HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2015 July 17.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2010 December ; 55(0 1): S37–S42. doi:10.1097/QAI.0b013e3181f9c0b6.

Infectious Disease Co-Morbidities Adversely Affecting Substance Users with HIV: Hepatitis C and Tuberculosis

Gerald Friedland, MD

AIDS Program, Section of Infectious Diseases, Yale School of Medicine, New Haven, CT

Abstract

The linkage between drug use, particularly injection drug use, and HIV/AIDS, hepatitis C (HCV), and tuberculosis (TB) has been recognized since the beginning of the HIV pandemic. These co-morbid conditions affect drug users worldwide and act synergistically, with resultant adverse biologic, epidemiologic and clinical consequences.

Prevention, care, and treatment of TB and HCV can be successful, and both diseases can be cured. Special clinical challenges among drug users, however, can result in increased morbidity, mortality and decreased therapeutic success. Among these are limited disease screening, inadequate and insensitive diagnostics, difficult treatment regimens with varying toxicities, and complicated pharmacokinetic and pharmacodynamic drug interactions. These may result in delayed diagnosis, deferred treatment initiation, and low completion rates, with the potential for generation and transmission of drug resistance organisms.

Strategies to address these challenges include outreach programs to engage substance abusers in non-medical settings, such as prisons and the streets, active screening programs for HIV, HCV and TB, increased and broadened clinician expertise, knowledge and avoidance of drug interactions, attention to infection control, use of isoniazid preventive therapy, and creative strategies to insure medication adherence. All of these require structural changes directed at comprehensive prevention and treatment programs and increased collaboration and integration of needed services for substance abusers.

Keywords

TB; HIV HCV; substance abuse

Introduction

Substance abusers were at an increased risk of mortality and morbidity prior to the HIV epidemic[1]. HIV/AIDS, however, has increased rates and severity of a wide array of co-morbid conditions among drug users, including psychiatric, neurologic, hepatic, renal and pulmonary, and infectious diseases. This paper focuses on hepatitis C virus (HCV) and tuberculosis (TB), as these co-infections are responsible for most of the morbidity and

Correspondent: Gerald Friedland, AIDS Program, 135 College St, New Haven CT 06437, Tel: 203-688-6959, Fax: 203-737-4040, gerald.friedland@yale.edu.

mortality among HIV- infected drug users worldwide. HCV is a particular concern in the U.S. and in industrialized countries of Western Europe, while rates of TB in these countries have fallen sharply. In Eastern Europe and in many of the most populous countries of Asia, HCV is widespread. In these countries, injection drug use (IDU) is an increasingly significant contributor to the spread of HCV, TB, and HIV/AIDS.

Hepatitis C Virus (HCV)

Epidemiology and transmission

An estimated 130–180 million people are infected with HCV worldwide. HCV infection is the most common blood-borne infection in the U.S., with an estimated 3.2–4.1 million chronically infected persons nationwide.[2–4] Approximately 20%–30% of people living with HIV/AIDS (PLWHA) and 60–90% of IDU are co-infected with HCV in the U.S.[5, 6] High rates of HCV co-infection have been reported in China[7] and in other Asian countries, and in countries of the former Soviet Union.[8] IDU is the predominant mode of HCV transmission and accounts for more than 60% of new cases in Western countries.[2] HCV titers in blood are significantly higher than those of HIV, and as a consequence HCV is transmitted more easily than HIV through the sharing of drug using paraphernalia. Acquisition of HCV is common among new and younger IDU, with incidence rates ranging from 10 to 40 per 100 person years.[9] Although far less common, sexual transmission of HCV has recently been reported among gay men, and often in the context of non-injection drug use.

