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Topics in Antiviral Medicine™

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Invited Reviews

Topics in Antiviral Medicine™

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

- Describe the synthetic production and potential of bacteriophages in the battle against antimicrobial resistance.
- Deliver affirming, respectful health care in HIV treatment and prevention settings when caring for transgender and gender-diverse individuals.
- List current recommendations for prevention of hepatitis B virus infection among people with HIV.

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Invited Review

Providing Gender-Affirming Care to Transgender and Gender-Diverse Individuals With and at Risk for HIV

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Transgender and gender-diverse populations have unique medical and psychosocial needs. It is important that clinicians address these needs with a gender-affirming approach in all aspects of health care for these populations. Given the significant burden of HIV experienced by transgender people, such approaches in providing HIV care and prevention are essential both to engage this population in care and to work toward ending the HIV epidemic. This review presents a framework for practitioners caring for transgender and gender-diverse individuals to deliver affirming, respectful health care in HIV treatment and prevention settings.

Keywords: transgender health, HIV, HIV prevention, gender-affirming care

Introduction

Gender and sex are complex constructs that have garnered considerable attention recently across multiple spheres including health care.[1] In the United States, more than 1.6 million people older than 13 years identify as transgender or gender nonconforming, representing approximately 0.5% of adults and 1.4% of youth.[2] This population experiences enormous health disparities, particularly related to sexual health. Transgender women in the United States have an estimated HIV prevalence of 42%[3] as well as prevalence rates for bacterial sexually transmitted infections (STIs) that are higher than those for other populations.[4] These disparities are worsened by suboptimal engagement in health care by transgender people, which itself is driven by stigma, discrimination, and limited access to affirming practitioners.[5] The aim of this review is to equip clinicians with tools to provide culturally sensitive, gender-affirming health care for transgender and gender-diverse populations, specifically in the setting of HIV treatment and prevention.

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Gender and Sexual Identity Terminology

Although transgender and gender-diverse people have always existed, the current shifting cultural and political landscape toward recognition and support for these individuals underscores the importance of health care practitioners having better

Sex refers to the physiologic and genetic characteristics of an individual, such as genitalia, reproductive anatomy, and composition of X and Y chromosomes; it is assigned at birth. Gender, by contrast, is a social construct defined by the behavioral or cultural norms of either men or women

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Table 1. Common Gender Identity Terms and Their Characteristics[a]

Gender identity term	Characteristics
Cisgender female or woman	Person assigned female sex at birth whose gender identity is female or woman
Cisgender male or man	Person assigned male sex at birth whose gender identity is male or man
Genderqueer	Person who does not follow gender identity or expression for their sex assigned at birth; they may identify as neither, both, or a combination of binary genders
Nonbinary	Person who does not identify with binary expectations of being strictly a man or a woman
Transgender	Person whose gender identity and sex assigned at birth do not correspond • Transgender female or transgender woman or male-to-female (MTF)[b] • Transgender male or transgender man or female-to-male (FTM)[b]

[a] The terms included are the most common, but dozens more are used, and terminology continually evolves.

[b] Medical model terms (not recommended for use unless an individual prefers them).

understanding for the needs of these people. Basic needs include the correct use of common gender identity terms and an appreciation that each gender identity has several components.

Sex refers to the physiologic and genetic characteristics of an individual, such as genitalia, reproductive anatomy, and composition of X and Y chromosomes; it is assigned at birth.[6] Examples of sex include male, female, or intersex.[7] *Gender*, by contrast, is a social construct defined by the behavioral or cultural norms of either men or women.[6] Every person, regardless of the sex assigned at birth, has a gender identity, which is the individual's internal subjective sense of being a boy or girl, a man or woman, or another gender identity.[7] *Gender expression* is the manner in which individuals express their gender identity to society in terms of physical appearance and clothing.[7] *Sexual identities* such as sexual and romantic attractions are distinct from *gender* but similar to *gender identity;* each individual has a personal sexual identity. Notably, these concepts exist on a spectrum, and assumptions about any of them for an individual should be avoided.

Transgender individuals are those whose sex assigned at birth does not align with their gender identity, whereas *cisgender* individuals experience congruence between their sex assigned at birth and gender identity. Many individuals do not feel that the binary genders of "male" and "female" describe their identity, so they may identify as another gender such as *gender nonconforming*, or *nonbinary*. Table 1 lists common gender identities and their characteristics.

Gender-Affirming Health Care

Gender affirmation refers to the process of recognizing, accepting, and expressing one's gender identity; as applied to health care practitioners, it refers to supporting patients in these areas.[8] Gender affirmation is often conceptualized in 4 domains: medical, social, psychologic, and legal.[9] Although this review focuses largely on the medical domain, the other 3 domains are important for clinicians who care for gender-diverse people to be familiar with so that they can provide comprehensive, gender-affirming care.

Methods for socially affirming gender identities can include asking about and using the person's chosen name and pronouns during all clinic encounters. For psychologic and legal gender affirmation, clinicians may provide support and refer individuals to appropriate resources such as gender-affirming mental health clinicians and legal professionals who may be able to help with gender-marker (ie, the designated gender on an individual's identifying documents such as driver licenses) and name-change processes, respectively.

An essential component of providing gender-affirming medical care is appropriate documentation of all encounters to ensure that costs are covered by insurance. At this time, we recommend that clinicians document each patient's experience of *gender dysphoria*, which refers to the distress related to having incongruence between gender identity and sex assigned at birth and has a specific ICD-10 code. Importantly, not all patients seeking or receiving gender-affirming therapies experience dysphoria related to their gender. However, billing these visits using a gender dysphoria code is the easiest way to ensure insurance coverage.

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Table 2. Common Gender-Affirming Hormone Therapy Regimens[a]

Medication class	Route	Suggested starting dose range	Suggested maximum dose
Feminizing hormone therapy			
Estrogens			
	Oral or sublingual estradiol	2.0 mg daily	8.0 mg daily
	Transdermal estradiol patch	0.1 mg daily	0.4 mg daily
	Parenteral estradiol valerate (IM/SQ)	20 mg every 2 weeks	40 mg every 2 weeks
	Parenteral estradiol cypionate (IM/SQ)	2 mg every 2 weeks	5 mg every 2 weeks
Antiandrogens			
	Oral spironolactone	100 mg daily	200 mg twice daily
	Oral cyproterone acetate[b]	10 mg daily	same as starting dose
	Parenteral GnRH agonists (IM/SQ)	3.75–7.50 mg monthly	same as starting dose
	Parenteral GnRH agonist depot formulation (IM/SQ)	11.25 mg every 3 months or 22.5 mg every 6 months	same as starting dose
Progesterone			
	Oral micronized progesterone	100 mg daily	200 mg daily
Masculinizing hormone therapy			
	Parenteral testosterone enanthate/cypionate (IM/SQ)	50–100 mg weekly or 100–200 mg every 2 weeks	same as starting dose
	Parenteral testosterone undecanoate (IM)	1000 mg every 12 weeks or 750 mg every 10 weeks	same as starting dose
	Transdermal testosterone patches	2.0 mg daily	8.0 mg daily
	Testosterone topical gel 1%	50 mg daily[c]	100 mg daily

Abbreviations: IM, intramuscular; GnRH, gonadotropin-releasing hormone; SQ, subcutaneous.

[a] Adapted from Coleman[11] and Deutch.[12]

[b] Not available in the United States.

[c] 30 mg = 1 pump.

Several sets of clinical guidelines are useful for practitioners caring for transgender and gender-diverse people; these include guidelines from the Endocrine Society, the World Professional Association of Transgender Health, and the University of California San Francisco.[10–12] All discuss approaches to the 2 main components of gender-affirming medical care: gender-affirming hormone therapy (GAHT) and surgical care.

Gender-Affirming Hormone Therapy

Despite nuanced differences in approach among the various guidelines, all share the same basic tenets of GAHT, which are described in Table 2. In general, masculinizing hormone therapy consists of administering exogenous testosterone via either long-acting injectable routes (eg, subcutaneous, intramuscular) or shorter-acting topical routes (eg, gels, patches). Feminizing hormone therapy involves the administration of exogenous estrogen as well as adjunctive therapies aimed at blocking testosterone. Estradiol can be administered orally, transdermally via patches, or injected intramuscularly or subcutaneously. The choice of route for these medications is best determined on an individual basis, accounting for insurance coverage, safety, patient preference, and cost. Testosterone-blocking adjunctive therapies for feminizing hormone regimens include spironolactone, gonadotropin-releasing hormone (GnRH) agonists, and finasteride.

