CHAPTER 6 CONCURRENT MEDICAL CONDITIONS

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6.1. Introduction

People who use drugs may experience a wide spectrum of medical complications and typically experience worse health outcomes compared to people who do not use drugs. Some of these conditions are urgent or life threatening. Therefore clinicians in OTPs need to be able to recognize and address these conditions at initial contact and address them even when the sedating and analgesic properties of opioids have the potential to mask symptoms. Chronic conditions that result from drug use may last a lifetime and require the OTP clinician's ongoing care, compassion, and advocacy.

The main objectives of this chapter are to: (1) describe some of the common, urgent needle-related illnesses and other serious medical complications encountered when caring for persons who inject drugs; (2) outline a general approach to the prevention and treatment of viral hepatitis and HIV disease in persons who use drugs; and (3) recommend how to screen for and manage the reportable infections seen more frequently in persons who use drugs. One framework for thinking about the medical complications of drug use organizes conditions according to routes of drug administration; drug contamination or adulteration; drug-specific effects; behaviors or conditions associated with drug use; and co-occurring mental health disorders.

6.2. Medical Complications from Routes of Drug Administration

6.2.1. Needle-Induced Illness or Injuries

Needle related injuries can be categorized into infections (bacterial, fungal, viral), intravascular reactions (venous thrombosis, arterial insufficiency), cutaneous reactions (tracks, foreign body granulomas), and scarring. The first two require urgent medical attention, and clinicians working with persons who inject drugs need to be able to recognize their presentations and treatment.

Needle-related infections

Needle-related infections can be further characterized as local skin and soft tissue infections, systemic infections, or the transmission of infectious viral agents.

Skin and soft tissue infections may present as cellulitis, abscesses, lymphangitis, and septic thrombophlebitis [195]. The most common bacterial organisms are Group A streptococcus (GAS) and Staphylococcus aureus. Less common causes are enteric organisms, anaerobes, Clostridia, oral flora, fungi (Candida albicans), and polymicrobial infections. Risk factors for developing abscesses include: subcutaneous or intramuscular drug administration, repeated flushing and pulling back on the plunger while injecting, injecting heroin and cocaine mixtures, injecting frequently, untreated HIV disease; non-sterile injecting equipment, and poor skin hygiene [196].

Differentiating between cellulitis and an abscess is primarily clinical, but can be aided by bedside ultrasonography in unclear cases. An abscess is a localized collection of pus within the dermis and deeper skin tissues. It is indurated, warm, red, and tender, and eventually fluctuant. Staph aureus is the most common pathogen. When not associated with cellulitis, incision and drainage is the main treatment. Antibiotics may be given for complicated abscesses, meaning if they are large or incompletely drained, significantly surrounded by cellulitis, signs or symptoms of systemic infection are present, or the patient is immunocompromised. Cellulitis is an acute spreading infection of the skin, involving the subcutaneous tissues. It presents as an expanding superficial redness with warmth, and tense skin. If untreated with antibiotics, cellulitis may lead to more serious systemic infections. Beta hemolytic streptococci are the most common pathogens and usually respond to beta lactam therapy. Staph aureus is a less common pathogen but may be methicillin resistant. The choice of empiric outpatient treatment of cellulitis should be guided by antibiotic resistance patterns in the community, which can be obtained from a local hospital's antibiogram (see https://idmp.ucsf.edu/). Prevention includes use of clean needles and cleaning of skin areas prior to injection.

Necrotizing fasciitis is a deep soft tissue infection characterized by fulminant destruction of the muscle fascia and subcutaneous fat, systemic toxicity, and high mortality (30-80%), even with optimal therapy [197]. These infections are polymicrobial (type I) or monomicrobial (type II), predominantly Group A strep and other beta hemolytic strep. The affected area is usually red, swollen, warm, shiny, and exquisitely tender. Subcutaneous gas can be detected as crepitus in type II infections. Rapid progression of skin color changes from red-purple to patches of dusky blue and gray, bullae and frank cutaneous gangrene can develop in a few short days. Necrotizing infections of the skin and fascia are surgical emergencies. The goal of operative management is aggressive debridement until healthy, viable, bleeding tissue is reached. The wound is closed only after all necrotic tissue is completely removed and, in some cases, the resulting defects require allografts and tissue reconstruction. In other cases, amputation may be required to control the infection.

Needle-related systemic infections are among the most serious complications of injecting drug use. Intravenous injection of microbes or particulate matter can result in vascular endothelial damage and infection, most commonly heart valves as with infective endocarditis, but also arteries (e.g., mycotic aneurysms) and veins (e.g., septic thrombophlebitis). In any person who injects drugs and presents with fever, the clinician must seek an endovascular source [196]. Other needle-related systemic bacterial infections that require hospitalization include epidural abscess or discitis, osteomyelitis, septic arthritis, and sepsis. These will not be discussed in detail here, but should always be on the differential for febrile patients who inject drugs.

Infective endocarditis (IE) is defined as bacteremia with endocardial involvement and has a high prevalence among febrile persons who inject drugs. It is most often right-sided, involving the tricuspid valve in 70% of cases, and mortality is high (6%). Predisposing risk factors are colonization with community-acquired methicillin resistant Staph aureus, prior IE, cocaine injection, daily injecting, and untreated HIV disease [197]. The most common pathogens are Staphylococcus aureus, followed by streptococci and enterococci. Infective endocarditis may present with fever, dyspnea, pleuritic chest pain, and cough; a murmur may be absent. Complications can range from abscesses and fistulas to septic embolization, pericarditis, and ring abscesses causing heart failure, valve rupture, and death. Serious left-sided complications can occur in the presence of a patent foramen ovale, which allows septic emboli to reach organs like the brain and spleen. Suspicion for endocarditis requires hospital admission. The cornerstones of diagnosis are blood cultures to detect bacteremia, echocardiogram, and clinical observation. Early empiric therapy should cover staph, strep and enterococci. Intravenous vancomycin is the appropriate initial therapy for most patients. Transthoracic echocardiogram is 88-94% sensitive in persons who inject drugs. Confirmed cases require 4-6 weeks of intravenous antibiotics based on in vitro susceptibility, and early consultation with a cardiac surgeon is recommended for potential valve replacement.

Needle-related viral infections

The most common needle-related viral infections are due to blood contamination by hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV. The "Rule of 3's" is a memory tool to estimate the relative risks of viral transmission from an occupational percutaneous needle stick exposure after a needle is used on an infected patient: HIV (0.3%), HCV (3%), HBV (30%). The probability of acquiring HIV when sharing needles to inject drugs is estimated to be 63 per 10,000 exposures or about 0.6% per act [198]. Additional information about the estimated per-act probability of acquiring HIV from an infected source, by exposure act, is provided by the CDC and can be found at: https://www.cdc.gov/hiv/risk/estimates/riskbehaviors.html.

Prevention starts with access to sterile injecting and all other drug use equipment including pipes, tourniquets, and water. Skin hygiene and appropriately discarding used equipment are also important. Clinicians at OTPs should screen for these viral infections. HBV infections are preventable with immunizations in those who are susceptible and should be made available wherever persons who use drugs access care. A preventive HCV vaccine is not yet available but under investigation in clinical trials with high-risk negatives. Post-exposure prophylaxis antiretroviral regimens can be given within 72 hours of exposure to blood or other potentially infectious body fluids from a known HIV-positive or high-risk source. Pre-exposure prophylaxis (PrEP) has been associated with an impressive 49% reduction in HIV incidence in a randomized trial of high-risk people who inject drugs in Bangkok [199]. Therefore, all persons who inject drugs, and their partners, should be screened and offered PrEP against HIV. National guidelines and free expert telephone consultation services (http://nccc.ucsf.edu/) can help clinicians to assess and treat persons with or at risk of viral exposures.

