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Subscription Information
Topics in Antiviral Medicine is published 4 to 6 times a year. To obtain a subscription or notify the IAS–USA of a change in address, please create or update your user profile at www.iasusa.org.

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On the Web
Current and previous issues of Topics in Antiviral Medicine (as well as Topics in HIV Medicine) are available online at www.iasusa.org/pub.
ISSN 2161-5861 (Print)
ISSN 2161-5853 (Online)

Printed in USA on acid-free paper
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Grant Support
This activity is part of the IAS–USA national educational effort that is funded, in part, by charitable contributions from commercial companies. Per IAS–USA policy, any effort that uses commercial grants must receive grants from several companies with competing products. Funds are pooled and distributed to activities at the sole discretion of the IAS–USA. Grantees have no input into any activity, including its content, development, or selection of topics or speakers. Generous support for this activity has been received from the following contributors:

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Perspectives

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On completion of this activity, participants will be able to:

- Describe components of the basic reproduction number of HIV infection and describe strategies aimed at reducing HIV transmission
- Describe the characteristics of hepatitis B virus infection and its prevention and treatment in individuals infected with HIV
- List the latest updates to guidelines for the prevention and treatment of opportunistic infections in HIV-infected individuals
- Identify the best strategies for management of chronic pain in HIV-infected individuals

Intended Audience

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

This activity is also relevant for other practitioners, including nurse practitioners, nurses, physician assistants, pharmacists, and others.

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Financial affiliations with commercial entities: Dr Smith has received grants and research support paid to his institution from ViV Healthcare/AbbVie and Pfizer, Inc. Dr Sherman has received research grants or contracts awarded to his institution from AbbVie, Chimerix, Gilead Sciences, Inc, Inovio Pharmaceuticals, MedImmune, Merck & Co, Inc, and Vertex Pharmaceuticals, Inc, and has served as an advisory board member or a consultant to Merck & Co, Inc, and MedImmune. He has also served on data and safety monitoring boards for Janssen Therapeutics, SynteractHCR, and Medpace. Dr Merlin has no relevant financial affiliations to disclose. Dr Masur was awarded grants, paid to his institution, from Gilead Sciences, Inc. Dr Richman has been a consultant to Bristol-Myers Squibb, Chimerix, Gilead Sciences, Inc, Hera Therapeutics, and Monogram Biosciences, Inc. Dr Benson serves on a data and safety monitoring board for GlaxoSmithKline/ViV Healthcare. She has received research grants awarded to the University of California San Diego from Gilead Sciences, Inc, and ViV Healthcare. Her spouse, Dr Robert Schooley, was awarded research grants, paid to his institution, from Boehringer Ingelheim Pharmaceuticals, Inc, and Bristol-Myers Squibb. His institution has received payment for his consultative advice or data monitoring committee service from GlobelImmune, Gilead Sciences, Inc, and Monogram Biosciences. He serves as a consultant to CytoDyn, Hera Therapeutics, and Farmak, and he has stock options from CytoDyn, Hera Therapeutics, and GlobelImmune. Dr Hirsch has no relevant financial affiliations to disclose. Ms Jacobsen has no relevant financial affiliations to disclose.

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October

IAS–USA Fall 2015 Live Courses

Management of Hepatitis C Virus in the New Era: Small Molecule Bring Big Changes: Full-Day Courses

San Francisco, California — Friday, October 16, 2015
Co-Chairs: Marion G. Peters, MD; David L. Wyles, MD

Chicago, Illinois — Friday, October 30, 2015
Co-Chairs: Kenneth E. Sherman, MD, PhD; Donald M. Jensen, MD

Evolving Strategies in Hepatitis C Management: Small-Group Workshops

Philadelphia, Pennsylvania — Thursday, October 22, 2015
Workshop Leaders: Andrew Aronsohn, MD; Charles W. Flexner, MD; Arthur Y. Kim, MD

October

Interactive Webinars With IAS–USA Faculty

HIV Screening: What’s New and Why It’s More Important Than Ever — Tuesday, October 20, 2015
Presenter: Howard Libman, MD

Coming Soon

Cases on the Web

Opioid Agonist Treatment Considerations in HIV-Infected and HIV/Hepatitis C Virus–Coinfected Patients
Authors: Jeanette M. Tetrault, MD, FACP; David A. Fiellin, MD

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Perspective
What Can We Learn From Measles? No New HIV Infections

Reducing the incidence of HIV infection until there are no new infections depends on driving the number of secondary infections produced by a typical source infection in a completely susceptible population (basic reproduction number; $R_0$) down to less than 1. Components of $R_0$ that must be addressed are the number of sexual contacts the infectious person makes per unit of time ($C$), the probability of transmission per single sexual contact with the infectious person ($P$), and the duration that the infected person is infectious to others ($D$) ($R_0 = C \times P \times D$). Numerous strategies may contribute to driving transmission of HIV infection down to zero, including early initiation of antiretroviral treatment and pre- or postexposure prophylaxis. This article summarizes a presentation by Davey M. Smith, MD, at the IAS–USA continuing education program held in San Francisco, California, in March 2015.

**Keywords:** HIV, transmission, transmission probability, infectiousness, duration of infectiousness, susceptible populations, basic reproduction number, reproductive rate, getting to zero

On World AIDS Day in 2012, the goal of “getting to zero” new cases of HIV infection was articulated. More than 2 years later, there are approximately 1.2 million people in the United States living with HIV, and approximately 1 in 5 are unaware of their infection. The incidence of HIV infection has remained stable for the past decade at an estimated 50,000 new infections each year. After 30 years of research, there is still no globally effective vaccine or cure for HIV infection.

**Basic Reproduction Number**

The goal of driving a communicable disease down to no new cases can be evaluated by determining what proportion of susceptible (ie, uninfected) people in a population must be protected (eg, by vaccination, preexposure prophylaxis [PrEP], etc) in relation to the particular reproductive rate of the infectious disease. In standard epidemiology, this is often characterized as the basic reproduction number ($R_0$). The $R_0$ is calculated by the number of sexual contacts an infectious person makes per unit of time ($C$) multiplied by the probability of transmission per single sexual contact with an infectious person ($P$) and the duration that an infected person is infectious to others ($D$) ($R_0 = C \times P \times D$).

The $R_0$ is the number of secondary infections produced by a typical source infection in a completely susceptible population. If a certain infectious agent has an $R_0$ of 4, for example, then an infected individual is expected to pass the infection to 4 individuals and each of those 4 would then pass the infection to 4 more individuals. If a preventive measure, such as a vaccine or PrEP, is used to protect 3 of 4 susceptible people at each step of this progression, then each infected person would pass the infection to only 1 susceptible person at each step. If the $R_0$ of an infection can be reduced to less than 1, the epidemic eventually dies out (ie, there are no new transmissions). For an infection with an $R_0$ of 4, 75% of the susceptible population must be rendered unsusceptible. Figure 1 shows $R_0$ values for communicable diseases and the estimated herd immunity threshold (proportion protected from transmission) needed to halt transmission.

The $R_0$ for HIV infection varies among susceptible populations. For example, it would differ greatly between gay men and heterosexual men in San Diego, California, or between heterosexual individuals in Uganda and injection drug users in Southeast Asia. However, it is estimated that the $R_0$ of HIV infection is between 2 and 5 and that the herd immunity threshold needed to achieve an $R_0$ of less than 1 ranges from 40% to 80%.

**Number of Sexual Contacts**

Each component of $R_0$ is subject to considerable variation. For $C$ (number of sexual contacts the infectious person has per unit of time), factors such as “sexual budget” (how many times a person has sex in a given period of time) or frequency of needle sharing for injection drug use should be taken into account. With regard to sexual transmission of HIV infection, monogamy, serial monogamy, and concurrency (one person having sex with various partners over a given period of time) or frequency of needle sharing for injection drug use should be taken into account. With regard to sexual transmission of HIV infection, monogamy, serial monogamy, and concurrency (one person having sex with various partners over a given period of time).