Monitoring of people receiving GAHT requires laboratory testing every 3 months for the first year of therapy. The 3 guideline documents differ slightly in this aspect but in general agree that practitioners should consider testing for testosterone and estradiol levels, electrolyte levels, hematocrit values (for people receiving testosterone), lipid levels, and liver function. It is also important for clinicians to ask patients at these intervals about their perceived progress since starting hormone therapy, including positive and negative effects

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of medications on their body or mood. Counseling to set appropriate expectations for the changes they may experience from GAHT is essential. The majority of people experience the most dramatic results within the first 6 months, but treatment can take up to 3 years for some individuals to reach desired results.

Gender-Affirming Procedures and Surgery

Although many individuals desire gender-affirming procedures and surgeries, it is important to understand that not all wish to pursue such treatments. Early in the patient–clinician relationship, practitioners should assess the individual's goals for desired procedures as well as any previous procedures the person may have undergone, whether under the supervision of licensed health care practitioners or otherwise. In general, data on outcomes for various procedures are limited because gender-affirming surgery is a growing field; however, available studies suggest promising outcomes for patient satisfaction and quality of life for transgender individuals who have undergone these procedures.[13,14] Colloquially, gender-affirming surgeries are grouped as "top" surgery (ie, involving the chest or breasts), "bottom" surgery (ie, involving the genitourinary or reproductive organs), or cosmetic surgery.

Among transgender women, approximately 4% to 25% undergo gender-affirming surgical procedures.[15] These procedures include breast augmentation, orchiectomy, chondrolaryngoplasty, facial feminization surgery, vaginoplasty, labioplasty, and vulvoplasty.[11] In recent years, increasing numbers of transgender women are undergoing genital surgeries,[16] likely aided by increases in the number of health care practitioners gaining this expertise and offering such procedures as well as by changes in insurance coverage that make these procedures more financially feasible.[16] Despite this increased utilization, cost remains a substantial barrier preventing many transgender people from pursuing desired surgical procedures.[17,18]

Cosmetic procedures are also utilized by this population, including fillers, which are used by an estimated 10% to 17% of transgender women. Most commonly, loose fillers are injected into the breasts, face, hips, and buttocks to achieve a more feminine-appearing silhouette. Whereas licensed clinicians safely inject substances such as silicone and other fillers in many patients, people desiring such treatments may seek unlicensed individuals to overcome barriers of cost and availability.[19] Thus, counseling should be given on the potential risks of accessing such procedures outside of the health care system; risks include potential for acquisition of bloodborne pathogens (eg, HIV, viral hepatitis), filler migration, inflammation, emboli, disfigurement, and death.

For transgender men, an estimated 25% to 50% undergo gender-affirming top surgery, which often involves breast reduction or chest reconstruction.[15] Hysterectomy and bilateral salpingectomy-oophorectomy (estimated prevalence, 14%)[20] not only offer gender-affirmation via removal of reproductive organs, but also may provide dysphoria relief by eliminating menstruation or the risk of becoming pregnant. Bottom genital surgeries are also available, although less common (prevalence, 2%–5%), including metoidioplasty, phalloplasty, urethroplasty, and scrotoplasty.[15] However, these genital procedures can be complex and require extensive surgical expertise and close follow-up.

HIV in Transgender Populations

In the general US population, the estimated prevalence of HIV is 0.39%, which is significantly lower than estimates among transgender women and transgender men (42.0% and 3.2%, respectively).[5,21] Transgender people of color experience the most significant HIV burden, with 51% of transgender women and 58% of transgender men with HIV identifying as Black or African American.[22]

Significant data demonstrate that transgender women with HIV have poorer outcomes across the entire HIV care cascade, including lower rates of retention in care, use of, as well as adherence to, antiretroviral therapy (ART), and viral suppression.[23–27] Data from the Ryan White HIV/AIDS Program in 2020 showed that viral suppression rates among transgender women were significantly lower than those of other populations. For

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example, 89.5% of cisgender individuals were virally suppressed compared with 84.2% of transgender women.[28] Within this group of transgender women, rates of viral suppression were even lower for those who were African American (81%), aged 20 years to 24 years (73.9%), aged 25 years to 29 years (79%), experiencing unstable housing (71.6%), and particularly those who were Black and experiencing unstable housing (66.9%).[28]

Several factors have been associated with viral non-suppression among transgender women, including prioritization of transition-related medical care over HIV care, concerns about drug–drug interactions between ART and GAHT, negative experiences with health care professionals and systems, fear of discrimination, HIV stigma, and mental health and substance use comorbidities.[29,30]

Drug–Drug Interactions

Although drug–drug interactions between ART and GAHT medications are cited as major concerns among transgender women with HIV, there are relatively few such interactions. According to the 2022 US Department of Health and Human Services HIV/AIDS Treatment Guidelines, ART regimens with the least potential to interact with GAHT are those that are most commonly prescribed as part of first-line therapy: all nucleoside reverse transcriptase inhibitors (nRTIs), unboosted integrase strand transfer inhibitors (InSTIs), and nonnucleoside reverse transcriptase inhibitors (NNRTIs), particularly rilpivirine and doravirine.[31]

ART regimens with the least potential to interact with GAHT are those that are most commonly prescribed as part of first-line therapy: nRTIs, unboosted InSTIs, and NNRTIs

Some medication classes have the potential to increase or decrease levels of GAHT components, so monitoring patients on these medications and adjusting GAHT drug dosages based on the desired clinical effects, adverse effects, and serum hormone concentrations are essential. Medications that may decrease estradiol levels include protease inhibitors boosted with ritonavir, efavirenz, etravirine, and nevirapine, with the latter 3 also having the potential to decrease testosterone and finasteride levels. Medications that may increase testosterone, finasteride, or dutasteride levels include boosted elvitegravir as well as protease inhibitors boosted by either cobicistat or ritonavir. The effects of boosted elvitegravir and protease inhibitors boosted with cobicistat on estradiol levels are unclear.

Medical Comorbidities

People with HIV who are receiving ART are at risk of long-term medical comorbidities, including weight gain, cardiovascular disease, low bone mineral density, and renal dysfunction. For transgender individuals on GAHT, these comorbidities have the potential to be augmented and can yield similar sequelae.

Weight Gain. Certain components of ART regimens, particularly InSTIs and tenofovir alafenamide (TAF), have been associated with weight gain.[32,33] This phenomenon is multifactorial for most individuals, with lifestyle factors such as diet and exercise likely having roles. Further, especially for people with advanced, long-standing HIV infection, weight gain may represent a reversal of HIV-related wasting and a return to a healthy weight. However, there are situations for which initiation of ART can contribute to weight gain and associated metabolic sequelae such as diabetes and hyperlipidemia. For persons on GAHT, weight-related changes are also commonly observed, including changes in fat distribution and muscle mass. For transgender individuals taking estrogen as part of a feminizing GAHT regimen, loss of muscle mass and weight gain are frequently observed. Increased muscle mass is expected for individuals taking testosterone as a part of masculinizing GAHT, but the weight gain is variable. In addition to the stress associated with transition, weight gain in people initiating GAHT can thus be multifactorial.[34]

For transgender individuals with HIV who are on ART as well as GAHT, weight gain may be compounded; thus, shared decision making on how

to approach such changes is imperative. For many, changes in fat distribution, weight gain, and muscle mass are desired as part of their transition, so monitoring other metabolic parameters (eg, levels for hemoglobin A1c and lipids) is reasonable. Currently, switching ART components is not recommended for most people experiencing weight gain, and lifestyle modifications should be prioritized. As an alternative, if an ART switch is deemed appropriate using a patient-centered approach, an NNRTI-based regimen could be considered.[31] If individuals taking estrogen are experiencing significant weight gain with which they are not happy, reducing their estrogen dose could be discussed if the person is amenable.

Cardiovascular Risk. Inflammation, associated with HIV infection, increases the risk of cardiovascular disease, especially in aging populations.[35] Compounding that risk is the potential for certain components of ART regimens, namely protease inhibitors and abacavir, to potentially increase cardiovascular risk as well.[36,37] More recently, associations between TAF and dyslipidemia have also been proposed.[38]

GAHT regimens with estrogen are associated with increased venous thromboembolic risk[39] as well as potential increased risk of hypertension, dyslipidemia, and stroke.[40] Notably, these associations are extrapolated from data in cisgender women being treated with estrogens for menopause-related symptoms. Discussions of these potential adverse events are important to have with people who are with HIV and taking estrogens as part of a feminizing GAHT regimen.

Transgender people experience poorer cardiovascular outcomes than their cisgender counterparts for multifactorial reasons, including the likely major drivers of psychosocial and minority stress factors

With ART, avoiding regimens containing protease inhibitors, abacavir, and TAF may be considered to decrease cardiovascular risk. Estrogen injectables and patches should also be considered for people older than 40 years, given their lower potential for adverse cardiovascular events versus oral treatment.[41] These considerations are particularly important in older populations, as cardiovascular risk increases with age.

