommodation. Parents with HIV deserve our respect, not our suspicion, and have a right to make informed, supported, uncoerced decisions about infant feeding. And when they choose to breastfeed, support from their health care team is essential to their success.

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Reviewer 1 reported consultant or received advisor fees from Antiva, Assembly Biosciences, Generate Biomedicines, and IGM Biosciences, and fees for participation in review activities, eg, data monitoring boards, statistical analysis, or endpoint adjudication committees for Gilead Sciences, Inc. (Updated November 22, 2023) Reviewers 2 and 3 reported no relevant financial relationships with ineligible companies. (Updated November 22, 2023)

All relevant financial relationships with ineligible companies have been mitigated.

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