Figure 1. $R_0$ and herd immunity thresholds for select communicable diseases. In standard epidemiology, $R_0$ is equal to the number of sexual contacts the infectious person makes per unit of time ($C$) multiplied by the probability of transmission per single sexual contact with the infectious person ($P$) and the duration that the infected person is infectious to others ($D$) ($R_0 = C \times P \times D$). Adapted from Fine et al.
time period or set of sexual encounters) yield different infection rates. In particular, if 1 in 8 persons is HIV infected and is serially monogamous, then 1 new infection would be expected after 1 round of sexual partnership and 3 new infections would be expected after 2 rounds. If 1 in 8 HIV-infected persons was concurrently having sex with a main partner and regularly with 2 additional partners, 3 new infections would be expected after 1 round of sexual partnerships and 6 new infections would be expected after 2 rounds.

**Probability of Transmission**

Many factors influence the probability (probability of transmission per sexual contact with the infectious person) of HIV infection, including biologic factors such as stage of infection, viral load in blood and genital secretions, presence of other sexually transmitted infections (STIs), circumcision, host genetics, and use of antiretroviral agents (eg, PrEP, postexposure prophylaxis [PEP], and microbicides), as well as behavioral factors such as sexual contact and positioning, serosorting, condom use, and substance use (eg, methamphetamines).

With regard to stage of HIV infection, the rate of infection per number of sexual contacts is highest during early infection and during very late infection, reflecting higher blood viral loads during these periods. In association with such factors as immune activation and increased viral load in genital secretions, STIs (eg, chlamydia, syphilis, gonorrhea, trichomoniasis, and herpes simplex virus) markedly increase the risk of HIV transmission, especially in Africa. Circumcision has been shown to reduce the risk of HIV transmission to uninfected men but not to female partners of HIV-seropositive men.

Use of vaginal tenofovir microbicide gel reduced HIV transmission in the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 trial among heterosexual African women, although the “messiness” of the gel affected adherence. PrEP with tenofovir and emtricitabine in the iPrEx (Chemoprophylaxis for HIV Prevention in Men) study was associated with a significant (P = .005) reduction in HIV transmission. However, questions remain about when microbicides and PrEP should be used, appropriate dosage, how they will be paid for, and how many people in a population should receive them.

With regard to protective vaccines, one study showed the protective effect (P = .04) of a candidate vaccine given to more than 16,000 heterosexual men and women. However, the borderline significance of the protective effect and the absence of knowledge of correlates of protection require further study.

**Duration of Infectiousness**

With regard to D (duration that the infected person is infectious to others), a primary factor to consider is that potent antiretroviral therapy allows HIV-infected individuals to live longer, increasing the number of individuals living with HIV. Limiting the duration of infectiousness in a growing population of HIV-infected individuals who are living longer should be a primary focus.

Testing for acute HIV infection may impact the duration of infectiousness. In San Diego, the institution of a program for testing for acute HIV infection in a region with the highest incidence and prevalence of HIV infection among 5 regions in the same county was associated with a marked reduction in HIV incidence versus expected incidence in that region, whereas incidence in the other regions remained relatively constant. Analysis suggested that this was not attributable to differences in the prevalence of other STIs or to viral suppression rates during treatment in HIV clinics. It is thought that testing for acute HIV infection linked infected individuals to care sooner, limiting the period of high infectiousness during early infection.

There is considerable evidence that antiretroviral treatment and earlier initiation of treatment reduce infectiousness. Cohen and colleagues showed that initiation of antiretroviral treatment in HIV-infected persons at time of diagnosis reduced the risk of transmission to uninfected partners compared with waiting to start treatment until CD4+ cell count was below 350/µL. A meta-analysis in 2009 reported a transmission rate of near 0 per 100 person-years among HIV-infected individuals taking antiretroviral therapy who had plasma HIV RNA levels below 400 copies/mL. The transmission rate increased from 2.06 per 100 person-years to 9.03 per 100 person-years among HIV-infected individuals not on antiretroviral treatment whose HIV RNA levels increased from in the range of 400 copies/mL to 3499 copies/mL to greater than or equal to 50,000 copies/mL.

Figure 2 shows a model developed by Granich and colleagues that estimates the incidence of HIV infection over time with no antiretroviral treatment, antiretroviral treatment initiated at CD4+ cell counts of less than 350/µL, or universal voluntary HIV testing with antiretroviral treatment initiated at time of diagnosis of HIV infection. Universal HIV testing and immediate treatment are estimated to ultimately produce an incidence rate approaching 0.

**Figure 2.** Changes in HIV incidence with no antiretroviral treatment (A), antiretroviral treatment initiated at CD4+ cell counts of less than 350/µL (B), or universal voluntary HIV testing with antiretroviral treatment initiated at time of diagnosis of HIV infection (C). Adapted from Granich et al.
The Gardner Cascade, based on a report by Gardner and colleagues in 2011, shows where improvements are needed in the HIV care continuum in order to substantially reduce HIV transmission and the duration of infectiousness (Figure 3). Of the approximately 1.2 million people estimated to be living with HIV infection in the United States, approximately 86% are diagnosed, 40% are engaged in care, 37% have been prescribed antiretroviral therapy, and 30% are virally suppressed. Thus, duration of infectiousness is prolonged in approximately 70% of HIV-infected individuals.

Future Directions

A plan to drive $R_0$ down to less than 1 in the United Kingdom involves promoting condom use, behavioral changes, and use of PrEP and PEP, microbicides, or antiretroviral treatment. A similar plan in San Francisco, California, involves promoting the use of PrEP, rapid HIV testing and treatment, and retention in care. Successful strategies are likely to depend on HIV testing and treatment; retention in care; testing and treatment for other STIs; use of PrEP, PEP, or microbicides; condom use; clean needle programs; circumcision; and likely other measures that have yet to be defined.

Presented by Dr Smith in March 2015. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Smith in August 2015.

Financial affiliations in the past 12 months: Dr Smith has received grants and research support paid to his institution from ViiV Healthcare/Pfizer, Inc.

References

Perspective

Management of the Hepatitis B Virus/HIV–Coinfected Patient

All patients with HIV infection should be screened for hepatitis B virus (HBV) infection. Preventive HBV vaccination is less effective in HIV-infected patients than in those without HIV infection. Emtricitabine, lamivudine, and tenofovir disoproxil fumarate (tenofovir) each have activity against HIV and HBV. In HBV/HIV-coinfected patients, if HBV or HIV treatment is needed, it should be initiated with tenofovir and emtricitabine or tenofovir and lamivudine as the nucleoside analogue reverse transcriptase inhibitor backbone of a fully suppressive antiretroviral regimen. If HBV treatment is needed and tenofovir cannot be used safely, entecavir is recommended in addition to a fully suppressive antiretroviral regimen. Initiation of treatment for HBV infection is based on the presence of cirrhosis and on HBV DNA level, alanine aminotransferase level, and biopsy results. Current HBV treatments are associated with low functional cure rates. This article summarizes a presentation by Kenneth E. Sherman, MD, PhD, at the IAS–USA continuing education program held in San Francisco, California, in March 2015.