Overlying these medication factors are the roles of lifestyle and equity components as well as stress in cardiovascular risk. Transgender people experience poorer cardiovascular outcomes than their cisgender counterparts for multifactorial reasons, including the likely major drivers of psychosocial and minority stress factors (eg, discrimination, lack of affordable housing, and limited access to health care).[42] The provision of comprehensive medical and social services to populations such as transgender people with HIV has the potential to reduce some of this stress and possibly improve cardiovascular outcomes.

Another major lifestyle factor to be considered is tobacco use. Counseling patients on smoking cessation at initiation of GAHT with estrogens is very important. However, withholding estrogens altogether is not recommended for people who continue to smoke. Harm reduction strategies can be applied in a shared decision-making process to help people identify ways to reduce and eventually quit smoking entirely.

Bone Health and Renal Impairment. Although limited, some data suggest that transgender women may be at risk of osteoporosis, especially with underutilization of hormones after gonadectomy or the use of androgen blockers with insufficient estrogen.[12,43,44] Long-term use of ART regimens containing tenofovir disoproxil fumarate (TDF) have also been associated with decreases in bone mineral density.[45] For transgender women with HIV, balancing the need for estrogen and androgen blocker is essential, especially after gonadectomy. Avoiding ART regimens containing TDF in favor of those containing TAF, which has less impact on bone mineral density, can also help promote bone health. Health modifications such as addition of regular, light-weight-bearing exercise are also beneficial.

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In addition to its impact on bone mineral density, TDF also adversely affects renal function. Therefore, TAF-containing regimens are preferred for people with underlying renal disease.[46] In monitoring renal parameters for transgender people, clinicians need to recognize that changes in body composition and lean body mass associated with GAHT can affect creatinine levels. Therefore, after a person has taken GAHT longer than 6 months, monitoring creatinine clearance and calculations of ideal body weight should be based on gender identity rather than on sex assigned at birth.[47]

HIV Prevention and Transgender Populations

Within the past decade, several biomedical options for HIV prevention have become available, including 2 oral antiviral combinations of tenofovir and emtricitabine, TDF/FTC and TAF/FTC, and 1 long-acting injectable antiretroviral, cabotegravir (CAB-LA).[48] Despite the demonstrated efficacy and safety of HIV pre-exposure prophylaxis (PrEP) in transgender populations, the uptake, adherence, and persistence of PrEP among transgender men and transgender women have been suboptimal.[49–52] Reasons include concerns about drug–drug interactions with GAHT, competing health care priorities, and limited access to gender-affirming care practitioners.[52–54]

Some regions in the United States have had improvement in PrEP uptake in recent years, however. In San Francisco in 2013, for example, among a cohort of transgender women (n = 233), only 14% had heard of PrEP and 1% were willing to take it.[55] When the same survey was repeated there in 2019–2020, 94% of the cohort of 201 transgender women had heard of PrEP and 45% had taken PrEP in the previous 12 months.[56] Despite such improvements in PrEP awareness and uptake, PrEP persistence is still challenging among transgender populations. Another San Francisco study reported that the median days to PrEP discontinuation among transgender women who have sex with men was 120 days. As for reasons for low PrEP uptake, the explanations for low persistence are complex and require further study.[57]

The first step toward effective individual HIV prevention is identifying the person's risk of acquiring HIV infection. The 2021 CDC HIV PrEP guidelines provide useful risk assessment tools for sexually active persons, such as asking about HIV serostatus of partners and recent history of bacterial STIs.[48] It is important that clinicians assess transgender people for HIV risk factors as for patients of any gender identity. One qualitative study among transgender women in the southeastern United States found that when clinicians conflated HIV risk with gender identity and made assumptions about sexual behaviors based on gender identity, transgender women felt alienated and stigmatized.[53]

Practitioners should discuss the various options available with transgender people desiring to start HIV PrEP, taking into consideration each person's gender identity, sex assigned at birth, medical comorbidities, and sexual behaviors. Use of CAB-LA has been studied and deemed safe and effective in people of all genders; however, the medication cannot be used in individuals who have silicone injection or fillers involving the buttocks because the CAB-LA injection is administered there.[58] Oral options for transgender women include daily FTC/TDF and daily FTC/TAF; however, no studies have yet assessed efficacy of FTC/TAF in individuals participating in receptive neovaginal sex.[48] Given that people assigned female at birth were not included in the landmark clinical trial assessing efficacy of daily FTC/TAF, this option is not currently recommended for transgender men or nonbinary people assigned female at birth.[59]

For nondaily oral PrEP, also known as the "2-1-1" regimen or event-driven dosing of FTC/TDF, current CDC guidelines include this regimen as an option for cisgender men who have sex with men based on efficacy data from 2 trials that included this population.[48,60,61] However, the 2022 IAS–USA guidelines offer a CIII recommendation rating for prescribing event-driven PrEP for transgender individuals, extrapolating from pharmacokinetic data from the Ipergay trial.[62,63] Given no direct data on the efficacy of this dosing regimen in any transgender population engaging in any kind of sexual behaviors, we recommend shared decision making

between patient and clinician in the choice of dosing regimen.

Drug–drug interactions between GAHT and PrEP medications are a major concern of transgender individuals.[53] As such, the interplay between these 2 medication groups has been an area of active research in transgender health in recent years, and no evidence of bidirectional effects between PrEP and GAHT has been established. The iBrEATHe trial (Truvada for HIV Pre-exposure Prophylaxis Using Daily Directly Observed Therapy to Look at Potential Interactions Between Truvada and Hormone Therapy) demonstrated that among transgender women on estrogen therapy as well as transgender men on testosterone, serum hormone concentrations were not impacted after 4 weeks of therapy with FTC/TDF. In addition, dried blood spots had comparable serum FTC/TDF levels after 4 weeks of therapy regardless of gender identity and GAHT regimen.[64,65] Results of the DISCOVER trial (Emtricitabine and Tenofovir Alafenamide vs Emtricitabine and Tenofovir Disoproxil Fumarate for HIV Pre-exposure Prophylaxis) found comparable TFV–DP concentrations between transgender women on GAHT and cisgender men who have sex with men for those taking FTC/TAF. Finally, initial findings in a subset of patients (n = 53) from the HPTN (HIV Prevention Trials Network) 083 study suggest that GAHT does not impact CAB–LA concentrations.[66]

Improving HIV Prevention and Care Engagement in Transgender Communities

Creating care environments that facilitate gender affirmation is key to improving engagement in HIV prevention and care among transgender populations. Transgender people with HIV who have health care practitioners that affirm their gender by using their chosen name and pronouns are more likely to be virally suppressed.[67] Integration of gender health with HIV care is also associated with higher rates of viral suppression, fewer clinician visits, and facilitation of open discussions related to an individual's concerns about HIV and gender-related health care.[68]

Transgender representation in health care environments is also essential to creating safe spaces for people who have traditionally experienced blatant discrimination in these settings. Use of peer navigation services and hiring of transgender staff can ease the discomforts of engaging in care and promote advancement along the HIV care continuum.[69] Displays of allyship such as including transgender images throughout clinic spaces and providing gender-neutral restrooms are also impactful. Given the various forms of violence, stigma, and discrimination experienced by transgender people,[20] applying a trauma-informed lens to HIV care is another important consideration.[70]

The ways in which clinics collect gender-related data are key to creating an affirming environment for the transgender and nonbinary community. This process begins with clinic and health-system intake forms, including how these data are entered into electronic medical records by staff. Collecting such data has been deemed acceptable not only by transgender and gender-diverse populations, but also by cisgender, heteronormative populations.[71] Either via direct questions on intake forms or when conversing with individuals, clinic staff should ask each person for their preferred name and pronouns. In addition, we recommend using the 2-step method that allows clinicians to reconcile both current gender identity and sex assigned at birth.[12] Other best practices include obtaining and maintaining organ inventories for patients that account for any prior gender-affirming procedures, as well as the use of neutral, nongendered language in general.[12]

Conclusion

Transgender patients are highly impacted by the HIV epidemic as well as many other health care disparities. Creating gender-affirming care environments and providing evidence-based, high-quality care for those with and at risk for HIV are essential components of ending the HIV epidemic.

This article is based on a presentation given by Dr Blumenthal on December 8, 2022. The initial presentation is presented as a webcast here: https://www.youtube.com/watch?v=1tp8Lu1upuc

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Invited Review

Chronic Hepatitis B and HIV Coinfection

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Hepatitis B virus (HBV) infection is common among people with HIV owing to shared modes of viral transmission. Compared with individuals with HBV infection alone, people with HIV/HBV coinfection experience an accelerated progression of liver disease, including increased risks for hepatocellular carcinoma, liver-related mortality, and all-cause mortality. Therefore, HBV screening and appropriate treatment are crucial for people with HIV. This article reviews the epidemiology, natural history, and management of HIV/HBV coinfection, as well as recommendations for prevention of HBV infection among people with HIV.