Hepatitis B virus (HBV) is transmitted through percutaneous and mucosal contact with infected blood or body fluids and

will infect a high proportion of persons who inject drugs if they are not immunized in childhood or adolescence. While the rate of new HBV infections declined from 1990–2014 as a result of universal childhood immunization, an increase in HBV incidence since 2014 has been attributed to increasing injection drug use [200]. Determining who needs immunization or treatment for chronic HBV infection requires understanding the different serologic courses of infection. The CDC offers free online hepatitis serology training at: https://www.cdc.gov/hepatitis/resources/professionals/training/serology/training.htm. All unvaccinated or non-immune patients who are in a drug treatment program should receive HBV immunizations, according to CDC guidelines at https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/hepb.pdf.

The presence of hepatitis B core and surface antibodies generally indicate recovery and immunity from re-infection. The presence of hepatitis B surface antibody alone suggests prior immunization. Some 5-10% of acute adult cases progress to chronic HBV infection, in which both surface antigen and core antibody remain persistently detectable, generally for life. By contrast, 90% of infants infected at childbirth progress to chronic infection. A helpful guide to interpret HBV test results is at: https://www.cdc.gov/hepatitis/hbv/pdfs/SerologicChartv8.pdf. While chronic infection is less common than with HCV infection, the prevalence of chronic HBV is still 10-20 times higher among persons who inject drugs than that of the general U.S. population. About 15% of those who become chronically infected as adults die prematurely from cirrhosis or liver cancer, and the majority remain asymptomatic until onset of cirrhosis or end-stage liver disease. The American Association for the Study of Liver Diseases (AASLD) Practice guidelines for the treatment of chronic hepatitis B are useful, updated frequently, and available at: https://www.aasld.org/publications/practice-guidelines.

Hepatitis C virus (HCV) infection is the most common blood-borne infection in the U.S. with a conservative estimate of 3.5 million chronically infected persons. The prevalence of HCV infection among persons who inject drugs ranges from 38.1% to 68.0% [201], and antibodies to HCV in OTPs range from 67-96% [202]. Chronic HCV infection accounts for more than 50% of new cases of hepatocellular carcinoma, which is the fastest-growing cause of cancer-related death, and is one of the leading indications for liver transplantation in the U.S. Death certificate data show that HCV-related deaths have outpaced deaths due to HIV.

The natural history of HCV infection has wide variability. Factors that decrease the risk of progression include female gender and younger age at infection. Factors that increase disease progression include alcohol consumption and co-infection with other viruses, such as HIV and hepatitis B virus (HBV). Once cirrhosis is established, the risk of hepatocellular carcinoma is 1 to 4 percent per year. The care of the OTP patient with cirrhosis requires attention to effects on multiple organ systems. Patients may be greatly debilitated by symptoms that include anorexia, fatigue, muscle wasting, ascites and edema, and bleeding diatheses. In patients at risk of active gastrointestinal bleeding, opioid withdrawal with onset of nausea and vomiting becomes potentially life threatening. Sudden or abrupt decreases in methadone dose should be avoided. Men with cirrhosis also may experience erectile dysfunction, gynecomastia, and testicular atrophy. High ammonia levels result in encephalopathy, which may cause the patient to demonstrate confusion, memory loss, and erratic behavior. In advanced disease, the liver is unable to metabolize methadone efficiently. The usual methadone dose may need to be gradually reduced to avoid oversedation. Methadone blood levels and clinical observation assist in re-establishing the correct dose.

OTPs have a unique opportunity to screen and assess persons for HCV infection, to educate them about HCV prevention and treatment, and to administer onsite curative treatment. Since only 1 in 5 patients infected with HCV presents with acute symptoms, most infections are diagnosed when chronic, by screening patients who are at risk. Past or present injection drug use is the most important risk factor for HCV acquisition. Screening is recommended for persons who have a history of injecting drugs, persons with specific medical conditions, past recipients of transfusions or organ transplants and persons with a recognized exposure. Screening should also be considered for persons with high-risk sexual behaviors including multiple partners, HCV-positive partners, and men who have sex with men, persons who have received an unregulated tattoo and persons with a history of intranasal drug use. Additionally, people born between 1945 -1965 should be screened at least once regardless of other risk factors [203]. See here for a summary of testing recommendations: https://www.hcvguidelines.org/evaluate/testing-and-linkage.

In May 2013, the CDC recommended a new testing sequence for diagnosing HCV infections [204]. The algorithm shown in Figure 6.2.1. consists of initial testing for HCV antibody, followed by HCV ribonucleic acid (RNA) testing of all positive antibody tests. The HCV antibody test may be performed with a blood specimen that is sent to a laboratory or with a rapid, on-site finger stick. Currently, the HCV RNA test must be drawn as a blood specimen and sent to a laboratory for testing.

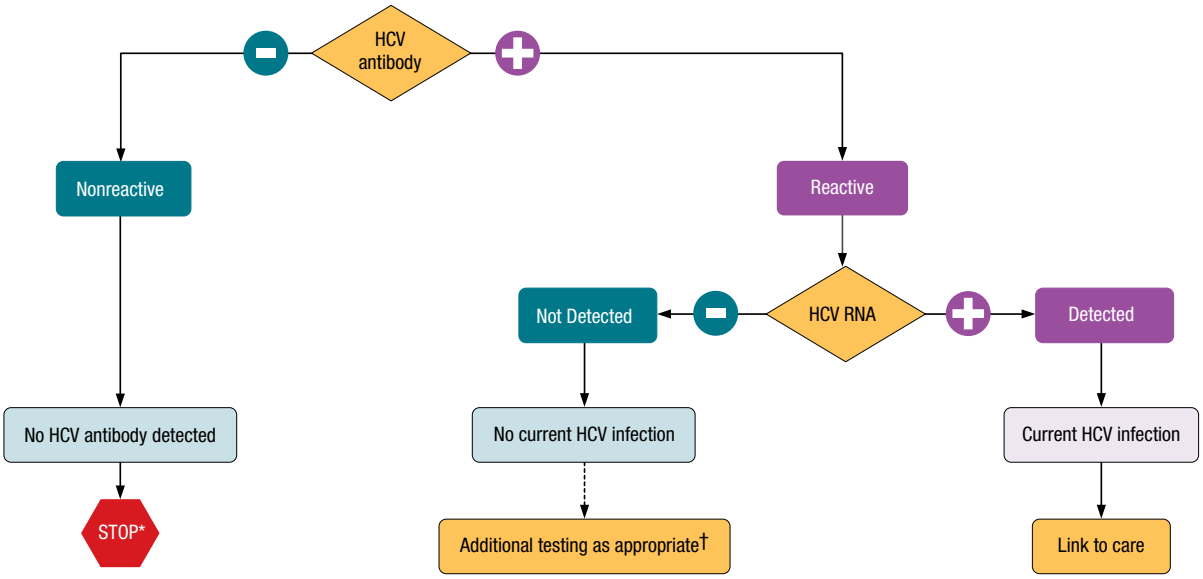
The HCV antibody test detects the presence of antibodies to the virus, indicating exposure to HCV. The HCV RNA test detects the presence (qualitative) or amount (quantitative) of virus to diagnose current infection. Between 20-25% of patients with antibodies to hepatitis C have spontaneously resolved infections (antibody reactive, HCV RNA not detected). In patients with current HCV infection (antibody reactive, HCV RNA detected), a minority of those will develop cirrhosis. For patients whose infections have been successfully treated, subsequent testing will reveal a reactive antibody but undetected HCV RNA. Table 6.2.1 describes the interpretation of HCV test results and further actions.

A model for HCV screening in an OTP has been developed by the Opiate Treatment Outpatient Program at San Francisco General Hospital and may be used as resource for other OTPs (see Table 6.2.2).

The treatment of patients living with chronic HCV is guided by the ability to reduce individual morbidity and

Figure 6.2.1

Recommended Testing Sequence for Identifying Current HCV Infection



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Source: https://www.cdc.gov/hepatitis/hcv/pdfs/hcv_flow.pdf

mortality and the risk of transmission to others. Current recommendations include liver protective advice (i.e. HAV/HBV immunizations, avoidance of hepatotoxic agents like alcohol and large dosages of acetaminophen). Patients should be given medical counsel about the risk of alcohol use. Aggressive intervention, including medications for alcohol use disorder, is recommended for patients who continue to drink alcohol. Referral to a higher level of care may be considered. HCV-infected patients also should receive patient-centered counseling about safer injecting and sexual practices, engagement in medical care for evaluation, and curative treatment with a relatively short course of highly effective and well-tolerated directly acting antiviral (DAA) medications.