Natural History

HCV is a major cause of morbidity and mortality among IDU, and the HCV infection is adversely affected by HIV at various points in its natural history. First, spontaneous recovery from HCV infection occurs in 15%–35% of those who are mono-infected, but only 5–10% of those co-infected with HIV.[10] Second, the long term consequences of HCV infection, including cirrhosis, hepatic failure, and hepatic carcinoma are increased with HIV infection. HCV has become the principal cause of death from liver disease in the U.S.,[11] and after HIV/AIDS, the second leading cause of death among those with HIV infection.[12] HIV is associated with more rapid progression of cirrhosis and end-stage liver disease (ESLD).[13, 14] Co-infected persons have a 6-fold relative risk (RR) of ESLD and a 2-fold RR of cirrhosis compared with HCV infection alone, leading to a 15%–25% prevalence of cirrhosis within 10–15 years of infection.[15] Factors contributing to accelerated fibrosis progression include low CD4 counts, detectable HIV-1 RNA levels, use of hepatotoxic medications, and frequent alcohol use. [16] Compared to other PLWHA, IDU are more likely to present with advanced disease, poorly controlled HIV, alcohol use, and accelerated progression to ESLD. Although HIV accelerates HCV disease progression, it remains unclear if HCV accelerates the progression of HIV disease. This may result from a diminished ability to tolerate antiretroviral therapy (ART) among HIV-infected persons with chronic hepatic disease.[14] Compared to mono-infected patients, increased risk of hepatocellular carcinoma has been found among those who are co-infected with HIV and HCV.[17] The mean age for development of hepatocellular carcinoma in HCV mono-infected individuals is 69 years compared to a mean age of 42 years among persons co-infected with HIV[18].

Diagnosis and Treatment

Because the prevalence of HCV is so high among IDU, all HIV- infected and non-infected IDU should be screened for HCV using a third generation enzyme linked immunoblot assay.[2] Similarly, because persons with HCV have shared risk factors with HIV, HCV- infected patients should be tested for HIV. For patients who have HCV antibodies, testing should be done for HCV- RNA because detection of viremia connotes active HCV disease. Staging of HCV infection usually requires liver biopsy to determine the degree of HC- related fibrosis before offering treatment. Co-infected patients should be tested for antibodies to hepatitis B and A, and if found to be negative, should be advised to receive immunization.

As opposed to HIV, HCV can be cured. Current therapeutic options for successfully treating HCV, however, remain limited and challenging, particularly in those co-infected with HIV and among IDU. The standard treatment for patients with genotype 1 (the most common circulating type in the U.S.) is the combination of pegylated interferon, given weekly, and weight-based daily ribavirin, given for a total of 48 weeks.[2], [18] Sustained virologic response (SVR), defined as negative serum HCV-RNA six months after completion of therapy, is achieved in approximately 50% in mono-infected patients with genotypes 1 and 4, and in approximately 70% among patients with genotypes 2 and 3 (more commonly found in Europe and parts of Asia). For patients co-infected with HIV, SVR is approximately 41% among all patients but only 29% in those with genotype 1, including IDU. [18], [19] In substance abusers and co-infected patients, SVR rates are lower, and side effects and dropout rates are higher. Side effects include anemia from ribavirin, granulocytopenia, fatigue, depression, and other neuropsychiatric effects from interferon. In addition, use of ART for HIV co-infection has been shown to increase risks of drug-related hepatoxicity.[18]

The timing of HCV treatment is important for HIV co-infected patients. Although there is often an urgency to begin HCV treatment, many experts recommend stabilization of HIV disease with ART, despite potential toxicities, before embarking on a course of HCV treatment.[2], [18], [19] Since HIV infection accelerates the progression of HCV-related liver disease, treatment of chronic HCV infection is generally recommended for co-infected patients, including IDU. Despite this, there is limited access and uptake of HCV treatment by IDU and most remain untreated. This may be related in part to inadequate systems for surveillance of HCV in the community and clinical care setting, particularly among IDU.[17], [20] Even among those in care with known HCV infection, treatment is the exception. In a recent study, only 6% of HCV infected IDU in care received treatment. [21] Clinicians were found to be reluctant to offer treatment, citing lack of expertise, poor treatment adherence, perceptions that HCV infection will remain asymptomatic, concerns about the complexity and toxicity of treatment, and pessimism about HCV treatment tolerability and the likelihood of successful outcomes for IDU. [20] Nevertheless, there is a growing body of literature demonstrating that treatment success is possible among co-infected IDU, particularly in the context of drug treatment [22–24] and in carefully managed HCV and HIV treatment programs among incarcerated populations.[25]

Treatment for co-infected IDU carries risks that need to be balanced with potential benefits. Withholding a life saving therapy for a class, such as IDU, is unethical.[26]. Recent treatment recommendations have been developed that take into account the importance of

individualization and the need to address substance use and psychiatric co-morbidities in HCV, prior to and during treatment.[2]

New antiviral therapy for HCV is urgently needed. A pipeline of new anti-HCV drugs is now in various stages of development, including HCV-specific protease and polymerase inhibitors, some of which are in advanced- to late-stage clinical trials. These will likely help to improve the outcomes of HCV treatment in the future, although because of risks for rapid selection of resistant mutants, such therapies will likely require co-administration with currently available therapies, i.e., interferon and ribavirin. Further, most agents have been or are being studied in mono-infected patients. Little information is available regarding the therapeutic response or toxicities among co-infected persons and IDU.