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

It is estimated that 350 million people worldwide have chronic hepatitis B virus (HBV) infection and that 4 million to 8 million people are coinfected with HBV and HIV. HBV/HIV coinfection has been shown to result in higher rates of liver-related morbidity and mortality. For example, in the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study, HBV infection was associated with an increased risk of liver-related death among HIV-infected participants (relative risk, 3.73).1

Characteristics of HBV

HBV is a hepatadnavirus with a partially double-stranded DNA and its own reverse transcriptase for viral replication. The viral genome encodes 4 primary open reading frames involved in protein synthesis: P (polymerase), Pre-S and S (surface glycoproteins), Pre-C and C (core; structural protein of the nucleocapsid), and X (regulatory protein; the gene is thought to have transactivating function and may be involved in the development of liver cancer). The genes have markedly overlapping reading frames, leading to a high conservation of gene function and considerable potential for therapeutic disruption of the virus life cycle.

Dr Sherman is Gould Professor of Medicine and Director of the Division of Digestive Diseases at University of Cincinnati College of Medicine in Cincinnati, Ohio.

During HBV infection, the virus binds to the hepatocyte surface using sodium taurocholate receptors. It enters the cell and uncoats, releasing a relaxed coil DNA that moves to the cell nucleus. In the nucleus, it is transformed into covalently closed circular DNA (cccDNA), which is then transcribed into messenger RNA, which encodes the translation of surface and X proteins and, as pregenomic RNA, the translation of the hepatitis B e antigen (HBeAg), polymerase, and core proteins. When replication occurs at high levels, HBeAg is secreted. The components of pregenomic RNA and polymerase are packaged in the formation of a new capsid, followed by the reverse transcription of pregenomic RNA into relaxed coil DNA, the envelopment of the core in surface antigens, and the budding of virus from the cell. In most cases of HBV infection, there is excess production of surface proteins and secretion of subviral particles (vs infectious particles).

HBV infection slowly progresses over several decades. The initial phase of infection is characterized by immune tolerance, with a normal or near-normal level of alanine aminotransferase (ALT) and a high level of HBV DNA. This is followed by the immune clearance phase, or HBeAg-positive chronic hepatitis, during which the immune response to infection results in liver damage, with ALT and HBV DNA levels fluctuating with variations in immune response. If the immune response controls infection, the HBV-infected person becomes a chronic carrier, with reduced HBV DNA and a lower ALT level. Chronic carriers are subject to spontaneous reactivation of infection (HBeAg-negative chronic hepatitis). Some individuals have occult HBV infection; these individuals’ test results are negative for HB surface antigen (HBsAg) and HB surface antibody (anti-HBs), are often positive for HB core antibody (anti-HBc) immunoglobulin G (IgG), and are intermittently positive for HBV DNA in serum and in the liver. Chronic HBV infection may be associated with HBsAg mutations that result in reduced production of surface antigens. Occult HBV infection may result in the reemergence of acute HBV infection in individuals who have undergone a liver transplant and in HIV-infected individuals, and is also associated with increased risk of hepatocellular carcinoma.

HBV Prevention

Efforts to prevent HBV infection include modification of risk behaviors, vaccination, and preexposure prophylaxis. Modification of risk behaviors has not proved to be a highly effective prevention strategy. A study in Amsterdam, the Netherlands, reported an increase in risk encounters during an HBV vaccination campaign.2 However, preexposure prophylaxis for high-risk persons (especially those who have not been successfully vaccinated) could be an effective strategy.
Use as HBV treatment include the fixed-dose combination of interferon alfa. Effective drugs that are not FDA approved for the treatment of HBV infection are lamivudine, adefovir, tenofovir, interferon alfa, and peginterferon alfa. Of note, although not yet included in the guidelines referenced above, for individuals who experience nephrotoxic effects attributable to tenofovir, substitution with the investigational nucleos(t)ide analogue reverse transcriptase inhibitor tenofovir alafenamide fumarate may be an option when and if it is FDA approved.

For individuals with HBV/HIV coinfection, treatment of both infections should be initiated following an initial workup and evaluation, in accordance with current DHHS guidelines. For those who choose to defer therapy for HIV infection, a representative schema for deciding when to treat HBV infection is shown in Figure 1. Treatment should be started for individuals with cirrhosis whose test results are positive for HBsAg. In HBV-infected patients without cirrhosis, treatment should be started for those with HBV DNA levels above 20,000 IU/mL and ALT levels above normal limits. Liver biopsy should be considered for those with normal ALT levels.

Current US Department of Health and Human Services (DHHS) and IAS–USA guidelines for use of antiretroviral therapy to treat HIV/HBV coinfection include the following:

- Prior to initiation of antiretroviral therapy, all individuals who test positive for HBsAg should be tested for HBV DNA using a quantitative assay to determine the level of HBV replication.
- Because emtricitabine, lamivudine, and tenofovir disoproxil fumarate (tenofovir) have activity against HIV and HBV, if HBV or HIV treatment is needed, antiretroviral therapy should be initiated with the combination of tenofovir and emtricitabine or of tenofovir and lamivudine as the nucleoside analogue reverse transcriptase inhibitor (nRTI) backbone of a fully suppressive antiretroviral regimen.
- If HBV treatment is needed and tenofovir cannot be used safely, then entecavir in addition to a fully suppressive antiretroviral regimen is the recommended alternative treatment option.

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**Treatment**

There are several outcomes of HBV treatment. Suppression generally refers to reduction of HBV DNA to below detectable levels. Seroconversion can refer to conversion from anti-HBe–positive status to an HBeAg-negative status, or to conversion to anti-HBe–positive status from an HBeAg-negative status. Durable seroconversion occurs when a patient’s test results are negative for HBeAg and positive for anti-HBe for 1 year after completion of treatment. A functional cure is characterized by undetectable HBsAg. A true cure occurs when HBV cccDNA is cleared; this is exceedingly rare in HBV-infected individuals, but is the ultimate aim of treatment. However, functional cure can prevent acute liver injury, reduce fibrotic progression to cirrhosis, and reduce the risk of developing liver cancer.

US Food and Drug Administration (FDA)-approved drugs for the treatment of HBV infection are lamivudine, adefovir, entecavir, telbivudine, tenofovir, interferon alfa, and peginterferon alfa. Effective drugs that are not FDA approved for use as HBV treatment include the fixed-dose combination of tenofovir and emtricitabine or emtricitabine alone.

**Figure 1.** Treatment algorithm for hepatitis B virus infection. ALT indicates alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus. Adapted from Keeffe et al.
and treatment should be started for those with inflammation and fibrosis confirmed via biopsy. Among patients whose test results are negative for HBeAg and who have HBV DNA levels above 2000 IU/mL, treatment should be started for those with ALT levels above normal limits; biopsy should be considered for those with normal ALT levels, and treatment should be initiated if biopsy results show inflammation and fibrosis. The lower HBV DNA level threshold for treatment in patients whose test results are negative for HBeAg reflects the fact that many such patients have HBV mutations that result in disease that is more difficult to treat.

Patients receiving treatment for HBV infection should be tested every 6 months for HBV DNA. Those receiving tenofovir should have creatinine and urinalysis testing performed every 6 months (more frequently for those with creatinine clearance < 60 mL/min). If HBV DNA level is greater than 1000 IU/mL after 1 year, the patient’s HBV resistance profile should be checked and, if cirrhosis is present, the regimen should be intensified; adherence to and malabsorption of drug should also be considered.

A comparison of characteristics of available anti-HBV drugs is shown in Table 1. Rates of functional cure of HBV infection (ie, loss of HBsAg) with established treatments are low, with rates of approximately 8% to 15% in those receiving an extended regimen of peginterferon alfa or peginterferon alfa plus lamivudine and rates of 0% to 10% in those receiving extended treatment with an nRTI-based regimen.8

HBV mutations are common, owing to the low fidelity of HBV polymerase. Most of the mutations associated with resistance to anti-HBV drugs appear on the tyrosine-methionine-aspartic acid-aspartic acid (YMDD) motif within the HBV polymerase. Persons with viral breakthrough caused by a mutation emerging during treatment with a single agent tend to experience disease flares. Persons with advanced disease sometimes develop hepatic failure and die. If the ineffective single agent is not stopped in the setting of viral breakthrough, compensatory mutations develop over time that render the virus resistant to virtually all available agents. Rates of treatment failure and emergence of resistance are higher in individuals with HBV/HIV coinfection than in those with HBV monoinfection, when lamivudine is the primary treatment for HBV infection. The risk of these events has declined with the use of more potent drugs, including tenofovir and entecavir. As seen with the management of HIV infection through antiretroviral treatment, adherence to HBV antiviral treatment is a cornerstone of effective care for HBV infection.