The advent of DAA medications in 2011 revolutionized the treatment of chronic HCV infection, such that more than 90% of HCV mono-infected and HIV-HCV co-infected persons can now be cured regardless of HCV genotype with 8-12 weeks of oral therapies, most of which are taken as once daily doses. The AASLD now recommends treatment for all patients with chronic infection who have a life expectancy greater than 6 months. Co-infected patients ideally are initiated on treatment for HCV following establishment of HIV viral suppression and treated using the same medications as HIV uninfected patients. OTP clinicians providing treatment for co-infected patients will need specific and ongoing training to review possible drug-drug interactions before starting HCV medication. Frequently updated AASLD guidelines for the treatment of mono-infected and co-infected patients and drug-drug interactions can be found at: https://www.hcvguidelines.org/.

Historically, patients who injected drugs were denied HCV treatment. However, given new evidence about the effectiveness of treatment in PWID and the importance of treatment as prevention, **persons who actively inject drugs are among the highest priority populations for treatment in California** [206]. Therefore, all persons with current HCV infection should be linked to care, which increasingly can be delivered within the OTP. Indeed, HCV treatment has been delivered successfully to individuals in a number of OTP clinics across the country that integrate the identification, evaluation, and treatment of HCV under one roof [207]. Addiction treatment programs can play a significant role in HCV elimination, and their involvement is strongly encouraged in the American Society of Addiction Medicine policy statement on HCV infection [208]. Model programs typically offer directly observed treatment (DOT) to facilitate HCV medication adherence, support patients who are undergoing treatment, and educate patients about how to avoid reinfection once cured.

No clinically significant drug interactions are expected between methadone and most DAAs. Small increases in the methadone dose are sometimes required during

Table 6.2.1

Interpretation of Test Results for HCV Infection and Further Actions

TEST OUTCOME	INTERPRETATION	FURTHER ACTIONS
HCV antibody nonreactive	No HCV antibody detected	Sample can be reported as nonreactive for HCV antibody. No further action required. If recent exposure in person tested is suspected, test for HCV RNA.*
HCV antibody reactive	Presumptive HCV infection	A repeatedly reactive result is consistent with current HCV infection, or past HCV infection that has resolved, or biologic false positivity for HCV antibody. Test for HCV RNA to identify current infection.
HCV antibody reactive, HCV RNA detected	Current HCV infection	Provide person tested with appropriate counseling and link person tested to care and treatment.†
HCV antibody reactive, HCV RNA not detected	No current HCV infection	No further action required in most cases. If distinction between true positivity and biologic false positivity for HCV antibody is desired, and if sample is repeatedly reactive in the initial test, test with another HCV antibody assay. In certain situations,§ follow up with HCV RNA testing and appropriate counseling.

* If HCV RNA testing is not feasible and person tested is not immunocompromised, do follow-up testing for HCV antibody to demonstrate seroconversion. If the person tested is immunocompromised, consider testing for HCV RNA.

† It is recommended before initiating antiviral therapy to retest for HCV RNA in a subsequent blood sample to confirm HCV RNA positivity.

§ If the person tested is suspected of having HCV exposure within the past 6 months, or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Source: https://www.cdc.gov/hepatitis/hcv/pdfs/hcv_graph.pdf

treatment with the less commonly used DAAs, boceprevir and telaprevir. In addition, no clinically significant drug interactions are expected between buprenorphine and most commonly covered DAAs in 2018 (e.g., elbasvir/grazoprevir, glecaprevir/pibrentasvir). Concentrations of buprenorphine may increase when administered with other common DAA regimens containing ledipasvir, velpatasvir, and voxilaprevir; however, this is a potentially weak interaction unlikely to be of clinical significance; additional action or monitoring is unlikely to be required. Review of specific drug-drug interactions, particularly for HIV-HCV co-infected patients, can be conducted in consultation with a pharmacist or by use of various online tools: https://www.hep-druginteractions.org/checker.

HCV cure is defined as sustained virologic remission with an undetectable HCV RNA test at 12 weeks after treatment (SVR-12). Persons who achieve SVR-12 should be monitored for re-infection at least annually and more frequently when reporting risk behavior. Cured persons with cirrhosis should continue to be monitored every 6 months by ultrasound for the development of hepatocellular carcinoma (HCC). Patients that develop decompensated cirrhosis or non-metastatic HCC may require liver transplantation. Notably, liver transplant outcomes are improved with DAA-treated patients, and there are OTP patients who have received liver transplants. Some transplant services do not accept patients on methadone treatment. In this situation, the role of the OTP clinician is essential as an advocate on behalf of the patient.

Free clinician-to-clinician consultation on HCV mono-infection and coinfection management is available from the UCSF Clinician Consultation Center at: http://nccc.ucsf.edu/clinician-consultation/hepatitis-c-management/

HCV Provider Education Resources:

- Addiction Technology Transfer Center, HCV Current Initiative
  http://attcnetwork.org/projects/HCV_Home.aspx
- Association for the Advanced Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) HCV Treatment Guidelines
  http://www.hcvguidelines.org/

Table 6.2.2

A Model for HCV Testing in an Opioid Treatment Program

With only 24% of substance use treatment programs across the United States offering HCV testing in 2012 [205], OTPs offer the ideal setting to screen for HCV in this highest risk population. Co-localization of treatment for OUD with screening for infectious diseases that are more prevalent among persons who inject or use drugs has been effective in identifying and treating both HIV and HCV. An OTP has the following advantages for integrating services:

- The OTP is often the patients' setting of choice for care.
- TB and syphilis screening are mandated at intake and annually, and can be linked to HCV screening.
- Frequent if not daily attendance is required initially, allowing for close follow up for results and referrals.
- Counseling services are on site.
- Maintenance treatment with methadone or buprenorphine has been shown to reduce HCV incidence among young people who inject drugs by 60% and has the potential to reduce HCV reinfection and support HCV treatment.

The goals of a model testing program are to provide universal, opt-out testing for HCV, identify persons with chronic HCV and refer for treatment, provide risk reduction education and counseling, and do this with minimal additional workload. A laboratory algorithm and process steps are depicted in the three diagrams below. Key elements to consider:

- If phlebotomy for mandated labs (TB and syphilis) is not performed onsite, coordination with the OTP's service lab may be needed for HCV lab testing.
- Provide education and training for the medical staff who will order and review labs, and for the counseling staff on HCV risk, risk reduction, results disclosure and linkage to HCV care and treatment.
- Identify a project champion to promote and monitor the HCV screening, testing, and linkage program.
- Expect 15-20% HCV antibody positivity and 60-75% HCV RNA positivity in an OTP setting, along with the associated high volume of HCV treatment linkage.
- OTPs licensed to offer clinical care, such as hospital-based programs, may consider offering on-site HCV treatment, including directly observed therapy.
- Establish relationships with HCV treatment providers as part of program implementation (or alert medical provider partners to the program to prepare them for HCV-related referrals/linkages).