Clearly, prevention of HCV is a priority in light of the limited treatment options for HCV disease among IDU, with and without HIV. The Institute of Medicine recommends that government agencies expand programs to reduce the risk of HCV infection among IDU by providing comprehensive HCV prevention programs.[17] These should include access to sterile needle and syringes and drug-preparation equipment and increased testing to detect HCV infection. In addition to supportive treatment environments and increased provider expertise, a comprehensive and holistic clinical approach is needed, one that attends to factors that contribute to progression of HCV disease and which are amenable to intervention, including antiretroviral therapy, avoidance of hepatotoxic agents (which does include some ART medications), and the avoidance of alcohol.

Tuberculosis

Epidemiology and transmission

Mycobacterium tuberculosis infection is present in an estimated one-third of the world's population, or roughly 2 billion people. In the past year, there were an estimated 8–9 million new cases of TB, leading to 2–3 million deaths.[27] TB and HIV have been tightly linked since the early years of the HIV/AIDS epidemic.[28] Worldwide, TB is second only to HIV/AIDS in causing death from a communicable disease, [29] and among those with HIV infection, TB is the most common opportunistic infection and major cause of morbidity and mortality.[30] IDU in developed countries have rates of latent TB infection (LTBI) approaching 30%, and are two to six times more likely to contract TB compared to nonusers. One third of IDUs with TB are estimated to be HIV infected.[31], [32] Patients with TB and HIV infection are five times more likely to die during anti-TB treatment compared to patients who are HIV negative.[31] TB incidence has fallen or stabilized among IDU in many industrialized countries but not in Eastern Europe and countries of the former Soviet Union.[30]

There are two major reasons why HIV- infected IDU have an increased risk of TB. First, HIV- induced immunosuppression results in high rates of LTBI reactivation among co-infected IDU. This is estimated to occur at an annual rate of 9%[33], similar to the lifelong risk in HIV negative populations. Second, TB transmission occurs in settings that are crowded and poorly ventilated, such as those that are often populated by IDU (e.g., prisons, drug treatment programs, homeless shelters, and soup kitchens).[34], [35] IDU may also be more

contagious because of advanced TB, unattended disease, and higher rates of treatment failure.[32]

Diagnosis and Treatment

Diagnosis and treatment of TB in IDU in the context of HIV infection present numerous health and medical challenges. HIV reduces the sensitivity of TB diagnostic tests, including the tuberculin skin test and interferon-gamma release assays. In late stages of HIV, pulmonary disease presents in atypical fashion and the sputum smear, the most common diagnostic tool worldwide, becomes increasingly insensitive. In addition, extra-pulmonary TB, notoriously difficult to diagnose, increases to close to 50% of cases. TB laboratory diagnostic tests are outmoded and cumbersome, and their availability is limited worldwide, which adversely affects vulnerable populations such as IDU. Even when available, current TB culture and drug-sensitivity testing can take weeks to months. Thus, TB diagnosis among IDU with and without HIV infection is often not confirmed or is delayed, leading to high rates of morbidity and mortality and ongoing transmission in congregate and public settings.[34]

When properly implemented, TB treatment can be highly successful, with cure rates of greater than 95%. The standard TB regimen worldwide includes a 2- month intensive phase of four drugs, designated as the “first line” drugs, isoniazid (INH), rifampin or rifampicin (RIF), ethambutol (EMB) and pyrazinamide (PZA). This is followed by a continuation phase of INH and RIF only daily for 4 months, administered most effectively by directly observed therapy (DOT). Reasons for lower rates of treatment success among IDU include TB program deficiencies, poor patient medication adherence, increased toxicity, and high rates of patient attrition.