Keywords: HIV, HBV, HIV/HBV coinfection, hepatitis B virus, coinfection

Introduction

Hepatitis B virus (HBV) is a partially double-stranded DNA virus that can be transmitted through blood and bodily fluids.[1] HBV infection can cause acute and chronic hepatitis and over time can lead to liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease (ESLD).[2] In 2019, the World Health Organization estimated that 296 million people, or 3.8% of the global population, had chronic HBV infection, with most residing in low- and middle-income countries.[3] Despite the availability of effective treatment with antiviral medications and prevention by vaccination, HBV infection remains a major driver of morbidity and mortality around the world, with an estimated 820,000 related deaths in 2019.[4]

Owing to shared modes of transmission, chronic coinfection with HBV is common among people with HIV. In the era of antiretroviral therapy, cirrhosis, ESLD, and HCC account for an increasing proportion of deaths among individuals with HIV.[5-8] In this article we outline key epidemiologic and natural history features of HIV/HBV coinfection and review important principles in the management and prevention of HBV infection among people with HIV.

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Epidemiology of HIV/HBV Coinfection

Globally, an estimated 8% to 10% of people with HIV have chronic HBV infection, although the prevalence of coinfection varies significantly by region.[9-14] A recent meta-analysis of HBV infection among people with HIV reported the prevalence of HIV/HBV coinfection as highest in the World Health Organization Western Pacific region (11.4%) and sub-Saharan Africa region (10.0%) and lowest in the regions of Europe (6.7%) and the Americas (5.3%).[9] Modes of transmission for HBV also vary significantly by region. In high-prevalence countries, HBV is most commonly transmitted perinatally, from mother to child, and rates of HIV/HBV coinfection are broadly similar across different HIV risk groups, including individuals engaging in heterosexual sex, pregnant persons, men who have sex with men (MSM), and children.[14] In low-prevalence countries, including the US, sex and injection drug use are more common modes of transmission, with few reported cases of perinatal transmission.[1,15]

In the US, the prevalence of chronic HBV infection in the general population is estimated to be 0.3% to 0.7%, with most infections occurring among foreign-born individuals.[16-19] In contrast, an estimated

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5% to 10% of people with HIV in the US have chronic coinfection with HBV.[11,20] In a large US-based observational cohort study of people with HIV from 1996 to 2007, the prevalence of HBV coinfection was higher among MSM than in other subgroups, including heterosexual individuals and people who inject drugs. However, these data were collected largely before the opioid epidemic in the US, and newer data from the Centers for Disease Control and Prevention suggest that injection drug use is the most common risk factor for HBV infection among the general US population, followed by having multiple sexual partners.[11,21]

Natural History of HIV/HBV Coinfection

Compared with individuals with HBV infection alone, people with HIV/HBV coinfection can experience an accelerated progression of liver disease, including increased risks for HCC, liver-related mortality, and all-cause mortality.[22-26] In a large US-based cohort study of MSM from the era before and shortly after the advent of antiretroviral therapy, liver-related mortality among individuals with HIV/HBV coinfection was 8 and 18 times higher than in those with HIV or HBV infection alone, respectively.[22] Among invidividuals with coinfection in this study, liver-related mortality was highest among those with a low nadir CD4+ cell count, a finding that was replicated in this same cohort later in the antiretroviral therapy era.[26] Although antiretroviral therapy has been shown to improve liver fibrosis among persons coinfected with HIV and HBV,[27,28] HBV infection remains a major contributor to ESLD well into the modern antiretroviral therapy era. In a large observational study of 12 clinical cohorts in the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design), investigators evaluated incident ESLD outcomes among more than 34,000 people with HIV from 1996 through 2010.[29] Despite substantial increases in the use of antiretroviral therapy active against both HIV and HBV, as well as high rates of HIV viral suppression among those receiving antiretroviral therapy in this cohort, there were no differences in the incident rates of ESLD in individuals with HIV/HBV coinfection among the early (1996-2000), middle (2001-2005), and modern (2006-2010) antiretroviral therapy eras. The authors hypothesized that this surprising finding might be due to the fact that 35% of the cohort was not receiving optimal anti-HBV therapy with tenofovir, or perhaps to insufficient power and follow-up time.[29]

The impact of HBV infection on the natural history of HIV infection is less clear. Although some studies have indicated that people coinfected with HIV and HBV experience lower CD4+ cell counts,[30,31] HIV/HBV coinfection has not been associated with an increased risk of AIDS progression or mortality in large cohort studies.[32-34]

Management of HBV Infection in People Coinfected With HIV

Given the high prevalence of chronic HBV infection among people with HIV, and the elevated risk of liver-related complications among invidividuals with coinfection, it is crucial that all individuals with HIV are screened for HBV. Screening identifies not only individuals who need treatment for HBV infection but also those who would benefit from HBV vaccination.[35] For people with HIV, the American Association for the Study of Liver Disease (AASLD) recommends screening with the following tests: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs).[35] People with HIV who test positive for HBsAg should undergo further testing with an HBV DNA level to determine the magnitude of HBV replication, as well as testing for hepatitis B e antigen (HBeAg) and hepatitis B e antibody (anti-HBe).[36]

Major guideline committees recommend initiating antiviral therapy for the treatment of HBV infection in all HIV/HBV-coinfected persons regardless of CD4+ cell count or HBV-related factors (such as viral level or liver aminotransferase elevation). The immediate goal of therapy is to reduce necroinflammation and HBV DNA replication, and the ultimate goal is to avert or delay the development of cirrhosis, ESLD, and HCC, and improve overall survival (Table 1).[35-38] There are 6 oral antiviral agents and 2 injectable interferon alfa formulations

Table 1. Summary of Guideline-Based Treatment Recommendations for HIV and HBV Coinfection

Guidelines	When to initiate	What to initiate
AASLD HBV update, 2018[35]	All patients with HIV/HBV, regardless of CD4+ cell count	2 HBV-active agents: tenofovir (TAF or TDF) with lamivudine or emtricitabine
DHHS antiretroviral guidelines, 2022[36]	All patients with HIV/HBV, regardless of CD4+ cell count	Tenofovir (TAF or TDF) with emtricitabine; chronic administration of lamivudine or emtricitabine as the only HBV-active agent as part of ART should be avoided.
EASL HBV guidelines, 2017[37]	All patients with HIV/HBV, regardless of CD4+ cell count	Tenofovir (TAF or TDF)–containing ART regimen
APASL HBV update, 2015[38]	All patients with HIV/HBV, "irrespective of immunologic, virologic, or histologic considerations"	2 HBV-active agents: tenofovir with lamivudine or emtricitabine

Abbreviations: AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; ART, antiretroviral therapy; DHHS, US Department of Health and Human Services; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

that have been approved for the treatment of HBV infection by the US Food and Drug Administration (Table 2). However, only 3 oral agents—entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF)—are considered first-line, because of their potency against HBV, high barrier to resistance, and favorable adverse effect profile.[35] Although lamivudine was the first oral antiviral agent approved for the treatment of HBV, and the first to show a reduction in disease progression and incidence of HCC, its use as HBV monotherapy is no longer recommended because of the substantial risk of developing drug resistance, with a 5-year cumulative resistance rate of 70%.[37,39,40] The use of adefovir is similarly not favored owing to its toxicity, relatively low potency, and moderate risk of resistance. Telbivudine is no longer manufactured in the US, and interferon alfa is generally not used as a first-line agent because of significant adverse effects.

For individuals with HIV/HBV coinfection, the Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiation of an antiretroviral therapy regimen that contains a nucleoside reverse transcriptase inhibitor backbone of TDF or TAF plus emtricitabine (FTC) or lamivudine.[36] Although combination antiviral therapy is generally not used in HBV monoinfection, dual therapy with a combination of TDF or TAF plus FTC or lamivudine is recommended in invidividuals with coinfection, as these agents provide activity against both HIV and HBV and are generally coformulated. Individuals with HIV being considered for a tenofovir-sparing regimen, including the 2-drug regimens of dolutegravir-lamivudine and cabotegravir-rilpivirine, should first be evaluated for HBV to confirm the absence of coinfection. Entecavir, although highly active against HBV, has only partial activity against HIV and can produce an M184V mutation in people with HIV infection if it is not given in conjunction with a fully suppressive antiretroviral therapy regimen.[36]

For tenofovir, in addition to being highly active against HBV and HIV, data suggest that long-term use can lead to improvements in liver necroinflammation and to regression of fibrosis. In an open-label study of TDF for the treatment of patients with HBV monoinfection, 304 of 348 (87%) had histologic improvement on liver biopsy and 176 (51%) had regression of fibrosis by year 5 of treatment.[41] Despite these encouraging findings for HBV monoinfection, similar results have not been replicated in HIV/HBV coinfection.[42]

Table 2. US Food and Drug Administration–Approved Oral Antiviral Therapy for HBV Infection

Medication	Potency against HBV	Barrier to HBV resistance	HIV activity	Selection of HIV resistance
Lamivudine	Moderate	Low	Yes	Yes
Adefovir	Low	Moderate	No[a]	No
Entecavir	High	High[b]	Partial	Yes
Emtricitabine	Moderate	Low	Yes	Yes
Telbivudine	High	Low	Partial[c]	No
Tenofovir[d]	High	High	Yes	Yes

Abbreviation: HBV, hepatitis B virus.