- U.S. Centers for Disease Control and Prevention (CDC), Division of Viral Hepatitis
  www.cdc.gov/hepatitis
- California Department of Public Health Office of Viral Hepatitis Prevention
  www.cdph.ca.gov/programs/pages/ovhp.aspx
- Hepatitis B and Hepatitis C Screening Toolkit for Primary Care Providers
  https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/HepatitisBandCScreeningToolkitforPrimaryCare.pdf
- Clinical Care Options
  http://www.clinicaloptions.com/hepatitis.aspx
- Hepatitis C Online (University of Washington)
  https://www.hepatitisc.uw.edu/
- Medi-Cal Hepatitis C Treatment Policy
  http://www.dhcs.ca.gov/Pages/HepatitisC.aspx
- National Clinical Consultation Center – Hepatitis C Warmline
- Access the Warmline toll-free at: 1-844-437-4636
  (Monday-Friday, 9 a.m.- 8 p.m. ET).
  http://nccc.ucsf.edu/clinician-consultation/hepatitis-c-management/
- University of California San Francisco, HCV Project ECHO
  http://echo.ucsfhealth.org/

Human immunodeficiency virus (HIV) infection is transmitted through percutaneous and mucosal contact with infected blood or body fluids, most commonly through risky sexual behaviors and sharing needles, syringes, and other injecting equipment. An estimated 1.1 million people in the U.S. were living with HIV at the end of 2015, and as many as 15% were unaware of their infection [209]. Men who have sex with men are most severely affected, and blacks or African Americans face the most severe burden of disease. While the number of AIDS diagnoses in persons who inject drugs (PWID) peaked in the U.S. in 1993, injecting drug use still accounts for about one-third of all HIV infections. Annual HIV diagnoses among black and Hispanic/Latino PWID decreased by about 50% between 2008–2014, but diagnoses among white PWID dropped by only 28% between 2008-12 and not at all between 2012-14 [210]. An outbreak of HIV in the small, rural town of Austin, Indiana in 2014 underscored the changing landscape of injecting drug use and HIV risk in nonurban areas where

access to syringe service programs and addiction treatment are scarce.

Figure 6.2.4 is the New CDC Recommendations for HIV Testing in laboratories and describes the natural history of HIV infection, which until the development of effective combination antiretroviral therapy (ART) in 1996 led almost uniformly to death. While ART cannot cure HIV, it reduces the amount of virus in the body, protects the immune system, prevents disease progression to AIDS, and reduces HIV transmission. Diagnosis of HIV infection is delayed more often among persons who inject drugs, persons of color, and older adults than in other populations—many of whom develop AIDS-defining illnesses within 1 year of diagnosis. Some patients entering substance use treatment have never been tested for HIV or hepatitis because they are very fearful that they may already have one or both of these infections and have decided that if they do, they would rather not know. The stigma of HIV and addiction are significant barriers to the detection and effective treatment of both diseases.

To reduce diagnostic and treatment delays, the CDC recommends opt-out HIV testing at least once as a routine part of medical care for everyone aged 13-64 and testing at least once a year for people at high risk for HIV [211]. This guidance applies to OTPs in the private and public sectors. HIV testing should be encouraged and offered annually on-site if possible.

There are three main types of HIV tests: (1) antibody tests, (2) combination antibody/antigen tests, and (3) nucleic acid tests (NAT) [212]. Antibody tests check blood or oral fluids for HIV antibodies only. The window period for antibody tests is somewhere between 3-12 weeks from the time of infection. A combination 4th generation assay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen from serum or plasma specimens reduces the window period to between 2-6 weeks. This antibody/antigen assay is being used more commonly and is recommended for all HIV testing done in labs. When combined with a NAT, the recommended HIV testing strategy (Figure 6.2.4.) permits earlier detection of infection by as much as 3-4 weeks.

The U.S. DHHS recommends immediate initiation of ART for all persons with HIV regardless of CD4 cell count to achieve the primary goal of reducing the morbidity and mortality associated with HIV infection. An important secondary goal of treatment is to prevent HIV transmission [213]. With an increasing array of co-formulated regimens with fewer toxicities, many patients can take a single pill once daily to achieve viral suppression. HIV disease in PWID can be treated successfully and with great public health impact. British Columbia enhanced its outreach through "test and treat" programs,

Figure 6.2.2

HCV Screening and Assessment Algorithm

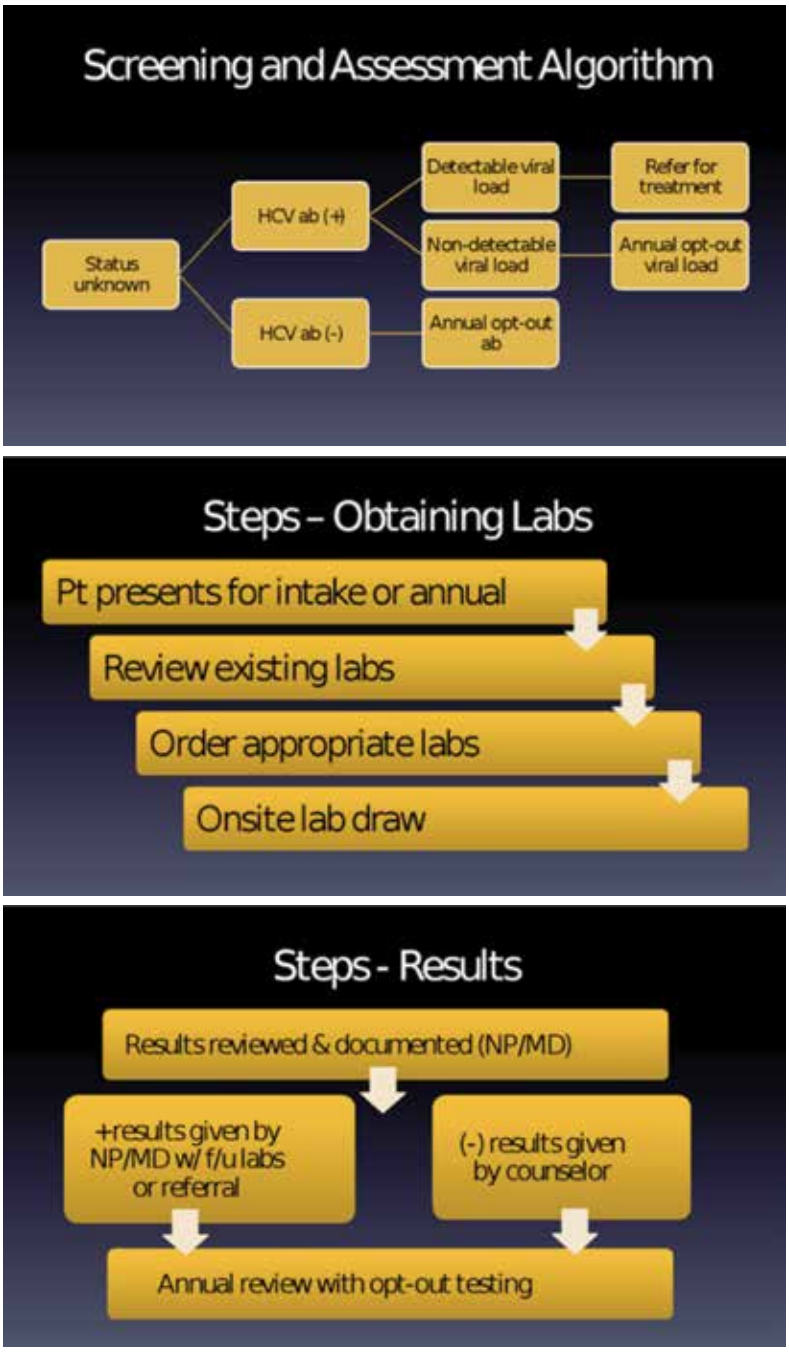


Figure 6.2.3

New Treatments for Hep C

Source: http://www.endhepcsf.org/portfolio-items/opiate-treatment-outpatient-program/

and demonstrated an association between expanded ART coverage, decreased community HIV viral load, and a 50% reduction in new HIV diagnoses among PWID. For persons with opioid use disorders and HIV, life-saving ART has been administered with methadone at OTPs efficiently and effectively as directly observed therapy (DOT) by dispensing nurses.

Patients and providers are often concerned about potential drug interactions between opioid agonist pharmacotherapies and HIV medicines. The two most clinically significant interactions occur with ART medications that are no longer among the recommended initial regimens for most people living with HIV: (1) the induction of methadone metabolism by efavirenz (EFV); and (2) the inhibition of buprenorphine metabolism by ritonavir-boosted atazanavir (ATV)/r.