Emergence of TB drug resistance is particularly notable in countries with large populations of IDU.[36] Multi-drug resistant TB (MDR-TB), defined as resistance to at least the first-line drugs isoniazid and rifampin, is increasingly becoming extensively drug resistant (XDR-TB) because of resistance to the “second line” fluoroquinolones and to injectable agents. WHO estimated in 2007 that there were more than 500,000 incident cases of MDR-TB and one million prevalent cases and 40,000 incident cases of XDR TB.[36] China, India, and the Russian Federation are countries where IDU contributes significantly to high HIV and TB rates, and together accounted for an estimated 62% of the global burden of TB drug resistance.[36] Drug resistant TB is a product of treatment failure and transmission of resistant organisms to susceptible hosts in congregate settings, such as hospitals, drug abuse treatment programs, and prisons. Hence, it would be expected that drug users would be disproportionately represented among patients with drug resistant TB; these patients are at increased risk of treatment failure and mortality when they are also HIV- infected.[37] Available drugs and regimens are less potent, more complex, more toxic, and more expensive; and they require administration for longer periods of time, such as 4 or 5 drug combinations over a period of 18–24 months. A recent report on XDR-TB in HIV-infected patients in South Africa [38] has renewed global awareness of drug-resistant TB and the threat it poses to individual patients and to public health, further challenging the success of TB, HIV/AIDS and substance abuse treatment programs.[39]

Treatment of drug susceptible and drug resistant TB among IDU, particularly in the context of HIV, can be complicated by additive toxicities, the immune reconstitution syndrome (IRIS), and drug interactions. Highly prevalent hepatic, renal, neurological, psychiatric, gastrointestinal, and hematologic co-morbidities among IDU[1] can increase the risks for drug toxicities. IRIS occurs in all populations with TB and HIV co- infection as a result of immune restoration after ART administration, which uncovers unsuspected TB or the worsening of already diagnosed TB. These complexities have resulted in concerns regarding the treatment of TB and HIV simultaneously, however, observational and demonstration studies[40], [41] and a recently completed randomized controlled trial[42] make clear that concomitant treatment of HIV and TB is feasible, safe, and life saving, and is associated with reductions in mortality of 55% among co-infected patients.

The provision of care and treatment of drug users with TB is complicated by well known and problematic pharmacokinetic (PK) and pharmacodynamic (PD) drug interactions among TB drugs, ART, and therapies for substance abuse. Drugs used for the treatment of each of these diseases share metabolic pathways (i.e., cytochrome P450, isoenzymes 3A4 and 2D6, and UGT1A1 enzymes) which can result in drug interactions that diminish the effectiveness of one, both, or all three therapies, in opiate withdrawal, or in different levels of anti-infective agents, with corresponding decreases in their therapeutic effects or increases in their side effects and toxicities.[43–48]

Rifampin, an important component of standard TB regimens, is a powerful inducer of hepatic enzymes[47], [49] and results in interactions with both substance abuse and HIV therapies. The PK and PD interaction between rifampin and methadone has been known for more than 40 years. In 1976, Kreek et al[50] showed that 70% of patients receiving methadone and being treated for TB developed symptoms and signs of opiate withdrawal, while those patients receiving non-rifampin TB regimens had no withdrawal symptoms. Methadone plasma levels were 33%–68% lower during rifampin treatment. This interaction complicates the treatment of TB among opiate-addicted patients. Opiate withdrawal is often either not suspected by clinicians or discounted. This important drug interaction can be avoided by the substitution of rifabutin for rifampin, since the former is less capable of inducing hepatic enzymes.[47] Unfortunately, rifabutin is expensive and only available in developed countries, meaning that IDU in other parts of the world are usually unable to receive one of the better treatments for opiate addiction and TB. Rifampin also reduces levels of ART, including the non-nucleoside reverse transcriptase inhibitors, efavirenz and nevirapine,[47] although the former has been found to remain effective in this context.[51] Rifampin dramatically lowers levels of all protease inhibitors, further limiting treatment options for IDU patients who are TB and HIV co-infected. Opiate substitution therapies have minimal PK and PD effects on TB or antiretroviral therapies. Methadone levels, however, are markedly reduced by efavirenz and nevirapine, which may lead to moderate to severe opiate withdrawal; methadone levels may also, but to a lesser extent, be reduced by protease inhibitors[45]. The integrase inhibitor raltegravir does not affect methadone levels. Buprenorphine, another opiate substitution therapy, has not been studied as thoroughly as methadone. Research suggests that PK interactions may occur between buprenorphine and ART, but that they are less frequent and less severe than they are with methadone.[44]

Structural and behavioral impediments can confound treatment success. Substance abuse treatment is often prerequisite for successful HIV and TB treatment, but lack of access to effective drug treatment is also common where these co-morbid conditions occur. Resultant poor adherence to therapy, decreased retention in care, and poor continuity of care are also frequent, which increases risk for TB and HIV drug resistance.