Table 1. Comparison of Efficacy, Resistance, and Cost of Drugs for Treatment of Hepatitis B Virus Infection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Resistance</th>
<th>Cost</th>
</tr>
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<tbody>
<tr>
<td>Lamivudine</td>
<td>+++</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Adefovir</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Entecavir</td>
<td>++++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>++++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>++++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Peginterferon alfa</td>
<td>++++</td>
<td>+</td>
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</tr>
</tbody>
</table>

Path to Cure

A substantial proportion of hepatitis C virus (HCV) infections can now be cured. However, HBV is a more complicated virus to cure. As opposed to an RNA virus that replicates only in the cytoplasm, HBV is a DNA virus that effectively forms its own minichromosome in the nucleus of the host cell, which is passed through divisions from generation to generation of hepatocytes. Strategies to improve rates of functional cure and ultimately achieve true cure include exploitation of other viral targets, development of more potent nucleos(t)ide analogue inhibitors, therapeutic vaccination, and immune modulation.

There has been little progress in the development of more potent nRTIs. With regard to other viral targets, entry inhibitors such as myrcludex B that block sodium taurocholate receptors are being evaluated and have shown promise. Cyclophilin inhibitors such as alisporivir, which was evaluated for the treatment of HCV infection, interfere with host factors necessary to viral replication. Clinical trials of such approaches are likely to provide information in the near future. It has been hypothesized that zinc finger endonucleases could be used to target HBV cccDNA; however, targeting endonucleases to the hepatocyte nuclei and determining whether endonuclease activity can be focused on cccDNA remain challenging. Other nucleases, including transcription activator-like effector nuclease and homing endonuclease, are also being investigated.

In addition to targeted approaches, immunologic therapies also show promise. One basic strategy for therapeutic vaccination involves reduction of HBV replication via nucleos(t)ide analogue inhibitor treatment, achieving HBsAg seroconversion via protein prime vaccination, and achieving viral clearance via recombinant vector boost vaccination.9 A number of vaccination options have been attempted but have met with little success thus far, including vaccines that carry proteins or peptides (eg, HBV recombinant subunits or pieces of C or pre-S regions) that might improve immune response; use of modified vaccinia vectors; direct placement of DNA into cells that produce pre-C, C, and S antigens and to X, S, and C antigens was augmented to cure. As opposed to an RNA virus that replicates only in the cytoplasm, HBV is a DNA virus that effectively forms its own minichromosome in the nucleus of the host cell, which is passed through divisions from generation to generation of hepatocytes. Strategies to improve rates of functional cure and ultimately achieve true cure include exploitation of other viral targets, development of more potent nucleos(t)ide analogue inhibitors, therapeutic vaccination, and immune modulation.

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The use of targeted molecular immunogens is one approach being investigated. For example, one study examined a yeast-based immunotherapy platform that expresses X, surface, and core HBV antigens. As shown in Figure 2, T-cell response—measured by production of gamma interferon—to S and C antigens and to X, S, and C antigens was augmented in uninfected persons, but was also greater in patients with chronic HBV infection who were receiving adefovir.10

Other approaches being evaluated involve use of inhibitors of immune checkpoint molecules such as programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1),
decision to treat HBV infection is closely linked with the decision to treat HIV infection. Effective HBV treatment decreases fibrosis and the risk for hepatocellular carcinoma. Long-term suppression of HBV rarely leads to functional cure (an HBsAg-negative state), and other modalities are needed in order to clear the HBV cccDNA reservoir.

Presented by Dr Sherman in March 2015. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Sherman in August 2015.

Financial affiliations in the past 12 months: Dr Sherman has received research grants or contracts awarded to his institution from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc, Inovio Pharmaceuticals, Medimmune, Merck & Co, Inc, and Vertex Pharmaceuticals, Inc, and has served as an advisory board member or a consultant to Merck & Co, Inc, and MedImmune. He has also served on data and safety monitoring boards for Janssen Therapeutics, SynteractHCR, and Medpace.

Conclusion

All patients with HIV infection should be screened for HBV infection and evaluated for HBV treatment candidacy. HBV vaccination is a crucial element of prevention, but current vaccination methods are imperfect. The goal of HBV treatment is to achieve complete suppression of viral replication. The

References

Recently, the global community of HIV/AIDS researchers, academics, and clinicians felt the loss of 2 of its highly esteemed members. Their outstanding contributions and legacies are remembered below, and we extend our condolences to their friends, family, and colleagues.

**Suniti Solomon, MD, 1939-2015**

On July 28, 2015, Dr Suniti Solomon, the Founder and Director of the YR Gaitonde Center for AIDS Research and Education (YRGCARE) in Chennai, India, passed away. Dr Solomon was a pioneer in the HIV/AIDS research community. In 1986, she and her colleagues documented the first evidence of HIV infection in India, while serving as a Professor of Microbiology at Madras Medical College and the Government General Hospital in Chennai.

She established India’s first voluntary testing and counseling center and was deeply committed to community education and mobilization and was a passionate supporter of HIV research and of women, including those from disadvantaged and disenfranchised populations. In 1993, she established YRGCARE as one of the first community-based research and education centers for HIV/AIDS research and treatment in India.

Dr Solomon received numerous awards and accolades and published extensively on HIV/AIDS epidemiology, prevention, care, research ethics, and issues related to gender. She will be sorely missed, not only as a pioneer in HIV/AIDS research but as a friend and colleague.

**J. Michael Kilby, MD, 1964-2015**

On August 10, 2015, Dr J. Michael Kilby, Professor of Medicine and Chief of the Division of Infectious Diseases at Medical University of South Carolina (MUSC), passed away. Dr Kilby also oversaw the Ryan White Part B and D programs funded by the Health Resources and Services Administration, helping to support clinical care for more than 1000 HIV-infected individuals in the United States.

His research interests included acute retroviral illness, the natural history and immunopathogenesis of HIV, and novel antiretroviral therapies. He published numerous textbook chapters and peer-reviewed papers on topics in the field of HIV medicine and research, was a fellow of the Infectious Diseases Society of America and the American College of Physicians, and served on the editorial board of the *Journal of Acquired Immune Deficiency Syndromes*.

At MUSC, Dr Kilby fostered a culture of collaboration and excellence that earned the respect of his colleagues and will live on in his absence. He will be deeply missed by his family, friends, and colleagues.
**Perspective**

**HIV-Related Opportunistic Infections Are Still Relevant in 2015**

The incidence of HIV-related opportunistic infections (OIs) has declined in the United States with the increasing use of effective antiretroviral therapy for the treatment of HIV infection. However, the absolute number of patients with OIs remains high and there continues to be considerable associated mortality. OI guidelines from the National Institutes of Health, Centers for Disease Control and Prevention, and Infectious Diseases Society of America continue to be updated on a regular basis, several times per year, as optimal strategies for prevention and therapy evolve. Recommendations that have changed in these guidelines include: screening for cryptococcal antigen and treatment of asymptomatic antigenemia; empiric treatment of shigellosis infection in light of the recent spread of multidrug-resistant strains; the relative roles of vancomycin and metronidazole in diarrheal illness related to Clostridium difficile; and diagnosis of Pneumocystis jiroveci pneumonia (PCP; formerly Pneumocystis carinii pneumonia). This article summarizes a presentation by Henry Masur, MD, at the IAS–USA continuing education program held in Washington, DC, in May 2015.