Updated drug interaction information is available at: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/367/overview

Protease inhibitor class: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/284/pi-drug-interactions

Non-nucleoside reverse transcriptase inhibitor class: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/285/nnrti-drug-interactions

Nucleoside reverse transcriptase inhibitor class: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/286/nrti-drug-interactions

Integrase inhibitor class: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/287/insti-drug-interactions

HIV care is rapidly evolving and requires open communication and partnership between patients and providers. For in-depth recommendations on high-quality HIV care to guide individual medical decision-making, the U.S. DHHS frequently updates national guidelines at: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0. Free peer-to-peer expert advice on the management of all aspects of HIV also is available to clinicians from the UCSF Clinician Consultation Center at http://nccc.ucsf.edu/clinician-consultation/hiv-aids-management/.

6.3. Medical Complications Caused by Drug Contaminants or Adulterants

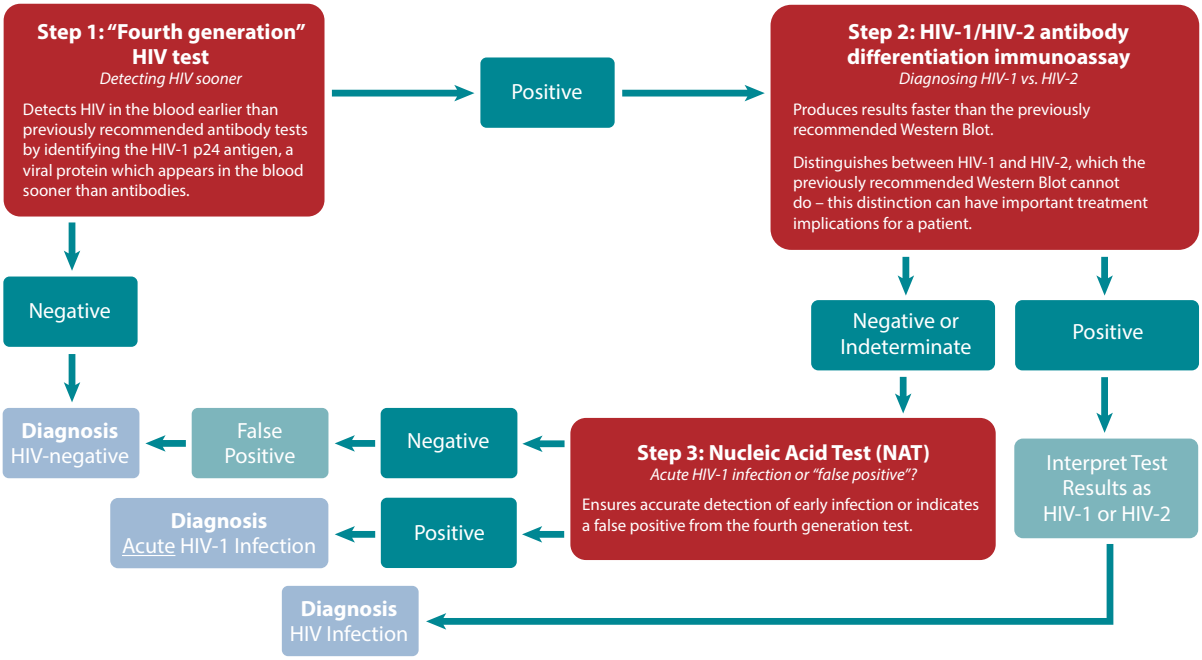
Contamination or adulteration of drugs can lead to severe illness or death in persons who use drugs. Examples of infectious agents that are known to have contaminated the heroin supply include clostridia species and anthrax [214]. In California and other western states, the contamination of black tar heroin with spores of the anaerobic bacteria Clostridium has been associated with outbreaks of wound botulism, tetanus, and necrotizing infections [215]. *C. botulinum* produces a potent exotoxin that binds to the presynaptic membrane and irreversibly disrupts acetylcholine release at peripheral cholinergic synapses. An acute descending paralysis involving autonomic and cranial nerves presents as dysarthria, diplopia, dyspnea, and progressive dysphagia that may require intubation. Ptosis, skin abscesses, sluggish pupils, and 6th cranial nerve palsies also can be seen on the

Figure 6.2.4

New CDC Recommendations for HIV Testing in Laboratories

CDC's new recommendations for HIV testing in laboratories capitalize on the latest available technologies to help diagnose HIV infections earlier – as much as 3-4 weeks sooner than the previous testing approach. Early diagnosis is critical since many new infections are transmitted by people in the earliest ("acute") stage of infection.

By putting the latest testing technology to work in laboratories across the United States, we can help address a critical gap in the nation's HIV prevention efforts.



This graphic is designed to illustrate key concepts of the new testing approach in laboratories. For more detail, please see the full guidelines here: http://www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf.

Source: https://www.cdc.gov/nchhstp/newsroom/docs/2014/hiv-testing-labs-flowchart.pdf

physical exam [216]. *Clostridium botulinum* may be detected in serum and cultured from abscess specimens. While an antitoxin is available, toxin production in situ may still require aggressive wound debridement.

Adulterants are substances deliberately added to bulk, dilute, complement, or enhance a drug's effects [217]. These substances range from sugars and acetaminophen as bulking agents to more active substances, such as lidocaine in cocaine and fentanyl in heroin. Levamisole is an anthelminthic and immunomodulatory agent that may have noradrenergic effects and has been an adulterant in cocaine since at least 2003. In 2010, it was detected in about three-quarters of all the cocaine seized by the Drug Enforcement Agency and nearly all (88%) of the cocaine-metabolite positive urine specimens tested at San Francisco General Hospital [218]. Thus far, levamisole is clearly involved in three debilitating autoimmune-mediated syndromes: agranulocytosis, thrombotic cutaneous retiform purpura, and pauci-immune cresenteric glomerulonephritis. They can occur together or separately and are associated with an ANCA-positive vasculopathy. Treatment consists of discontinuing the offending agent, and symptoms may recur after re-exposure. In 2018 in Illinois, adulteration of synthetic cannabinoids with brodifacum (an anticoagulant rat poison) led to multiple fatalities from hemorrhage.

Adulteration of the heroin supply with fentanyl analogues has led to an opioid overdose epidemic in the U.S. OTP staff may want to become familiar with fentanyl test strip technology, so that they can distribute test strips to patients as part of overdose prevention training. Useful results from a test strip pilot study can be found at: http://harmreduction.org/issues/fentanyl/. Fentanyl contamination has now spread beyond heroin to cocaine, methamphetamine, and street purchased opioid and benzodiazepine pills. Users of any street drugs should be counseled on this risks and provided with naloxone for overdose reversal.

6.4. Medical Complications Due to Drug-Specific Effects

There are numerous medical complications due to the specific effects of drugs. Opioids not only cause central respiratory depression but also affect endocrine and gastrointestinal systems. Stimulants have profound detrimental cardiac, neuropsychological, and renal effects. Alcohol is an established carcinogen that also causes gastrointestinal and neurologic disease. Tobacco use causes heart disease, stroke, chronic lung disease and is the leading cause of cancer and cancer deaths.

In the U.S., poisoning is the leading cause of death from injuries. The overwhelming majority are due to pharmaceutical and illicit opioids [219]. In 2016, there were more than 63,600 drug overdose deaths in the U.S., five times higher than in 1999. In 2015, annual drug overdose deaths surpassed the number of AIDS deaths at the height of the HIV epidemic in 1995. Increases in drug overdose deaths are involving not only heroin and synthetic opioids but also cocaine and psychostimulants.

The classic toxidrome of opioid overdose is apnea, stupor, and miosis, and the sine qua non is respiratory depressions. In opioid analgesic overdoses, clinicians should beware of multiple organ system involvement, altered pharmacokinetics that prolong intoxication, and the duration of action of different opioid formulations [221]. Overdoses are commonly the consequence of a higher dose or more potent formulation, the concurrent use of sedative hypnotics (e.g., alcohol, benzodiazepines), reduced opioid tolerance, or adulteration of the drug supply. At the community level, extraordinary efforts have been undertaken to train laypersons in the use of naloxone to reverse opioid overdoses. In addition to harm reduction and needle and syringe programs, hospitals, medical clinics (including OTPs) and physicians' offices have become effective venues for naloxone training and distribution to reach a wider population at risk for opioid overdose. The Drug Overdose Prevention and Education (DOPE) Project offers basic and comprehensive service provider trainings on overdose prevention: http://harmreduction.org/issues/overdose-prevention/dope-sf/.