Prevention

The World Health Organization has elaborated a new strategy for control of TB in IDU and other populations.[52] It includes the "3 Is": intensive case finding using community based screening for early identification of HIV and TB, infection control to reduce transmission of TB in community and health care settings, and isoniazid preventive therapy (IPT) to reduce reactivation of LTBI.

IDU are often wary of traditional medical settings, preferring to use emergency rooms intermittently and only when sick. Stigma, fear, and multiple co-morbidities may contribute to this reluctance, resulting in delayed entry into care and treatment. Intensified TB case-finding among IDU in non-medical settings, such as prisons, homeless shelters, and drug treatment programs, may help to address this issue.[52] Screening for HCV, TB, and HIV and interventions to prevent disease and provide early treatment could have an impact on the community spread of these infections and their ensuing morbidity and mortality. For TB, airborne infection control is a well recognized way to prevent the spread of infection, yet it is poorly implemented.[34] Enhanced airborne infection control in congregate settings can reduce the likelihood of drug-susceptible and drug-resistant TB transmission to IDU. Three major areas of infection control, administrative, environmental, and personal protective measures offer practical and feasible strategies to reduce the nosocomial and community-based transmission spread of TB.[34], [35] Preventive treatment for LTBI has been promoted as a method of reducing the incidence of active TB among HIV-infected patients in whom active disease has been ruled out, but only INH has been shown in randomized controlled trials to be efficacious and safe for this purpose. However, administration is prolonged (6 months to 1 year), with a risk of hepatitis and poor adherence. The greatest benefits have been achieved among adults who were tuberculin skin test-positive, with a 62% to 70% reduction in the development of active TB as well as a 20% to 25% reduction in mortality. Despite this recommendation, worldwide estimates suggest that only 0.08% of patients with HIV who have been screened have received isoniazid preventive therapy.[52] Demonstrated success with drug users has been noted but it requires ongoing substance abuse therapy to achieve completion. Drug treatment programs have been shown to be effective as sites for delivering IPT as a preventive measure. Use and adherence on ART has also been shown to reduce the risk of acquisition of TB in areas of high MTB prevalence.

Conclusion

Co-morbidities contribute to the substantial global burden of disease experienced by drug users with HIV, and HCV and TB are the most important of these. Effective strategies for screening, prevention, and treatment exist, and both HCV and TB can be prevented and cured, but there are often social, economic, and political barriers that limit the accessibility

of these services to drug users, thereby adversely impacting public health. A comprehensive approach that includes drug abuse treatment and HIV testing, treatment, and care holds the greatest promise for screening, treating, and curing drug users with HCV and TB infections because this would ultimately reduce the spread of HIV, HCV, and TB to the population.[53], [54]

Acknowledgments

This work was supported by grant R01DA025932-01, from the National Institute on Drug Abuse, National institutes of Health. The author is grateful for the assistance of Drs Monica Mercon and Robert Douglas Bruce in preparation of this manuscript.