[a]Anti-HIV activity at higher doses; more potent against HBV.

[b]In patients without lamivudine resistance.

[c]No in vitro activity observed against HIV, but HIV RNA decline reported.

[d]Either tenofovir disoproxil fumarate or tenofovir alafenamide.

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Although there are several short- and long-term health benefits of treatment for HBV infection, the key limitation of antiviral therapy is that it does not offer a functional cure, defined by the sustained loss of HBsAg and control of HBV viremia, even in the absence of antiviral therapy. Studies performed in individuals without HIV suggest that after 2 to 3 years of therapy, HBsAg loss ranges from 1% to 8% for entecavir, TDF, and TAF despite high rates of viral suppression with these antiviral agents (Table 3).[35]

Table 3. Antiviral Efficacy for HBV Infection in Persons Without HIV

Endpoint	Peginterferon alfa[a]	Entecavir[b]	Tenofovir disoproxil fumarate[b]	Tenofovir alafenamide[c]
Viral suppression, %	30-42	61	76	73
HBeAg loss +/– seroconversion, %	29-36	21-25	21	22
ALT normalization, %	34-52	68-81	68	—
HBsAg loss, %	2-7	4-5	8	1

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

[a]Assessed 6 months after completion of 12 months of therapy.

[b]After 3 years of therapy.

[c]After 2 years of therapy.

Among individuals with HIV/HBV coinfection, there is emerging evidence suggesting a possible advantage to TAF over TDF with regard to HBV viral endpoints. In an international multicenter trial of 234 individuals with HIV/HBV coinfection, participants were randomly assigned to receive either TAF/FTC/bictegravir or TDF/FTC plus dolutegravir for treatment of HIV and HBV infection.[43] Participants were followed for 48 weeks and monitored for key HIV and HBV virologic endpoints. Compared with those receiving TDF/FTC plus dolutegravir, the group receiving TAF/FTC/bictegravir had a higher proportion of HBsAg loss (12.6% vs 5.8%), HBsAb seroconversion (8.4% vs 3.3%), HBeAg loss (25.6% vs 14.4%), and alanine aminotransferase normalization (73.3% vs 55.3%). HIV viral suppression and mean CD4+ cell gains were comparable across both groups.[43] Interestingly, aside from alanine aminotransferase normalization, similar findings have not been seen in studies of HBV-monoinfected individuals, and replication of these results in larger-cohort studies is needed to establish whether there is indeed an advantage to TAF over TDF in individuals with HIV/HBV coinfection.

Staging of Liver Disease

Because treatment for HBV infection is indicated in all individuals with HIV/HBV coinfection, fibrosis staging does not affect treatment decisions as it does for HBV-monoinfected individuals. Nevertheless, determining whether a patient has cirrhosis remains important for their overall medical care and for making decisions surrounding the need for HCC screening. Although hepatic ultrasound may provide clues to the diagnosis (eg, splenomegaly, nodular hepatic contour), it is not sufficient for making the diagnosis of cirrhosis, and sensitivity may be as low as 40%.[44] Other noninvasive tests, including the aspartate aminotransferase–to-platelet ratio index and fibrosis-4 scores, have been well validated in patients coinfected with HIV and hepatitis C virus, but they have a limited ability to discriminate between fibrosis stages in individuals with HBV receiving antiviral therapy, and therefore have limited utility in the management of HIV/HBV coinfection.[45]

Transient elastography is an office-based, noninvasive method for determining liver stiffness in persons with chronic viral hepatitis and fatty liver disease. It propagates an elastic shear wave throughout the liver tissue and uses pulse-echo ultrasound to measure the shear wave velocity, which correlates with liver stiffness.[46] Although liver biopsy remains the gold standard for fibrosis assessment, transient elastography has emerged as the most accurate noninvasive modality for fibrosis staging among persons with HBV infection. Transient elastography has also been validated in patients with HIV/HBV coinfection and has been shown to have an accuracy of approximately 85% compared with liver biopsy.[47] The main disadvantages of transient

elastography are its expense and limited availability, as it requires a specific ultrasound machine that is not accessible in many medical practices.

Screening for HCC

Liver disease, including HCC, is one of the leading causes of non–AIDS-related death among people with HIV,[48] and people with HIV/HBV coinfection are at risk for developing HCC at an earlier age.[22-26] Cirrhosis is a major risk factor for HCC, with 70% to 90% of HBV-related HCC occurring in persons with underlying cirrhosis.[49] HBV DNA level has also been shown to be a major predictor of HCC incidence. In a retrospective analysis of 8354 individuals with HIV/HBV coinfection in the US and Canada, the risk of HCC was 1.77 times higher for those with an HBV DNA level of 201 to 200,000 IU/mL and 4.34 times higher for those with an HBV DNA level of more than 200,000 IU/mL compared with those with an HBV DNA level of 200 IU/mL or lower.[50] In this same study, sustained HBV suppression for 1 year or more was associated with a 58% reduction in HCC risk, with a dose-response relationship with duration of viral suppression.[50]

Because of the markedly elevated risk of HCC among people with cirrhosis, the American Association for the Study of Liver Disease recommends HCC screening for all individuals with HIV/HBV coinfection with cirrhosis, regardless of age.[35] In addition, HCC screening is indicated in the following groups with HBV infection irrespective of the presence or absence of cirrhosis[35]:

- Black men older than 40 years of age
- Asian men older than 40 years of age
- Asian women older than 50 years of age
- Persons with a first-degree family member with a history of HCC
- Persons with hepatitis D virus infection

Considering the faster progression of liver disease among HIV/HBV coinfected individuals, some experts would recommend HCC screening in all coinfected persons over the age of 40 years, although there is no standardized approach. Screening for HCC should be performed using hepatic ultrasound, with or without serum α-fetoprotein, every 6 months.[35] Individuals with suspected HCC should undergo further testing with multiphasic abdominal imaging, via either computed tomography or magnetic resonance imaging.[35]

HBV Vaccination for People With HIV

For people with HIV who do not have HBV coinfection, vaccination is a key pillar of prevention. HBV immunization is now universally recommended for infants, children, and adults aged 0 through 59 years, as well as select groups of adults aged 60 years and older, including people with HIV.[51] Although HBV vaccine recommendations have been simplified over time, HBV immunization has been recommended for MSM, people who inject drugs, and heterosexual individuals with multiple sexual partners since the 1980s, and for all individuals with HIV since 2006.[52] Nevertheless, HBV vaccination rates remain low for people with HIV. For example, in a nationally representative cohort of more than 18,000 adults receiving care for HIV infection between 2009 and 2012, more than one-third of individuals did not have documentation of HBV infection, immunity, or vaccination, and less than 10% of individuals eligible for the HBV vaccination received it during the study period.[53] In addition, almost 8% of this cohort had evidence of natural infection during the study period, an indication of ongoing risk for HBV infection in this population.[53]

The US Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV (OI Guidelines) outline the following indications for HBV vaccination among people with HIV[54]:

1. Individuals without chronic HBV infection (HBsAg negative), immunity to HBV (HBsAb <10 mIU/mL), or evidence of past exposure (anti-HBc negative)
2. Individuals with isolated anti-HBc (eg, anti-HBc positive, but anti-HBs and HBsAg negative)

The OI Guidelines offer several vaccine options for HBV, including the following[54]:

1. A double dose of hepatitis B vaccine intramuscularly (Engerix-B or Recombivax HB) at 0, 1, and 6 months; or

2. Combined hepatitis A and hepatitis B vaccine (Twinrix) at 0, 1, and 6 months; or
3. Vaccine conjugated to CpG (Heplisav-B) at 0 and 1 months