6.5. Hypogonadism

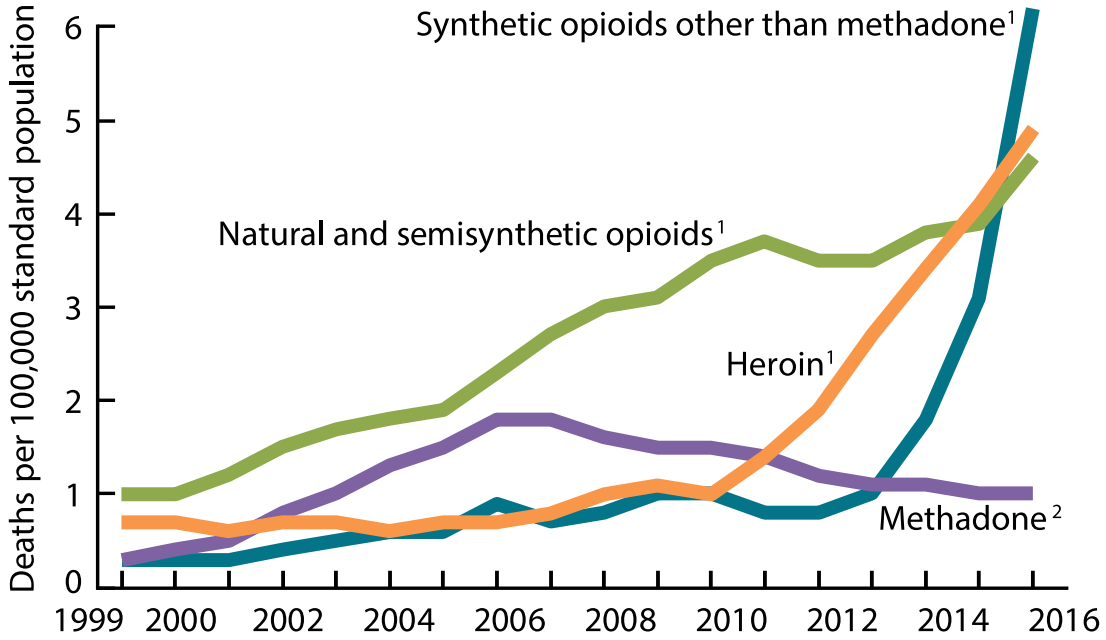
Research and clinical evidence suggest that all opioids, including methadone, impact gonadal function in both male and female patients. Opioids interfere with gonadal hormone regulation in two ways: they inhibit hypothalamic gonadotropin-releasing hormone (GnRH), resulting in reduced secretion of LH and FSH, and they exert direct effects on testicular and ovarian function. The net result is a decrease in testosterone and estrogen and an increase in prolactin levels.

Different opioids have hypogonadal and androgen-inhibiting effects to varying degrees. It appears that methadone has a greater impact on gonadal hormones than buprenorphine [222], and that higher doses of methadone have a greater effect than lower doses. Hypogonadism should be considered in all patients receiving daily opioid treatment in amounts equal to or greater than 100 mg morphine equivalents (~25 mg methadone) [223]. Because of the hypogonadal effects of opioids, both men and women on methadone treatment may experience weight gain, fatigue, depression, sexual dysfunction, hot flashes and increased sweating. Problems with decreased libido and sexual dysfunction may interfere with therapeutic adherence to methadone treatment. Clinical experience suggests that sexual difficulties may prompt some patients on methadone to use stimulants to enhance sexual interest and performance.

Clinical presentation, diagnostic testing and treatment recommendations are gender specific.

Figure 6.4.1

Age-adjusted Drug Overdose Death Rates, by Opioid Category: United States, 1999–2016 [220]



1. Significant increasing trend from 1999 to 2016 with different rates of change over time, $p < 0.05$.
2. Significant increasing trend from 1999 to 2006, then decreasing trend from 2006 to 2016, $p < 0.05$.

SOURCE: NCHS, National Vital Statistics System, Mortality.

Table 6.5.1

Screen Questions for Hypogonadism

- Have you experienced a decrease in sex drive?
- Have you noticed a decreased enjoyment in life or have you become depressed?
- Have you gained weight?
- Have you noticed increased sweating?
- Are you experiencing hot flashes?
- Have you noticed a lack of energy, strength, or endurance?
- Are you having difficulty with erections (men)?
- Have your menstrual periods become abnormal (pre-menopausal women)?

6.5.1. Male patients

Many men on MMT complain of decreased libido and erectile dysfunction. While hypogonadism is a likely explanation, other risk factors for erectile dysfunction are common in this population and include use of tobacco and/or alcohol and chronic medical conditions, such as diabetes or hypertension.

There is a high prevalence of reduced bone mineral density in men on methadone, which may be related to chronic low testosterone levels. Other risk factors for reduced bone mineral density are common in this population and include use of tobacco, alcohol or anabolic steroids or HIV disease. Mild anemia may be seen as testosterone maintains red blood cell production.

OTP practitioners should strongly consider screening patients by history and physical examination, laboratory testing and imaging (DEXA bone scan). For symptomatic male patients, a medical work-up is recommended. The workup may include laboratory testing for luteinizing hormone (LH), follicular stimulating hormone (FSH), total testosterone (TT), free testosterone (FT), estradiol (E2), dihydrotestosterone (DHT) and prolactin. Blood samples should be drawn early in the morning as testosterone levels vary during the day. Referral to an endocrinologist may be indicated for diagnostic and treatment recommendations including testosterone replacement.

Testosterone replacement in men with hypogonadism results in significant improvements in libido, sexual function, depression and hematocrit. Replacement can occur with topical or injected treatment. Due to the fact that testosterone can be diverted, OTP providers may need to work with consulting teams, helping them to develop safe and medically sound plans and advocating on behalf of patients with consulting teams in order to develop safe and medically sound plans. Testosterone replacement is also associated with mild decreases in pain scores. Unfortunately, illicit opioid usage does not change with testosterone replacement [224]. Patients should be evaluated for elevated hematocrit, prostate cancer, and obstructive sleep apnea, among other conditions, both prior to and during treatment. For males with decreased bone density, treatment with bisphosphonates or testosterone (in those who also have hypogonadism) may be indicated.

6.5.2. Female patients

In addition to opioid-induced impairment of GnRH production and impaired ovarian steroidogenesis, opioids also interfere with adrenal androgen production, which may produce a clinically significant deficiency in women. There is decreased adrenal production of dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS,) and androstenedione, which are themselves androgenic and are precursors of testosterone.

Many women on methadone treatment experience decreased libido and menstrual irregularities (amenorrhea and oligomenorrhea). Women with irregular menses may mistakenly believe they cannot become pregnant; others suspect they are pregnant when they are not. In view of the frequency of irregular menses in this population and the complications of pregnancy in the setting of substance use, discussions regarding patient preferences for family planning and the necessity of prompt identification of pregnancy are important. There is a trend toward menstrual cycle normalization when patients stay in methadone maintenance treatment long-term [225]. There is no definitive evidence for reduced bone mineral density in women.

For symptomatic female patients, a medical work-up is recommended. The patient's reproductive history and menstrual cycle history, both prior to and after the administration of methadone, are important. Luteinizing hormone (LH) and follicular stimulating hormone (FSH) levels in pre-menopausal women change with the menstrual cycle, so are of limited value in diagnosing androgen deficiencies. Pre-menopausal women with absent menses should be screened for pituitary abnormalities by checking prolactin levels, after ruling out pregnancy and thyroid dysfunction. Testosterone deficiencies in women are an area of controversy; there is little agreement about testosterone reference levels. DHEAS levels may be the best indicator of androgen production when a woman's clinical findings suggest androgen deficiency. Referral to an endocrinologist or gynecologist may be indicated to identify or rule out other medical conditions that can cause amenorrhea or oligomenorrhea and/or for treatment recommendations.