References

1. Bruce, R.; Altice, F.; Friedland, G. HIV Disease Among Substance Misusers: Treatment Issues. San Diego, CA: Elsevier Inc; 2007.
2. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. Apr; 2009 49(4):1335–1374. [PubMed: 19330875]
3. Centers for Disease Control and Prevention. Viral hepatitis: statistics and surveillance. Accessed January 2010http://www.cdc.gov/hepatitis/statistics.htm
4. Daniels D, Grytdal S, Wasley A. Surveillance for acute viral hepatitis - United States, 2007. MMWR Surveill Summ. May 22; 2009 58(3):1–27. [PubMed: 19478727]
5. Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol. May 7; 2007 13(17): 2436–2441. [PubMed: 17552026]
6. Amon JJ, Garfein RS, Ahdieh-Grant L, et al. Prevalence of hepatitis C virus infection among injection drug users in the United States, 1994–2004. Clin Infect Dis. Jun 15; 2008 46(12):1852–1858. [PubMed: 18462109]
7. Zhang C, Yang R, Xia X, et al. High prevalence of HIV-1 and hepatitis C virus coinfection among injection drug users in the southeastern region of Yunnan, China. J Acquir Immune Defic Syndr. Feb 1; 2002 29(2):191–196. [PubMed: 11832691]
8. Naoumov NV. Hepatitis C virus infection in Eastern Europe. J Hepatol. 1999; 31(Suppl 1):84–87. [PubMed: 10622566]
9. Hagan H, Campbell J, Thiede H, et al. Self-reported hepatitis C virus antibody status and risk behavior in young injectors. Public Health Rep. 2006; 121:710–719. [PubMed: 17278406]
10. Strader DB. Coinfection with HIV and hepatitis C virus in injection drug users and minority populations. Clin Infect Dis. Jul 1; 2005 41(Suppl 1):S7–13. [PubMed: 16265618]
11. Institute of Medicine. Hepatites and Liver Cancer: A national Strategy for Prevention and Control of Hepaptites B and C. Washington, DC: National Academies Press; 2010.
12. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med. Aug 14–28; 2006 166(15):1632–1641. [PubMed: 16908797]
13. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus co infected patients. The Multivirc Group. Hepatology. Oct; 1999 30(4):1054–1058. [PubMed: 10498659]
14. Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. Jama. Jul 10; 2002 288(2):199–206. [PubMed: 12095384]
15. Sulkowski MS. Hepatitis C virus infection in HIV-infected patients. Curr HIV/AIDS Rep. Sep; 2004 1(3):128–135. [PubMed: 16091233]
16. Schiavini M, Angeli E, Mainini A, et al. Risk factors for fibrosis progression in HIV/HCV co infected patients from a retrospective analysis of liver biopsies in 1985–2002. HIV Med. Jul; 2006 7(5):331–337. [PubMed: 16945079]
17. National Academies Press. Institute of Medicine, Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C. Washington, DC: 2010.

18. Sulkowski MS, Benhamou Y. Therapeutic issues in HIV/HCV-co infected patients. J Viral Hepat. Jun; 2007 14(6):371–386. [PubMed: 17501757]
19. Soriano V, Puoti M, Sulkowski M, et al. Care of patients co infected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. Aids. May 31; 2007 21(9):1073–1089. [PubMed: 17502718]
20. Scott JD, Wald A, Kitahata M, et al. Hepatitis C virus is infrequently evaluated and treated in an urban HIV clinic population. AIDS Patient Care STDS. Nov; 2009 23(11):925–929. [PubMed: 19827950]
21. Mehta SH, Genberg BL, Astemborski J, et al. Limited uptake of hepatitis C treatment among injection drug users. J Community Health. Jun; 2008 33(3):126–133. [PubMed: 18165889]
22. Litwin AH, Harris KA Jr, Nahvi S, et al. Successful treatment of chronic hepatitis C with pegylated interferon in combination with ribavirin in a methadone maintenance treatment program. J Subst Abuse Treat. Jul; 2009 37(1):32–40. [PubMed: 19038524]
23. Palepu A, Tyndall MW, Joy R, et al. Antiretroviral adherence and HIV treatment outcomes among HIV/HCV co-infected injection drug users: the role of methadone maintenance therapy. Drug Alcohol Depend. Sep 15; 2006 84(2):188–194. [PubMed: 16542797]
24. Waizmann M, Ackermann G. High rates of sustained virological response in hepatitis C virus-infected injection drug users receiving directly observed therapy with peginterferon alpha-2a (40KD) (PEGASYS) and once-daily ribavirin. J Subst Abuse Treat. Mar 31.
25. Maru DS, Bruce RD, Basu S, Altice FL. Clinical outcomes of hepatitis C treatment in a prison setting: feasibility and effectiveness for challenging treatment populations. Clin Infect Dis. Oct 1; 2008 47(7):952–961. [PubMed: 18715156]
26. Edlin BR, Seal KH, Lorvick J, et al. Is it justifiable to withhold treatment for hepatitis C from illicit-drug users? N Engl J Med. Jul 19; 2001 345(3):211–215. [PubMed: 11463019]
27. World Health Organization. Global tuberculosis control - surveillance, planning, financing 2009. Geneva: 2009.
28. Friedland G, Churchyard GJ, Nardell E. Tuberculosis and HIV coinfection: current state of knowledge and research priorities. J Infect Dis. Aug 15; 2007 196(Suppl 1):S1–3. [PubMed: 17624818]
29. World Health Organization. World Health Report 2004 – Changing History. Geneva, Switzerland: WHO; 2004. Deaths by cause, sex and mortality stratum in WHO regions, estimates for 2002.
30. World Health Organization. Global tuberculosis control - surveillance, planning, financing 2008. Geneva: 2008.
31. CDC. Reported HIV Status of Tuberculosis Patients—United States, 1993–2005. MMWR. 2007; 56:1103–1106. [PubMed: 17962801]
32. Oeltmann JE, Kammerer JS, Pevzner ES, Moonan PK. Tuberculosis and substance abuse in the United States, 1997–2006. Arch Intern Med. Jan 26; 2009 169(2):189–197. [PubMed: 19171816]
33. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med. Mar 2; 1989 320(9):545–550. [PubMed: 2915665]
34. Shenoi SV, Escombe AR, Friedland G. Transmission of Drug-Susceptible and Drug-Resistant Tuberculosis and the Critical Importance of Airborne Infection Control in the Era of HIV Infection and Highly Active Antiretroviral Therapy Rollouts. Clin Infect Dis. May 15; 2010 50(S3):S231–S237. [PubMed: 20397953]
35. World Health Organization. WHO Policy on TB Infection Control in Health-Care Facilities, Congregate Settings and Households. 2009. (WHO/HTM/TB/2009.419.)
36. World Health Organization. Anti-Tuberculosis Drug Resistance in the World: Fourth Global Report. 2008.
37. Gandhi NR, Shah NS, Andrews JR, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. Am J Respir Crit Care Med. Jan 1; 2010 181(1):80–86. [PubMed: 19833824]
38. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. Nov 4; 2006 368(9547):1575–1580. [PubMed: 17084757]