Because HIV infection is associated with suboptimal response rates to HBV vaccination, particularly among those with a low CD4+ cell count,[55] the OI Guidelines recommend checking an anti-HBs titer 1 to 2 months after completion of the vaccine series to document an immunologic response to vaccination.[54] Although vaccine response is better in persons with higher CD4+ cell counts, particularly those with CD4+ cell counts greater than 350/cell mm^3, the OI Guidelines do not recommend delay or deferral of HBV immunization until CD4+ cell recovery on antiretroviral therapy, as some individuals will respond to vaccination despite a lower CD4+ cell count.[54] Those patients who do not mount a seroprotective antibody response after immunization should undergo another complete vaccine series. In individuals with isolated anti-HBc, in lieu of providing a full vaccination series, it is reasonable to provide 1 standard dose of the HBV vaccine followed by an anti-HBs titer in 1 to 2 months. If the titer is less than 100 mIU/mL, then the complete vaccine series should be provided.[54]

Several strategies, including double dosing, have been studied to improve the immunogenic response to HBV vaccine; however, historically none have been consistently effective enough for widespread adoption. Nevertheless, more recently the Heplisav-B vaccine has emerged as a strategy to increase vaccine response rates, in both vaccine-naive adults and previous nonresponders to HBV vaccine. In phase III registration trials among persons without HIV, Heplisav-B was found to be safe and effective, producing higher rates of seroprotection than Engerix-B.[56-59] Furthermore, in studies involving previous vaccine nonresponders, Heplisav-B was shown to induce higher rates of seroprotection than single-antigen 3-dose hepatitis B vaccines (eg, Engerix-B and Recombivax-HB).[60,61] Similarly, among persons with HIV, there is emerging evidence for the use of Heplisav-B. Previous studies of Engerix-B versus Engerix-B plus a CpG adjuvant, small real-world observational studies, and preliminary results from an ongoing prospective, open-label study to evaluate immunogenicity of Heplisav-B, all suggest that this vaccine is safe and efficacious in persons with HIV.[61,62]

Conclusion

HBV infection remains a major contributor to liver-related deaths among people with HIV, despite effective treatment and prevention strategies. Tenofovir, either TDF or TAF, is the mainstay of therapy for coinfected patients owing to its potency and high barrier to resistance. Antiviral therapy does not offer a functional cure for HBV infection, but sustained HBV suppression with therapy has been shown to reduce the risk of liver-related complications. Because individuals with HIV/HBV coinfection are at increased risk for progression to cirrhosis, ESLD, and HCC, fibrosis staging and routine HCC screening are important interventions to help identify and prevent complications from HBV-related liver disease. For people with HIV without HBV infection, major guidelines recommend universal HBV vaccination, including for those with isolated anti-HBc.

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Invited Review

Exploring Bacteriophage Therapy for Drug-Resistant Bacterial Infections

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The golden age of antibiotics, which lasted from the 1930s until 2005, brought a brisk clip of antibiotic discovery and fueled optimism about the victory of modern medicine over bacterial infections. Since then, however, with a stalled antibiotic discovery effort and widespread antibiotic use, antimicrobial resistance has emerged as a major global health threat. Bacteriophages, or phages (literally viruses that infect certain bacteria), have coevolved with bacteria for almost 4 billion years and are the most abundant organisms on the earth. Substantial progress is being made such that selection, engineering, and synthetic production of phages may make it possible for these lethal enemies of bacteria to be harnessed as potent allies in our battle against antimicrobial resistance.

Keywords: bacteriophage, phage, antibiotic-resistant bacteria

Introduction

The golden age of antibiotics began in the 1930s with the introduction of sulfonamides into clinical medicine and ended in 2005 with the appearance of daptomycin. Since then, no truly novel antibiotics have been brought to the bedside. Throughout the golden age, the brisk clip of antibiotic discovery fueled optimism about the victory of modern medicine over bacterial infections. In large part because of the successful antibiotic discovery effort, the growing evidence that resistant microorganisms were emerging at an accelerating rate was not seen as a major threat, and investments in antibiotic discovery waned. With a stalled antibiotic discovery effort and widespread antibiotic use, antimicrobial resistance (AMR) has emerged as a major global health threat over the past 2 decades.

In a comprehensive assessment of the global impact of AMR published in 2022, it was estimated that in 2019, nearly 5 million deaths were associated with AMR and that 25% of these deaths were directly attributable to antibiotic-resistant pathogens.[1] The largest burden of morbidity and mortality from AMR was borne by lower- and middle-income countries, especially those in sub-Saharan Africa. Emerging data indicate that the incidence of AMR has further accelerated during the COVID-19 pandemic.[2] Modeling suggests that AMR-related deaths may increase to 10 million people per year and that the economic costs from lost productivity will be as high as $1 trillion yearly by 2050 unless current trends are reversed.[3] These alarming trends have stimulated interest in alternative modalities for tackling the problem of AMR. Bacteriophages (or phages), literally "bacteria eaters," have coevolved with bacteria for almost 4 billion years and are the most abundant organisms on the earth.[4] This article outlines the current evidence that these lethal enemies of bacteria can be harnessed as potent allies in our battle against AMR.

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Phage Discovery and Early Development

Beginning in the last decade of the 19th century, researchers noted that there were "factors" in the environment that were capable of lysing bacteria.

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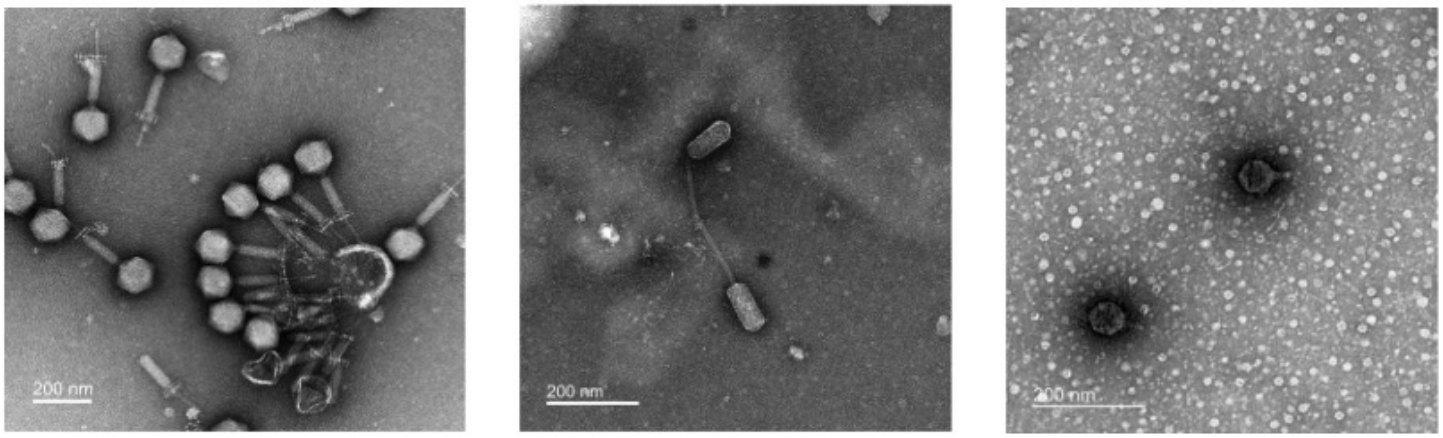

Figure 1. Electron micrographs of the myoviral (left), siphoviral (center), and podoviral (right) bacteriophage morphotypes. Photographs courtesy of Pooja Ghatbale and David Pride, IPATH Translational Research Laboratory, University of California San Diego School of Medicine.

The recognition that these "factors" were parasites of bacteria is attributable to the French microbiologist Félix d'Hérelle, who announced in 1917 that he had discovered an "invisible microbe" that lysed bacteria causing dysentery.[5] This agent could be propagated in bacteria and then passed through filters with pores that were too small for bacteria after the bacterial population had been destroyed. He recognized the potential for these agents to be used therapeutically, and by 1919 he had begun to experiment with them in humans. Although he was convinced that the agents he was working with were reproducing biologic organisms, others believed that the bacterial lysis was being caused by enzymes harbored within the bacteria. With the advent of electron microscopy, Helmut Ruska demonstrated that phages were actually viruses.[6]

The use of phages in medicine became widespread throughout Europe, North America, and the Soviet republics in the 1920s and 1930s and was central to Sinclair Lewis's novel *Arrowsmith*.[7] A failure to fully appreciate the narrow antimicrobial spectrum of phages and the lack of clinical investigations with rigorous microbiologic underpinnings led to an erosion of the phage fervor in the West. When penicillin emerged during World War II, the broader spectrum of penicillin and the antibiotics that followed resulted in the eclipse of phage therapy by antibiotics in the United States and Europe. Interest in phage therapy continued unabated in Eastern Europe and the Soviet republics, where phage therapy programs flourished throughout the last half of the 20th century.[7] Phage therapy has emerged in the West over the last half-decade as the failure of antibiotics to keep up with AMR has led to a broad awareness that new tools to address AMR are sorely needed. Advances in the understanding of phage biology and improved phage selection and production technologies, coupled with several high-profile anecdotal case reports of the use of phage therapy to cure infections for which antibiotics had failed, have led to a renaissance of interest in phage therapy in the US and Europe.[8,9]