**Keywords:** HIV, opportunistic infections, cryptococcal meningitis, shigellosis, *Clostridium difficile*, *Pneumocystis jiroveci* pneumonia

With the remarkable prolongation of life achieved among HIV-infected individuals, owing to the use of potent antiretroviral therapy, has come dramatic progress in reducing the incidence of HIV-related opportunistic infections (OIs). There has been considerable focus on antiretroviral therapy and HIV prevention, and most HIV practitioners are highly proficient at managing antiretroviral therapy. However, expertise in the management of OIs has waned as more and more physicians have little experience diagnosing or treating these life-threatening infections. Renewed attention to appropriate management is needed, because the absolute number of patients with OIs and the rates of associated mortality remain high, particularly in large urban settings in the United States.

Updates to the OI guidelines have been released online by the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America (IDSA). The following covers topics under discussion during preparation of these guidelines.

Cryptococcal Disease

There are nearly a million cases of cryptococcal meningitis worldwide each year, with an estimated annual death toll of 675,000. It has been suggested that in parts of the world with high burdens of disease, it is cost-effective to routinely screen asymptomatic patients for cryptococcal antigen.

As shown in Figure 1, a study in a cohort of 707 South African individuals showed that even when CD4+ cell count increased during the first year of antiretroviral therapy, there was still an appreciable incidence of cryptococcal meningitis during this initial year of antiretroviral therapy. This high incidence reflects a population that is nonadherent to or has a poor response to antiretroviral therapy, but also indicates that OIs can occur within the first few weeks or months after initiation of antiretroviral therapy. Such episodes may represent primary cryptococcal infection, relapsed infection, re-infection, or some manifestation of immune reconstitution inflammatory syndrome (IRIS).

Thus, starting antiretroviral therapy does not guarantee prevention of cryptococcal meningitis. Although the incidence of cryptococcal disease is much higher in sub-Saharan Africa than in the United States, the issues of screening for asymptomatic infection and treating in the United States are still important even if the incidence is lower than in other geographic areas.

In the South African study mentioned above, 7% of individuals screened before starting antiretroviral therapy had asymptomatic cryptococcal antigenemia, while in a study in the United States approximately 2.0% to 2.5% of individuals screened for cryptococcal antigenemia were positive.

**Keywords:** HIV, opportunistic infections, cryptococcal meningitis, shigellosis, *Clostridium difficile*, *Pneumocystis jiroveci* pneumonia

![Figure 1. Incidence of cryptococcal meningitis among 707 South African individuals during their first year of antiretroviral therapy. Adapted from Jarvis et al.](image-url)
starting antiretroviral therapy had it. A cryptococcal antigen titer result greater than or equal to 1:8 was 100% sensitive and 96% specific for predicting cryptococcal meningitis during the first year of antiretroviral therapy in those with no history of the disease. Only 56% of those who tested positive for cryptococcal antigen cleared their antigenemia with antiretroviral therapy alone. A short course of low-dose fluconazole was not effective in preventing meningitis. Thus, treatment for individuals with antigenemia should consist of a relatively high dose of fluconazole, as would be used to treat meningitis, or an alternative such as amphotericin B.

World Health Organization recommendations for resource-limited settings with a high burden of cryptococcal disease are to screen all HIV-seropositive patients with CD4+ cell counts below 100/µL for cryptococcal antigen and to treat patients with antigenemia with fluconazole 800 mg daily for 2 weeks and 400 mg daily for 8 weeks. Although logical and plausible, these treatment recommendations are not based on clinical evidence. Should practitioners follow these recommendations in the United States?

The findings in South Africa and in other resource-limited areas have prompted questions about the number of events of acute meningitis that represented IRIS rather than acute fungal disease, about whether lumbar punctures could have been used to distinguish between patients with antigenemia who did need therapy and those who did not need therapy, and about whether therapy with fluconazole would have changed outcomes.

Prior to 2015, the NIH/CDC/IDSA OI guidelines stated that for prevention of cryptococcal disease, screening for cryptococcal antigenemia was not recommended because of the low incidence of cryptococcal disease among HIV-infected individuals after initiation of antiretroviral therapy. However, recent data indicate that the burden of cryptococcal disease is probably more substantial in the United States than many clinicians suspect. As reported by McKenney and colleagues in Morbidity and Mortality Weekly Report in 2014 and in Clinical Infectious Diseases in 2015, the attack rate of cryptococcal meningitis among HIV-infected persons in the United States for 2006 was 2 to 7 cases per 1000 person-years, with a 12% rate of associated mortality.

McKenney and colleagues also evaluated the prevalence of asymptomatic cryptococcal antigenemia using stored sera from the MACS (Multicenter AIDS Cohort Study) and WIHS (Women’s Interagency HIV Study) cohorts from 1996 to 2012. Among 1872 samples with CD4+ cell counts below 100/µL, 2.9% were positive for cryptococcal antigen, including 4.6% of samples with CD4+ cell counts below 50/µL. There was a wide range of antigen titers. A minority of cases of antigenemia were associated with prior cryptococcal meningitis. It is unknown if any of the individuals whose samples were evaluated received treatment for active cryptococcal disease or for asymptomatic antigenemia. Survival was shorter in antigen-positive individuals compared with antigen-negative individuals (Figure 2). The investigators concluded that the prevalence of asymptomatic cryptococcal antigenemia is substantial in the United States, that survival rates are worse for individuals with antigenemia, and that specific therapy for cryptococcal disease in those with antigenemia is warranted.

In the United States, cryptococcal antigenemia is more common than many may have recognized. Data suggest that antiretroviral therapy is not uniformly effective for preventing cryptococcal syndromes from occurring. When is treatment for cryptococcal disease indicated? Some clinical syndromes may in fact be caused by the unmasking effects of IRIS or by reactivity to latent or cured disease. However, clinicians may be reluctant to assume that live organisms and active infection are absent.

Treatment for meningitis would be indicated in cases in which a lumbar puncture yields a positive culture from cerebrospinal fluid. Patients with meningeval disease can receive the same treatment as patients with pulmonary disease. A reasonable interpretation of available data supports screening all individuals with CD4+ cell counts below 100/µL for cryptococcal antigen and performing a lumbar puncture in antigen-positive individuals to identify active but asymptomatic meningitis. For patients who have cryptococcal meningitis, even if it is clinically silent, treatment should follow current guidelines (ie, should start with liposomal amphotericin B plus flucytosine). If a lumbar puncture result is negative for meningitis and there is no evidence of organ dysfunction, treatment with fluconazole is encouraged.

Diarrhea
Diarrhea is common in many individuals, including those with HIV infection, and many cases of diarrhea can be attributed to common infectious and noninfectious causes. However, clinicians should be aware that Clostridium difficile is also a common cause of diarrhea among HIV-infected persons. Although C difficile is not an opportunistic pathogen, it does occur frequently in HIV-infected individuals, presumably because of their regular interaction with health-care facilities. Clinicians should also be aware of changes in the antibiotic susceptibility patterns of enteric bacteria that often infect HIV-infected individuals.

Figure 2. Survival according to cryptococcal antigen test result in MACS (Multicenter AIDS Cohort Study) and WIHS (Women’s Interagency HIV Study) cohorts, from 1986 to 2012. Adapted from McKenney et al.7
Salmonella infection is a well-known HIV-related OI that frequently causes bacteremia, especially in individuals who live in the developing world. Campylobacter and Shigella infections are common in many populations, although they are not OIs. However, because these infections also occur in HIV-infected individuals and because men who have sex with men (MSM) have a particular predisposition to shigellosis, some of the new data on antimicrobial susceptibility and enteric pathogens are relevant to HIV practitioners.