6.6. Public Health-related Reportable Infections

Infections with significant public health impact are seen in higher frequency in persons who use drugs. Therefore, in addition to syphilis and tuberculosis, screening should be done for HIV, HBV, and HCV testing, and when indicated, other sexually transmitted infections. Immunizations should be provided to OTP patients that are susceptible to HAV and HBV. Annual testing of OTP patients for syphilis and tuberculosis is mandatory by Federal and State regulations.

Syphilis

Syphilis is a systemic sexually transmitted disease caused by the spirochete bacterium, *Treponema pallidum*. Syphilis infection is a medical complication of behavior associated with drug use. Outbreaks in men who have sex with men have been attributed in part to methamphetamine or alcohol as disinhibiting agents that lead to high risk sexual activity. Rates of syphilis have been increasing since 2001. Without treatment, patients remain chronically infected and progress through active clinical stages interrupted by periods of latent infection. Chronic disease can cause significant morbidity, affect multiple organ systems, and even result in death, including fetal demise in untreated pregnant women.

The CDC has published resources, which OTP providers may find useful when discussing STIs with their patients. Tips and tools for providers include:

- Guide to taking a thorough sexual history and list of essential sexual health questions to ask of patients
- Tips for productive conversations with patients
- Guidelines for testing and treatment

There are two types of serologic tests for syphilis; treponemal and non-treponemal. Both are required for diagnosis. Non-treponemal tests I (i.e. VDRL, RPR) are labor intensive to perform, may take days to be resulted, can have low sensitivity and false positive results. Results are reported as a qualitative result and a quantitative titer, which usually corresponds with disease activity. A four-fold change in titer is clinically significant. Newer assays that detect treponema-specific antibodies can be performed more easily and have high sensitivity but cannot be used to assess disease activity or treatment response. Treponemal tests include T. pallidum particle agglutination (TP-PA), fluorescent treponemal antibody absorption (FTA-ABS), and other enzyme or chemiluminescent immunoassays. Many laboratories now offer a reverse syphilis testing algorithm where a treponema-specific test is used for screening, followed by a non-treponemal test to assess disease activity and treatment status. Local health departments can often provide information on whether the patient has been reported as having had syphilis in the past, including reported serologic test results and treatment history.

Patients with primary, secondary or early latent syphilis, or syphilis of unknown duration with a nontreponemal titer greater than 1:32 should be referred to the local health department's STD program for interview, partner elicitation, and partner follow-up. It is a public health priority to follow up patients with early syphilis. All states require that persons diagnosed with syphilis infections be reported to public health authorities. Reporting can be provider-based or laboratory-based.

Syphilis infections can be divided into a series of clinical stages that are used to help guide treatment and follow-up. Long-acting benzathine penicillin G is the preferred drug for treating all stages. An intramuscular injection of 2.4 million units will cure a person with primary, secondary or early latent syphilis. An appropriate treatment response is a fourfold decline in non-treponemal titer 6-12 months after treatment. Three doses of the benzathine penicillin G at weekly intervals is recommended for the treatment of

Table 6.5.2

Opioid-Induced Deficiencies

Hypogonadism	Adrenal Androgen Deficiency	Symptoms
■ Decreased GNRH ■ Decreased LH ■ Decreased Testosterone	■ Decreased DHEA ■ Decreased DHEAS ■ Decreased Androstenedione	■ Anemia ■ Decreased Libido ■ Decreased Muscle Mass ■ Depression ■ Erectile Dysfunction ■ Fatigue ■ Hot Flashes ■ Menstrual Irregularities ■ Osteoporosis ■ Sweating ■ Weight Gain

late latent syphilis or latent syphilis of unknown duration. The CDC's 2015 STD Treatment Guidelines provide detailed information about the diagnosis and treatment of syphilis, including special considerations for pregnant women, neurosyphilis, and HIV coinfection: https://www.cdc.gov/std/tg2015/syphilis.htm. In addition, a self-study module is available as a free online learning experience that helps clinicians learn how to manage syphilis. It is frequently updated and integrates the CDC's most recent STD Treatment Guidelines: https://www.std.uw.edu/custom/self-study/syphilis.

Tuberculosis

Tuberculosis is a disease caused by the bacterium *Mycobacterium tuberculosis (MTb*). Mycobacteria are transmitted through the air, inhaled, and usually attack the lungs, but they also can attack any part of the body, such as the kidney, gut, spine, and brain. Untreated TB disease can be fatal, and was once the leading cause of death in the U.S. Persons who inject drugs are at high risk for contracting TB and more likely to progress from latent TB infection (LTBI) to active TB disease. This higher risk of active pulmonary TB disease results from crowded living conditions, delays in diagnosis, lower treatment adherence, drug sharing practices, and a higher prevalence of HIV disease. OTP staff should be instructed to be alert to coughing patients. The patient may be provided with a mask to cover his or her mouth. Coughing patients should be interviewed promptly regarding the common symptoms of TB (current cough, fever, weight loss or night sweats). Patients who are symptomatic require prompt screening by CXR. All OTP staff and patients should be screened with symptom review and testing annually unless they have a history of prior infection. Patients and staff with a prior TB infection are screened by symptom review and chest x-ray.

There are two testing methods for the detection of *MTb* infection: tuberculin skin tests (TST) and interferon-gamma release assays. A 2-step TST algorithm reduces the likelihood that a boosted reaction to a subsequent skin test will be misinterpreted as a recent infection.

A skin test reaction, the diameter of induration, is measured 48-72 hours after PPD placement and is recorded in millimeters. The skin test result depends on the size of the induration and on the person's risk of TB infection and progression to TB disease, if infected. For persons who inject drugs, a positive skin test is 10 or more mm of induration. For persons with HIV disease, a positive test is 5 mm or more of induration. Positive skin tests among PWID range from 14-28% in the U.S. OTP staff require special training to demonstrate proficiency in the administration and interpretation of the TST, and they should be familiar with the criteria for classifying positive TST reactions: https://www.cdc.gov/tb/publications/factsheets/testing/skintestresults.htm

The second testing method for MTb infection is the interferon gamma release assay (IGRA), which measures the immune response to TB proteins in whole blood. Compared to the skin test, the IGRA may be preferable in the OTP setting for a number of reasons: (1) a second visit is not required to read the patient's test result, (2) the test does not boost responses in subsequent tests, and (3) it will not give a false-positive result for patients with a history of BCG vaccination. However, the test does require a blood draw, which may concern patients with poor venous access, but it can be drawn at the same time as the mandatory syphilis test.

Persons with a positive TB screening result should receive a chest radiograph. Sputum cultures should be collected from those with an abnormal chest radiograph or symptoms. These steps will help differentiate whether a patient should be treated for LTBI or TB disease (see Table 6.6.1). Failure to make this determination risks inadequate treatment and development of drug resistance.

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifest active TB. LTBI treatment is essential to controlling and eliminating TB disease in the U.S.

Patients with a normal chest film should receive treatment for LTBI. In HIV positive patients, this should be a 9-month course of isoniazid (INH) prophylaxis (see Table 6.6.2), which substantially reduces the risk that infection will progress to active disease. The addition of pyridoxine (vitamin B6) reduces the incidence of INH-associated peripheral neuropathy. In non-HIV positive patients, options include 6 months of isoniazid, 12 weekly doses of rifapentine and isoniazid over a 3-month period, or 4 months of rifampin—however rifampin can substantially affect methadone metabolism and should be avoided if possible. OTPs that can deliver these regimens as DOT provide an ideal opportunity for maximizing medication adherence.