Phage Biology

Defined most simply, phages are viruses that infect bacteria. They are ubiquitous in nature, immensely diverse, and highly selective in their bacterial prey. The genomes of most, but not all, phages consist of double-stranded DNA. This DNA is tightly packed into the phage capsid and is usually attached to a "tail" of varying length (see Figure 1). The tips of the tail bind with high specificity to structures on the bacterial cell surface and play a major role in defining the breadth (or range) of bacteria that a given phage can infect. Some phages can infect a large proportion of bacterial strains in a given species. These phages are said to have a "broad" host range. Conversely, some phages may infect only a small fraction of bacteria within a species; these are designated as having a "narrow" host

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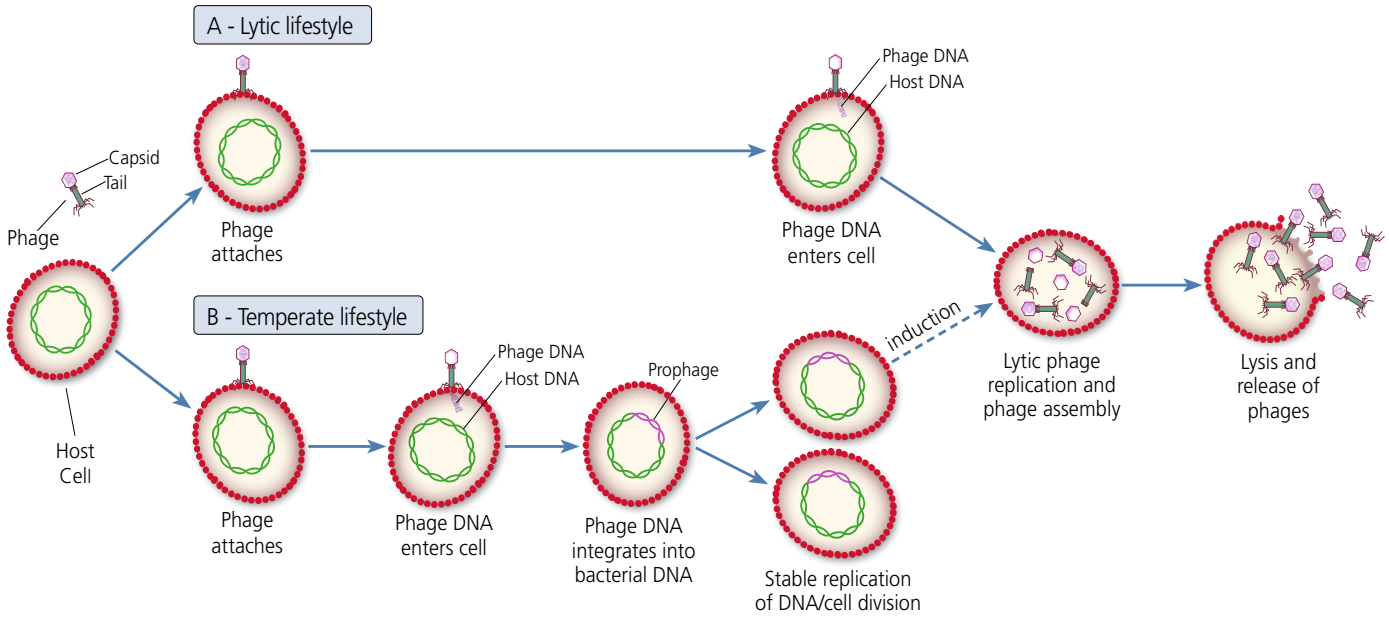

Figure 2. Phage life cycle. (A) Lytic lifestyle: Phage attaches to host bacterium and injects its DNA into the cytoplasm. Host metabolic activity is inhibited and phage production is initiated. Following assembly of daughter virions, phage lysins result in disruption of the cell wall and release of progeny phages. (B) Temperate lifestyle: Phage attaches to host bacterium and injects its DNA into the cytoplasm. Early phage gene expression represses the lytic life cycle and enables integration of phage DNA into the genome of the host bacterium or the establishment of a plasmid. This integrated or plasmid "prophage" replicates with the host cell until it undergoes induction and produces lytic phages.

Adapted from Brunton LL.[34]

range. The breadth of host range of a phage is dependent on cell-binding specificities as well as its resistance to intracellular bacterial defenses and is defined by millions of years of coevolution.[10] Phages of certain bacterial species such as *Staphylococcus aureus* may have a broad host range, whereas most phages of other species such as *Acinetobacter baumannii* have narrow host ranges.

Phage replication begins with binding of the phage tail to a ligand on the cell surface (Figure 2). Once the tail has bound to the cell surface, the nucleic acid of the phage is injected into the cytoplasm of the host bacterium and the phage can proceed with 1 of its 2 developmental programs, or "lifestyles." Based on which of these 2 pathways the phage pursues, a phage is classified as being lytic or temperate. Lytic phages quickly take over the host cell's metabolic machinery to initiate the phage genome expression, nucleic acid replication, and assembly of hundreds (or more) of progeny phages in as little as 20 minutes. When phage production is complete, lytic proteins are produced and the phages burst through the bacterial cell wall to repeat the process in additional bacteria.

Phages that follow a temperate development program can also follow the lytic pathway; however, at varying frequencies depending on the phage, the bacterium, and growth conditions, the genes essential for the lytic pathway can be turned off and the phage can establish "lysogeny."[11] In this situation the phage genome becomes a "prophage" and exists within the host bacterium as integrated DNA or as a plasmid. From time to time under the appropriate conditions, these prophages can be activated and resume a lytic lifestyle by creating a burst of progeny phages and lysing their bacterial hosts. When this occurs, phages may incorporate components of the bacterial genome and transfer these genetic elements to bacteria they infect. This transfer of bacterial DNA may enable lateral transfer of deleterious genes encoding antibiotic resistance or pathogenetic properties. In addition to the possibility of transferring deleterious genetic elements, prophages may encode repressors that inhibit the ability of lytic phages to infect their bacterial hosts. Because the primary goal of phage therapy is to kill bacterial hosts rather than to transfer genetic material and render bacteria less susceptible to infection

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by other phages, temperate phages are not suitable for clinical use.

Sourcing and Characterizing Phages and Preparing Them for Clinical Use

Phages are ubiquitous in the environment and can be found essentially anywhere bacteria are found. Until recently, most phages used in clinical medicine have been sourced and used "as is" from the environment after being prepared for clinical use, although substantial progress is being made in the area of phage engineering and synthetic phage construction.[12-14] Environmental phage searches are generally undertaken by passing extracts of water, soil, or another potential phage source through 0.22-μm filters, plating dilutions of the filtrate onto lawns of the bacterium of interest, and looking for holes in the lawn indicative of lytic activity.[15]

The likelihood of finding phages that are active against a given bacterial species may be enhanced by sampling from environmental sources where their host bacteria are likely to be found.[16] Such sources might, for example, include sewage treatment plants for phages active against enteric flora or discarded bandages if the target is a phage with antistaphylococcal activity. Phages can be plucked from regions of the agar where the bacterial lawn has been disrupted, passaged on their intended host for amplification, and then fully characterized. In non-emergency circumstances, this characterization should include whole-genome sequencing to search for genetic sequences indicative of lysogenic potential or genes conferring antibiotic resistance or pathogenetic factors.[17] After passing the genetic search for deleterious sequences, phages are amplified on prophage-free host strains and then purified using approaches that approximate good manufacturing practice conditions.[18] The process of identifying and purifying lytic phages remains one of the rate-limiting features for emergency use of phages. Fortunately, over the past decade a number of well-annotated phage banks have been developed in commercial and academic laboratories that contain phages covering broad spectra of individual bacterial species. When these phage banks can be used as a starting point, the process of preparing phages for clinical use can be substantially abridged.

Principles of Phage Therapy

The development of the principles of phage therapy is a work in progress. A recent review of animal and human experiences with phage administration identified very few safety concerns.[19] Although much has been learned from case reports, a more systematic approach to phage therapy will require the conduct of rigorous clinical trials based on the same paradigms that have been applied to antibiotic development over the past 80 years.[20,21]

Pharmacology

In perhaps the biggest departure from the experience with traditional antibiotics, phages will propagate on the pathogen at which they are directed once they are delivered to the site of infection. Advances in phage preparation and purification have made it possible to administer phages parenterally, and the clinical use of phages is increasingly shifting to intravenous administration for the treatment of systemic or deep infections.