**Shigellosis**

Approximately 500,000 cases of shigellosis occur each year in the United States among the total population of HIV-infected and uninfected individuals. Transmission of Shigella species occurs via person-to-person contact or via food and water and can be achieved with a low inoculum of 10 to 100 organisms. Shigella species are relatively resistant to stomach acid. Secondary cases of shigellosis are common (ie, spread from one infected person to another). In April 2015, Bowen and colleagues reported in Morbidity and Mortality Weekly Report that shigellosis with multidrug resistance, including resistance to quinolones, is spreading in the United States, particularly among MSM. Numerous other reports on the drug-resistant bacteria have appeared in popular press and media.

For individuals with persistent diarrhea, empiric treatment for shigellosis is reasonable if diarrhea is severe, with stools that occur more than 6 times a day, with bloody stools, or if a high fever is present. Because transmissibility is a concern, treatment for shigellosis among MSM to potentially reduce the period of infectivity should also be considered.

A 7- to 10-day regimen of quinolone treatment is the preferred empiric therapy option for treatment of shigellosis. However, Shigella species are becoming increasingly resistant to quinolones in the United States and abroad. The most resistant strain is Shigella sonnei, which is common among travelers and increasingly common among MSM. Treatment options in cases of resistance are limited. Individual antibiograms should be studied to determine if azithromycin, trimethoprim-sulfamethoxazole, or another agent should be selected. Campylobacter species infection, another common cause of diarrhea, is also becoming resistant to quinolones.

**Clostridium difficile**

Clostridium difficile infection is reported to be the most common identified cause of diarrhea in HIV-infected individuals, accounting for 55% of cases in one study, especially those who acquired it in health-care facilities and in association with antibiotic treatment. Campylobacter and Shigella (flexneri more commonly than sonnei) infections each accounted for 14% of cases of diarrhea, Salmonella infection accounted for 7% of cases, and mycobacterial infections accounted for 4% of cases.

The clinical manifestations of C difficile–related diarrhea are similar in HIV-infected and uninfected individuals. Individuals with low CD4+ cell counts have higher incidence rates for C difficile–associated diarrhea than those with high CD4+ cell counts. However, whether low CD4+ cell counts contribute to a higher incidence of clinically apparent disease or whether individuals with low CD4+ cell counts have a higher incidence of disease owing to more-frequent antibacterial therapy or more-frequent exposure to health-care facilities remains to be determined.

To diagnose C difficile as the cause of diarrhea, a nucleic acid amplification test (eg, a polymerase chain reaction [PCR] test) of a stool sample is now preferred by most laboratories. Many laboratories have used enzyme-linked immunosorbent assays (ELISAs). These assays are very specific for toxin but are not very sensitive. Thus, many cases of C difficile–related diarrhea are missed by ELISA testing even when 3 consecutive stools are sampled. Nucleic acid amplification tests are also very specific for toxin and their high sensitivity gives them a great negative predictive value. However, they are so sensitive that they may return positive results for C difficile in some patients with diarrhea even if only a small amount of toxin is present (potentially too little to cause disease). Thus, a positive PCR test result must be analyzed with caution.

Some laboratories screen stool samples with an antigen test, the lactic dehydrogenase test, to determine the presence of the C difficile organism and then use an ELISA test to detect toxin. This is also a reasonable diagnostic approach, although laboratories often resort to a PCR test if the results of stool antigen and ELISA tests are discordant.

A recent analysis of HIV-uninfected patients indicated higher clinical success rates and somewhat lower relapse rates with oral vancomycin than with metronidazole when used to treat mild, moderate, or severe C difficile infection. Updated guidelines recommend oral vancomycin over metronidazole to treat all HIV-infected individuals, particularly those with CD4+ cell counts below 200/µL. However, metronidazole can be used to treat HIV-infected patients with very mild cases of C difficile infection. Although combination therapy is controversial, there are data indicating the benefit of using vancomycin and metronidazole together for severe cases of C difficile infection.

**Diagnosis of Pneumocystis jiroveci Pneumonia**

Clinicians have long sought approaches to diagnosing Pneumocystis jiroveci pneumonia (PCP; formerly Pneumocystis carinii pneumonia) that do not require bronchoscopy or the evaluation of a respiratory specimen. There has been considerable literature on a variety of serologic tests that are purported to be useful for diagnosis of PCP.

Serum PCR testing is not sensitive enough to be useful diagnostically. Although PCR testing is useful for evaluation of respiratory secretions, as discussed below, it is not useful for evaluation of blood, plasma, or serum. Lactate dehydrogenase testing has been discussed in the literature for 2 decades; however, serum lactate dehydrogenase testing is nonspecific (its sensitivity depends on the severity of the lung disease). Serum beta-D-glucan testing has appeared promising.
in some reports, but this test measures a component of the cell wall that is present in many fungi, including Candida species. Moreover, false-positive results for PCP on beta-D-glucan tests may be caused by noninfectious entities or by fungal contamination of drugs. The use of beta-D-glucan testing has strong proponents, but its lack of specificity and its imperfect sensitivity would make it unreliable even if hospitals were able to obtain the results quickly. Thus, there is currently no useful serologic test for PCP.

With sputum and bronchoalveolar lavage (BAL) specimens, most laboratories establish a diagnosis of PCP by “spinning down” the respiratory specimen to concentrate it and then staining it with a colorimetric or immunofluorescent stain. Such stains are highly specific and sensitive for PCP when interpreted by experienced microscopists. However, many laboratories do not have access to an experienced microscopist and may need to find an automated system to establish the diagnosis of PCP.

PCR testing is nearly 100% specific and sensitive for PCP. The problem with this test is that it detects colonization of Pneumocystis organism as well as PCP. A negative result for PCP via BAL PCR testing will rule out PCP; however, a positive result might indicate colonization rather than disease. Therefore, PCR test results must be interpreted with caution. The gold standard for diagnosis of PCP is an immunofluorescent stain of concentrated BAL. Such testing may be done initially or only for those specimens that are positive for PCP by PCR testing. Thus, for both C difficile infection and PCP, PCR testing provides a highly sensitive and highly specific testing modality, although such testing may identify colonization in patients whose disease is in fact caused by some other process.

Conclusion

HIV practitioners must still manage OIs in their HIV-infected inpatients and outpatients. The epidemiology and management of OIs continues to evolve and will remain important as long as HIV infection is identified late in the course of illness or for individuals who do not achieve durable HIV suppression.

References


Perspective
Chronic Pain in Patients With HIV Infection: What Clinicians Need To Know

Chronic pain is common in individuals with HIV infection. The primary goal of treatment of chronic pain is not only to improve pain but also to improve physical and emotional function. Patients with chronic pain should be assessed for concurrent psychiatric and substance use disorders, as these conditions often coexist. Treatment of chronic pain may have limited success in the absence of treatment of psychiatric disorders. Treatments for chronic pain include nonopioid pharmacologic therapies and nonpharmacologic therapies (eg, cognitive and behavioral therapy, physical therapy), and the latter option is often the most effective for improving patient function. Care must be taken when initiating or continuing treatment with opioids, and the risks and benefits of treatment with opioids should be regularly assessed. This article summarizes a presentation by Jessica S. Merlin, MD, MBA, at the IAS–USA continuing education program held in New York, New York, in March 2015.