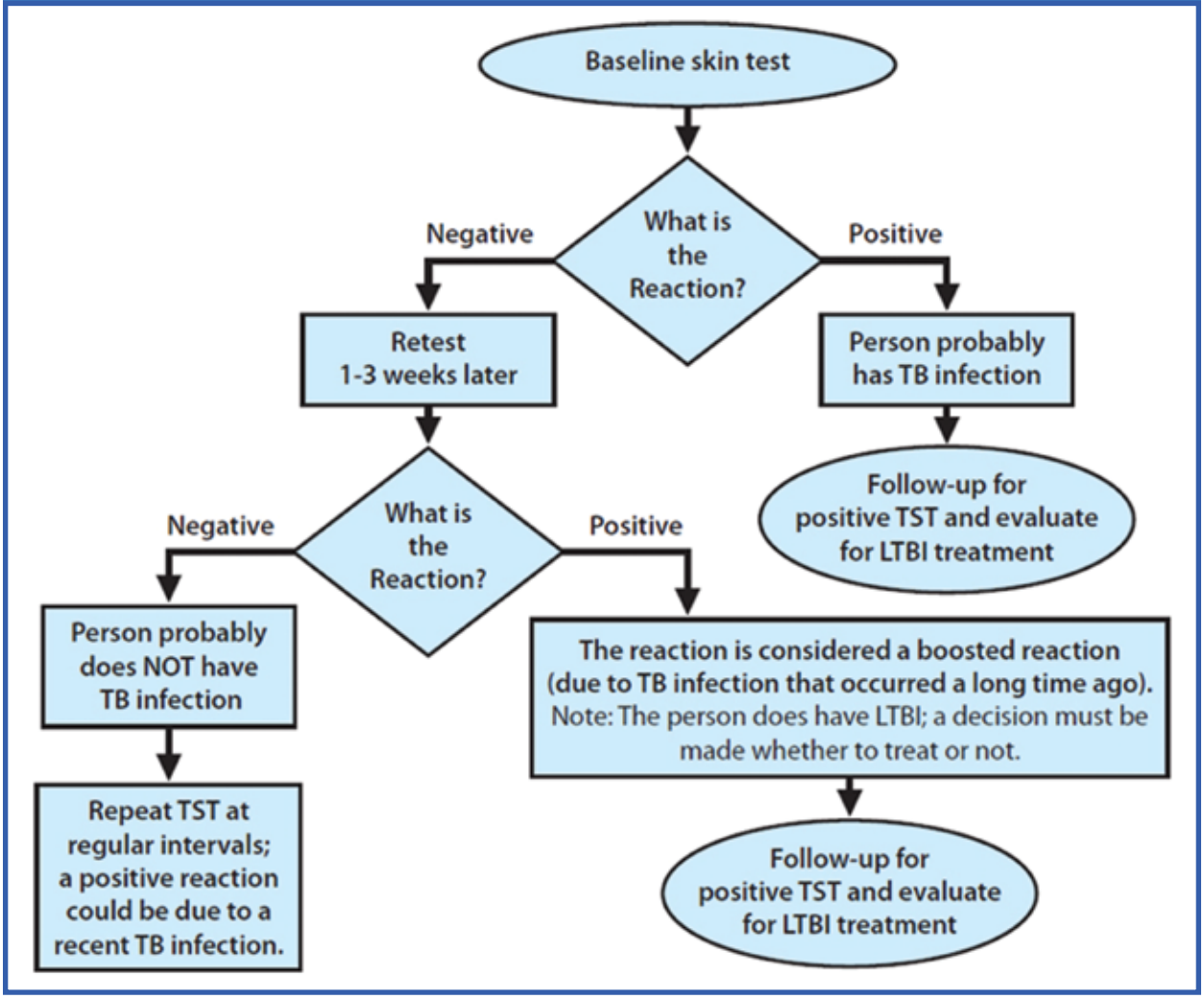
OTP providers should work closely with their local health departments to manage patients with active TB disease, which requires taking all of several medications for 6-9 months. Regimens for treating culture-positive TB disease typically include the medication rifampin, which is a potent inducer of methadone metabolism. Concomitant administration of rifampin can cause marked reductions in serum methadone levels and lead to the onset of opioid withdrawal symptoms. Therefore, rifampin should be replaced with rifabutin whenever possible for patients receiving methadone treatment. There is no drug interaction between the rifamycins and buprenorphine.

- TB resources for health care providers from the California Tuberculosis Control Branch (TBCB) can be found at: https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/TB-Resources-for-Healthcare-Providers.aspx.
- The CDC provides extensive professional resources and tools, including information on testing, treatment, and education and training for health care workers: https://www.cdc.gov/tb/topic/treatment/tbdisease.htm.
- The WHO released updated and consolidated guidelines for the management of LTBI in 2018: http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/

Hepatitis A virus (HAV)

Figure 6.6.1

Two-step TST Testing — 2



Source: https://www.cdc.gov/tb/publications/ltbi/diagnosis.htm

Hepatitis A virus (HAV) is a liver infection that occurs by fecal-oral transmission or by the consumption of contaminated food or water. Adults typically present with low appetite, fatigue, nausea, abdominal pain, pale stools, dark urine, and jaundice. While most infections are self-limited, fulminant hepatic failure with a high case fatality rate has been reported with HAV superinfection in persons with chronic HCV [226]. In the U.S., up to 48% of cases reported during HAV outbreaks are among persons who use injected and non-injected methamphetamine. In November 2016, an outbreak of HAV infections began in San Diego County and spread to Santa Cruz, Los Angeles, and Monterey counties. More than 700 cases were reported in CA with 461 persons requiring hospitalization and 21 deaths. Most cases were among persons experiencing homelessness and/or using illicit drugs in settings with limited sanitation.

HAV infection is preventable by inactivated vaccines, which have been included in the routine early childhood vaccination schedule since 2005. Following the end of the HAV outbreak in 2018, the California Department of Public Health continues to recommend providing hepatitis A vaccination for high-risk groups, including people experiencing homelessness, persons who inject drugs and use non-injectable drugs, and men who have sex with men. Post-exposure prophylaxis can be given within two weeks of exposure by administering either hepatitis A vaccine or immune globulin. In counties without an active HAV outbreak, the administration of viral hepatitis immunizations at OTPs play an important role in preventing an outbreak locally. OTPs should develop procedures to routinely identify and immediately vaccinate non-HAV-immune patients that lack a record of serologic immunity or completed immunization. Serologic screening for HAV immunity is not recommended prior to vaccination. Information and resources about the identification and prevention of hepatitis A virus infections can be found at the CDC website.

Table 6.6.1

Differentiating Between Latent TB Infection and TB Disease

LTBI	TB Disease
■ No symptoms or physical findings suggestive of TB disease. ■ TST or IGRA result usually positive. ■ Chest radiograph is typically normal. ■ If done, respiratory specimens are smear and culture negative. ■ Cannot spread TB bacteria to others. ■ Should consider treatment for LTBI to prevent TB disease.	■ Symptoms may include one or more of the following: fever, cough, chest pain, weight loss, night sweats, hemoptysis, fatigue, and decreased appetite. ■ TST or IGRA result usually positive. ■ Chest radiograph is usually abnormal. However, may be normal in persons with advanced immunosuppression or extrapulmonary disease. ■ Respiratory specimens are usually smear or culture positive. However, may be negative in persons with extrapulmonary disease or minimal or early pulmonary disease. ■ May spread TB bacteria to others. ■ Needs treatment for TB disease.

Source: https://www.cdc.gov/tb/publications/ltbi/diagnosis.htm

Table 6.6.2

Latent TB Infection Treatment Regimens

Drugs	Duration	Interval	Comments
Isoniazid	9 months	Daily	Preferred treatment for: ■ Persons living with HIV ■ Children aged 2-11 ■ Pregnant Women (with pyridoxine/vitamin B6 supplements)
		Twice weekly*	Preferred treatment for: ■ Pregnant Women (with pyridoxine/vitamin B6 supplements)
Isoniazid	6 months	Daily	
		Twice weekly*	
Isoniazid and Rifapentine	3 months	Once weekly*	Treatment for Persons 12 years or older Not recommended for persons who are: ■ Younger than 2 years old, ■ Living with HIV/AIDS taking antiretroviral treatment, ■ Presumed infected with INH or RIF-resistant M. tuberculosis, and ■ Women who are pregnant or expect to become pregnant within the 12–week regimen.
Rifampin	4 months	Daily	

*Use Directly Observed Therapy (DOT)