Phages are also administered topically for open wounds and burns, by nebulization for pulmonary infection, orally for gastrointestinal infection, and into the bladder for urinary infections. Phage dosage is expressed as "plaque-forming units" (PFUs), a measure of how many phage particles in a dose are capable of infecting the pathogen of interest in the laboratory. Depending on the dose administered, intravenously administered phages are removed from the circulation by the reticuloendothelial system and sequestered in the liver and spleen over 1 or 2 hours.

Regardless of the route of administration, a primary goal of therapy is to deliver a sufficiently large dose of phage to the site of infection to initiate self-propagating phage replication within the pathogen population. From a practical perspective, most phage regimens feature individual doses in the range of 10^9 PFUs per dose. Doses in this range have been associated with treatment success in a number of published case reports. With

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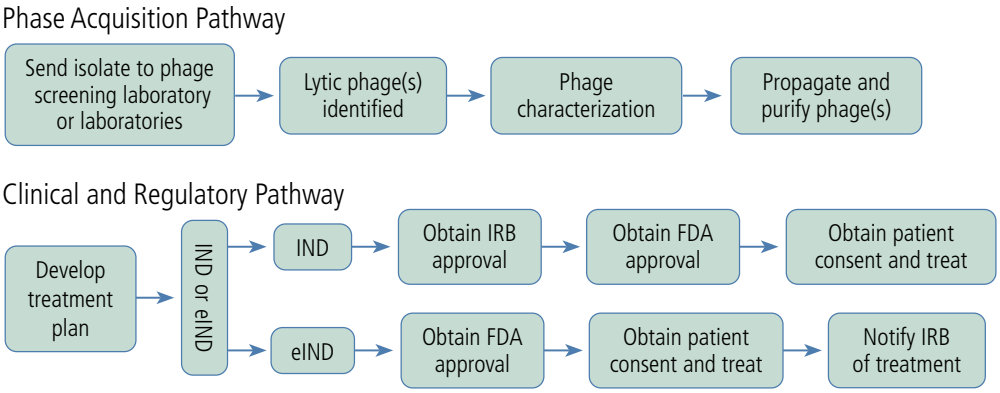

Figure 3. Steps required to identify and prepare phages for clinical use (top). Steps required for regulatory approval for clinical use of phages in the United States (bottom).
Abbreviations: IND, investigational new drug; eIND, emergency investigational new drug; IRB, institutional review board; FDA, Food and Drug Administration.

current approaches to the removal of endotoxin in the phage production process, higher doses can be difficult to achieve without exceeding US Food and Drug Administration (FDA)-recommended limits on endotoxin administration (5 endotoxin units [EU]/kg/h).

Phage Resistance

As with all antimicrobial agents, phages can select for organisms with lower levels of susceptibility.[8] Phage resistance can require a substantial tradeoff on the part of the bacterium in terms of fitness. This loss of fitness can come in the form of greatly reduced capsule formation, which can result in less invasiveness and more susceptibility to host immune responses.[8,22] Phages can also be targeted to bacterial efflux pumps that pump antibiotics out of the bacterial cytoplasm. In this case, resistance confers a major disadvantage to the pathogen by resensitizing it to antibiotics to which it was previously resistant.[23] Although phages are often administered as "cocktails" to mitigate this challenge, much additional knowledge is required to advance combination design from empiricism to a scientific basis. Solutions proposed include efforts to compose cocktails of phages with different receptor specificity or orthogonal resistance pathways.

Human Immune Responses to Phages

Phages can be immunogenic and have been used experimentally for decades to study host immune responses.[24] Humoral and cellular immune responses have been detected in patients receiving phage therapy.[25] Case reports have appeared that link treatment failure to the advent of phage-specific antibodies in an immunocompetent patient.[26] The same phage was used in the treatment of a lung transplant recipient for more than 2 years without immune-based loss of activity.[27]

The frequency and clinical significance of this issue are not yet fully understood, but currently available evidence suggests that it may be more problematic in the immunocompetent population. Replacement of phages inducing an immune response with phages capable of lysing the target bacterium but not sharing the epitopes of the strain inducing the immune response has been suggested as a strategy to enable extension of therapy should immune responses to the original phage or phages limit their efficacy.

Phage Susceptibility Testing

Development of tools for the assessment of phage susceptibility in the clinical microbiology laboratory is still in its infancy. The most commonly used approaches to determine phage susceptibility are the agar overlay technique, in which the ability of phages to create visible spots of lysis is assessed, and liquid methods, in which the ability of phages to block bacterial growth is assessed by quantifying bacterial metabolism.[28] The agar overlay method is a classic method for assessing phage susceptibility that has been in use for a century. It requires no specialized equipment, but the readout is subjective. Liquid-based assays can be mechanized for higher throughput and provide quantitative readouts. Efforts to standardize these assays within and across laboratories are in early stages.[29] Very little information is currently available about the extent to which either assay platform predicts clinical activity. As was the case with traditional antibiotics, clinical

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correlations will evolve over time in the context of clinical trials and clinical experience.

Practical Aspects of Phage Therapy

Phages have several major properties that make them particularly attractive as antimicrobial agents. Among them is that they are virtually limitless in nature yet highly targeted individually in terms of host range, resulting in potent antimicrobial activity with limited disruption of the microbiome. The ability to disrupt biofilms provides opportunities to dislodge bacteria from implanted prosthetic devices and from biofilms at mucosal surfaces or in wounds.[30] Phages can restore the susceptibility of bacteria to antimicrobial agents by disabling cellular antibiotic efflux pumps.[23]

A wider appreciation of these properties, coupled with advances in biotechnology that have enabled better access to phages suitable for clinical use, has resulted in an accelerating number of case reports of phage therapy in the peer-reviewed medical literature. Case reports of phage therapy that have appeared since 2017 largely reflect these properties.[31] Roughly one-third of the cases have involved implanted prosthetic devices including joints and cardiac devices. Twenty percent of the case reports have focused on pneumonia (mostly involving drug-resistant organisms), and 10% each have been about the treatment of osteomyelitis and urinary tract infections. Modern case series reflecting this diversity of clinical indications for phage therapy are consistent in focus with the distribution of case reports.[32,33] As with other clinical conditions, it is likely that selection bias results in overreporting of courses of therapy that were perceived to be successful. The fact that there has been so much perceived success in these areas, however, has driven interest in clinical trials to the same areas.

When a physician believes that a patient is a candidate for phage therapy, the first step is to find phages that are active against the patient's organism (see Figure 3). This requires that the organism be retrieved from the clinical laboratory where it was isolated. Because clinical laboratories discard organisms relatively quickly after they are characterized, it is important that the laboratory be asked to save any isolates for which phage therapy might be indicated. The organism then must be sent to a laboratory with access to phages for organisms of that species. This can be a confusing task for physicians who have not been closely following the field; assistance with identifying a laboratory with the correct microbial focus and a willingness to screen the isolate for active phages can be obtained from University of California San Diego's Center for Innovative Phage Applications and Therapeutics (IPATH; https://medschool.ucsd.edu/som/medicine/divisions/idgph/research/center-innovative-phage-applications-and-therapeutics/Pages/default.aspx). Physicians and staff members at IPATH are willing to give advice about the suitability of the patient for phage therapy, provide assistance with locating laboratories willing to screen for phages, provide assistance with the regulatory aspects of phage therapy, and discuss possible treatment plans. Over the past 5 years, IPATH has fielded more than 1500 phage therapy consultations.

In the US, phage therapy is still considered to be experimental by regulatory bodies and must be administered under the supervision of the FDA Office of Vaccines Research and Review in the Center for Biologics Evaluation and Research. Individual candidates for phage therapy are treated under the FDA's investigator-initiated investigational new drug (IND) regulations. The FDA should be contacted through its website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/physician-request-single-patient-ind-compassionate-or-emergency-use) or, in emergency situations, by telephone. The FDA scientist requests information about the case, the phage preparation to be used, and a description of the treatment plan. In emergency situations under the emergency IND (eIND) program, approval can be obtained on the same day. In this case, the patient (or an authorized patient representative) must provide informed consent, but review by a local institutional review board (IRB) is not required. The local IRB must subsequently be notified within 5 days of the initiation of therapy. In less emergent situations, the timeline is a bit longer because more details about the

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phage preparation and treatment plan are required and the local IRB must also opine before the initiation of therapy.

Summary and Conclusions

Over the past several years, phage therapy has become recognized as one of the more promising approaches to the challenge of AMR. Developments in biotechnology have greatly simplified isolation and preparation of phages for clinical use. Phages are being increasingly used in the clinic in the treatment of difficult-to-treat bacterial infections under FDA supervision. Various clinical trials have been launched in the US and Europe that are expected to provide much more detailed knowledge about the principles and practice of phage therapeutics over the years to come.

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