Keywords: HIV, chronic pain, functional impairment, opioid treatment, nonopioid treatment

Chronic pain is pain that persists for longer than 3 months, beyond the period of normal tissue healing. Musculoskeletal pain (eg, lower back, knee, or shoulder pain), fibromyalgia, and neuropathy are some examples of chronic pain. There is a great deal of basic science literature that describes the pathophysiologic underpinnings of chronic pain. From this literature, 2 key etiologies of chronic pain are peripheral sensitization and central sensitization (Figure 1). In peripheral sensitization, peripheral nervous system receptors are hypersensitized by local tissue inflammation (eg, from an inflammatory disease such as rheumatoid arthritis) or damage (eg, from physical trauma), causing pain to remain even after the inflammation or injury is no longer present. During central sensitization, there is no inflammation in the periphery, but the brain receives a strong signal of pain. A prime example of this is fibromyalgia. The pathways that control central sensitization are associated with conditions such as mood disorders and addiction, and as a result, these conditions commonly occur together. Chronic pain may also be caused by ongoing active inflammation, such as that seen in rheumatoid arthritis. However, even in this circumstance, it is important to consider the potential role central sensitization might play. For example, an individual with rheumatoid arthritis and depression may continue to have severe chronic pain if their depression is not adequately treated.

Chronic pain can lead to substantial functional impairment, including difficulty across several domains of function: physical function (eg, work and household chores, ability to participate in leisure activities), social function (eg, close personal relationships), socioeconomic status (eg, health-care costs, disability), and emotional function (eg, anxiety and depression). As a result, over the past few years, chronic pain itself has been increasingly regarded as a chronic condition.1

HIV Infection and Chronic Pain

In the current HIV treatment era, an estimated 39% to 85% of individuals with HIV infection also suffer from chronic pain compared with only 20% to 30% of the general population. Chronic pain in HIV-infected individuals is often musculoskeletal, although pain associated with peripheral neuropathy is observed in approximately 20% to 30% of individuals. Chronic pain in HIV-infected individuals often but not always coexists with mood disorders and addiction. Based on a cross-sectional study in a cohort of HIV-infected individuals, those with HIV infection and chronic pain are up to 10 times more likely to have functional impairment. Additionally, individuals with HIV infection and chronic pain who also report recent substance use are more likely to be retained in care, whereas individuals with HIV infection and chronic pain who do not report recent substance use are less likely to be retained in care. As a result of these factors and the minimal training most practitioners receive in this area, caring for individuals with chronic pain can be a substantial challenge for HIV practitioners.2–7

The reason for the high prevalence of chronic pain in individuals with HIV infection is unclear. Adverse effects associated with nucleoside analogue reverse transcriptase inhibitors (eg, peripheral neuropathy), with opportunistic infections (eg, herpes zoster virus infection), or with treatments...

![Figure 1](image-url)

**Figure 1.** The 2 key etiologies of chronic pain: peripheral sensitization and central sensitization.

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Dr Merlin is Assistant Professor of Medicine at the University of Alabama at Birmingham.
for opportunistic infections (eg, isoniazid-related polyneuropathy) contribute to chronic pain in individuals with HIV infection. However, these effects do not account for many cases of chronic pain, including cases of musculoskeletal pain, seen in many of these individuals. Some have hypothesized that even in the setting of virologic suppression, chronic pain may develop from persistent inflammation caused by HIV infection. To date, there is no evidence to support this, and this is an actively ongoing area of investigation. Another explanation might be that mental illness and addiction are commonly associated with chronic pain and with HIV infection. Therefore, individuals infected with HIV may represent a population that is saturated with individuals with chronic pain. Further research in this area is needed.

**Evaluation**

The experience of pain is highly subjective, which can be challenging for practitioners. The optimal approach is to assume that all patients who report having chronic pain suffer from chronic pain. When reviewing a patient’s history of chronic pain, the practitioner should note the effect chronic pain has on the patient’s function, mood, and sleep. Practitioners may be reluctant to ask patients about the relationship between pain and mood for fear of implying that the patient’s pain is purely psychological in nature or “all in their head.” One approach may be to tell a patient with depression that some patients with depression indicate that when their mood is down their pain is worse, and that when their pain is more intense it worsens their mood, creating a cycle and making it difficult to tell which came first. The practitioner can then ask if this is something the patient has experienced themselves. Practitioners should also note the level of pain a patient is experiencing on a standardized scale (eg, from 0 to 10). However, the impact of pain on a patient’s ability to function is as important if not more important than their level of pain. For example, a patient who reports severe pain and who works a full-time job is different than one who reports severe pain and is confined to their house or their bed.

Other key elements to consider when reviewing a patient’s history of chronic pain are the patient’s employment status and history of disability. Regardless of whether a patient is employed outside the home or is working inside the home (eg, caring for children or an elderly parent), they should be asked how they spend their time. It is helpful to have the patient describe their level of function before and after they began experiencing symptoms of chronic pain. It may also be useful to ask patients what they would ideally like to be doing. This can help the practitioner identify a patient’s skills and interests (eg, Are they social? Do they enjoy jobs that involve physical activity?), information which can eventually be used to help set functional goals for chronic pain treatment. A history of the patient’s psychiatric conditions and substance use should be elicited, as both are common and can be missed if no direct query is made. During the interview, it is also important to note the behaviors a patient exhibits during moments of pain.

**Table 1. Risk Factors for Disability Associated With Chronic Pain**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Disability Factor</th>
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<tbody>
<tr>
<td>Anxiety</td>
<td>Decreased function</td>
</tr>
<tr>
<td>Catastrophizing</td>
<td>Poor health</td>
</tr>
<tr>
<td>Compensation dependency</td>
<td>Poor health</td>
</tr>
<tr>
<td>High level of initial pain</td>
<td>Weak social support</td>
</tr>
<tr>
<td>Increasing age</td>
<td>Decreased function</td>
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<tr>
<td>Poor general health</td>
<td>Depression</td>
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<td>Depression</td>
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Practitioners should be aware of several known risk factors for disability, including fear avoidance (avoiding physical activity in order to avoid pain; eg, a patient will not leave bed for fear it will aggravate lower back pain), catastrophizing (eg, worry that a condition such as fibromyalgia will result in confinement to a wheelchair), depression, anxiety, decreased function, high levels of initial pain, increasing age, poor general health, and compensation dependency (Table 1). Noting such risk factors and discussing them with patients while a therapeutic relationship is built is an important part of chronic pain treatment.

When assessing etiology, the practitioner should attempt to determine if the patient’s chronic pain is neuropathic (eg, sciatica, postherpetic neuralgia, or alcohol- or diabetes-related neuropathy), musculoskeletal (eg, myofascial pain syndrome), inflammatory (eg, arthritis, tendinitis, or chronic infection), or mechanical or compressive (eg, pain related to tumors, cysts, or fractures). This can be done with a thorough initial medical history, a physical examination, and appropriate diagnostic testing. However, many patients with chronic pain do not fit neatly into one of these categories and may have a less well-defined musculoskeletal chronic pain syndrome. If this is the case, practitioners should not be discouraged, and patients should not be told that their symptoms cannot be explained or that their medical condition will be difficult to treat.

Additionally, a judicious, evidence-based approach to diagnostic testing for chronic pain is important. Chronic pain often does not have a radiographically identifiable cause, presenting a challenge to patients and practitioners who are both looking for a clear explanation. Patients in whom workups with blood testing or magnetic resonance imaging have revealed no explanation for chronic pain should be informed that their test results do not reveal a life-threatening condition or that their symptoms do not require a serious intervention such as surgery. Rather, they should be informed that they have chronic pain, which can be treated.

**Communication**

Communicating with patients about chronic pain is not always easy, for several reasons. First, patients might bring negative expectations to a meeting with a new practitioner based on previous experience. A patient may have been previously accused of drug seeking, may have been questioned about the existence of their pain, or may have received an inconclusive diagnosis. Encounters with previous patients
may influence a practitioner’s attitude toward a current patient. Additionally, pain is often referred to as the fifth vital sign and is often viewed by patients and practitioners as indicative of an emergency. Although it may be reasonable for acute pain, it is not appropriate to treat chronic pain as an emergency. As with other chronic conditions, improvement of chronic pain takes time. The focus of treatment of chronic pain should not be immediate pain relief, but rather, improvement in function over time. Communication about medications can also be difficult because some medications (eg, opioids) carry risks. Some patients may have an active psychiatric illness, substance use disorder, or personality type that influences the way they communicate with practitioners.

Initial discussions with patients with chronic pain should include education about chronic pain. Practitioners may refer to chronic pain as a medical condition with a known biologic basis and known treatments. Patience, partnership, and collaboration should be emphasized. Practitioners and patients should acknowledge that evaluation and management of chronic pain will take time, and practitioners should explain that pharmacologic and nonpharmacologic strategies to manage chronic pain exist and that they are best used together. Motivational interviewing can be useful for promoting partnership and a true understanding of patient concerns, and for discussing behavioral changes that might help a patient’s pain (eg, weight loss, improving physical activity, or reducing dependence on opioids for pain relief).

**Management**

Management of chronic pain should focus on evidence-based therapies. Procedures, surgeries, and medications that are not evidence based should be avoided. Concrete goals and timelines should be set, and therapies that do not work should be discontinued. If possible, practitioners should treat any psychiatric illness first, as chronic pain is most likely to improve in the context of well-controlled psychiatric symptoms.

**Nonopioid-Based Pharmacologic Therapy**

Nonopioid-based pharmacologic therapy includes acetaminophen (mostly studied in the context of osteoarthritis) given at under 3 g per day. It is important to remember that hepatitis C virus infection and alcohol use are relative contraindications for the use of acetaminophen. Nonsteroidal antiinflammatory drugs can be used to treat chronic back pain, but consideration should be given to potential risks for cardiovascular, gastrointestinal, and renal adverse events. Although they are frequently used, benzodiazepines carry risks, and no evidence exists that supports the use of these drugs for the treatment of chronic pain. Other agents include anticonvulsants, anti-depressants, and topical agents; lidocaine is used to treat post-herpetic neuralgia, capsaicin is used to treat postherpetic distal sensory polyneuropathy, and diclofenac is used to treat osteoarthritis.

**Opioids**

There is growing consensus that long-term opioid therapy is not an appropriate initial treatment for chronic pain. Opioids may be effective in treating chronic pain in some patients, but data on the benefit of opioids as a long-term treatment are limited. There is increasing awareness of the potential harms associated with opioid use. Currently, the United States is experiencing an epidemic of opioid overdoses. There is evidence of increased mortality risk for individuals who receive opioid doses greater than the equivalent dose of 50 mg to 200 mg of morphine per day, depending on the threshold used in the study, and mortality risk is greater for individuals who combine use of opioids with use of benzodiazepines.6,9-15

To mitigate risk, practitioners and patients should jointly review an opioid treatment agreement. The term agreement is preferred to contract, as agreement implies that both the patient and practitioner have responsibilities with regard to patient safety. An agreement should be written at a low literacy level, should include information about safe prescribing, should limit the patient to 1 prescribing physician and 1 pharmacy, should note the need to store medication safely, and should state that opioid prescription may be reconsidered if the patient is not able to adhere to these guidelines. Ideally, such documents also contain information about informed consent that explains the risks of, benefits of, and alternatives to opioid treatment. Strategies for monitoring individuals taking long-term opioid therapy should include routine checks of prescription drug databases and urine drug testing. Based on the consensus opinions of numerous groups, routine use of these strategies become the standard of care for individuals taking long-term opioid therapy. Official guidance regarding strategies for risk mitigation differs among states, and practitioners should be familiar with their state’s policies.

The decision to initiate or continue opioid treatment is guided by assessment of risks and benefits to the patient at regular intervals. Risk factors for misuse and abuse of opioids include personal or family history of substance use, younger age, history of sexual abuse, and history of depression. Evidence of benefit in patients taking opioids includes improvements in physical and emotional function as well as a reduction in pain. Evidence of harm in patients taking opioids includes adverse events such as falls, fractures, and poor physical or emotional function, and the development of depression, hypogonadism, or hyperalgesia.

Concerning behaviors, also referred to as aberrant behaviors, may also arise in individuals taking long-term opioid therapy. Such behaviors include unsanctioned dose escalation, reporting lost or stolen prescriptions, obtaining opioids from more than 1 prescriber, unwillingness to adhere to nonopioid-based aspects of the treatment plan, concurrent use of nonprescription substances including illicit substances, and aggressive behavior. These behaviors each represent a substantial clinical challenge to HIV primary care. When such behaviors arise, the practitioner should promptly discuss the
behavior with the patient and carefully consider the differential diagnosis of the behavior. Depending on the findings, strategies for addressing such behaviors include reeducating the patient on the appropriate use of and risks associated with opioids, closer monitoring (eg, smaller supplies of medication, more-frequent clinic visits to reassess clinical condition and further assess behavior), and involvement of pain, psychology, and substance use professionals. If behaviors are serious or if they persist over time and do not resolve with these strategies, tapering of opioid treatment should be considered. As patients are further evaluated during repeated office visits or by specialist colleagues, it may become apparent that they meet the criteria for addiction in individuals taking long-term opioid therapy, which include the 4 Cs: loss of control, compulsive use, craving, and continued use despite harm.

Regular office visits (eg, every 3-6 months) during which the above monitoring and risk-benefit assessments are conducted are becoming the standard of care during treatment of chronic pain with opioids. An important factor to consider during treatment and management of chronic pain is the lack of evidence that long-acting opioids are safer than short-acting drugs; some evidence indicates that long-acting drugs may be associated with greater risk of overdose. Repeated dose escalation should be avoided; high doses are not typically more efficacious than lower ones, but recent evidence suggests they are more dangerous.

It is important to remember that urine drug tests may be difficult to interpret. Initial urine drug tests are screening tests and may have false-positive or false-negative results (eg, use of quinolones causing a false-positive result for opiates, or a lack of detectable opioid levels in a patient who is taking them and who has a low urine concentration). Following up a urine drug test with a confirmatory test, usually a gas chromatography/mass spectrometry test or a liquid chromatography/mass spectrometry test, may be useful.

Additionally, knowledge of pathways of drug metabolism (eg, that hydrocodone is metabolized into hydromorphone and therefore may appear on a urine drug test as hydromorphone) is important. Documentation of the risk-benefit analysis of opioid treatment for an individual patient, as well as of the monitoring strategy employed and of any adverse events or concerning behaviors, is crucial.

Practitioners sometimes “inherit” patients who are taking long-term opioid therapy from outside clinics or colleagues. This transition of care provides an ideal opportunity to reassess a patient’s opioid therapy. The practitioner should take the steps described above, providing patients with basic pain education and basic monitoring. Keeping decisions regarding continuation of long-term opioid therapy within a risk-benefit framework is important and useful. If there is no evidence of harm, if the risk is judged to be low, and if the patient is benefiting from it, opioid therapy may be continued with standard monitoring as described above. However, concerning behaviors or active substance use disorders should be addressed promptly.

Nonpharmacologic Approaches

Cognitive-behavioral therapy and physical therapy are 2 important evidence-based nonpharmacologic approaches to treatment of chronic pain. These are often the most effective treatment options for improving function in patients with chronic pain. Other options include exercise, complementary or alternative therapies such as acupuncture, and surgery for specific indications.8,16-22

Summary

Chronic pain is common in patients with HIV infection and may cause substantial functional impairment. Therapies for chronic pain include many options in addition to opioids. Careful attention must be paid to psychiatric symptoms in patients with chronic pain, and psychiatric conditions should also be treated if treatment of chronic pain is to be effective.8

Presented by Dr Merlin in March 2015. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Merlin in September 2015.

Financial affiliations in the past 12 months: Dr Merlin has no relevant financial affiliations to disclose.

References


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