39. Friedland G. Tuberculosis, Drug Resistance, and HIV/AIDS: A Triple Threat. Curr Infect Dis Rep. May; 2007 9(3):252–261. [PubMed: 17430708]
40. Gandhi NR, Moll AP, Lalloo U, et al. Successful integration of tuberculosis and HIV treatment in rural South Africa: the Sizonq'oba study. J Acquir Immune Defic Syndr. Jan 1; 2009 50(1):37–43. [PubMed: 19295333]
41. Jack C, Lalloo U, Karim QA, et al. A pilot study of once-daily antiretroviral therapy integrated with tuberculosis directly observed therapy in a resource-limited setting. J Acquir Immune Defic Syndr. Aug 1; 2004 36(4):929–934. [PubMed: 15220699]
42. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med. Feb 25; 2010 362(8):697–706. [PubMed: 20181971]
43. Bruce RD, Altice FL, Gourevitch MN, Friedland GH. Pharmacokinetic drug interactions between opioid agonist therapy and antiretroviral medications: implications and management for clinical practice. J Acquir Immune Defic Syndr. Apr 15; 2006 41(5):563–572. [PubMed: 16652030]
44. Bruce RD, McCance-Katz E, Kharasch ED, Moody DE, Morse GD. Pharmacokinetic interactions between buprenorphine and antiretroviral medications. Clin Infect Dis. Dec 15; 2006 43(Suppl 4):S216–223. [PubMed: 17109308]
45. Bruce RD, Altice F, Friedland G. Pharmacokinetics drug interections between drugs of abuse and antiretroviral medications: inplications and management for clinical practice. Expert Review of Clinical Pharmacology. 2008; 1:115–127. [PubMed: 24410515]
46. Injection Drug Users. NIH, DHHS; Washington, DC: 2009. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 2009. AIDS info Web site. http://aidsinfo.nih.gov
47. CDC. Centers for Deasease Control and Prevention. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. 2008www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm
48. McCance-Katz EF, Mandell TW. Drug interactions of clinical importance with methadone and buprenorphine. Am J Addict. Jan 1; 2010 19(1):2–3. [PubMed: 20132116]
49. CDC. Centers of Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. MMWR - Morbidity & Mortality Weekly Report 2000. 2000; 49:185–189. www.cdc.gov/nchstp/tb/.
50. Kreek MJ, Garfield JW, Gutjahr CL, Giusti LM. Rifampin-induced methadone withdrawal. N Engl J Med. May 13; 1976 294(20):1104–1106. [PubMed: 1256526]
51. Friedland G, Khoo S, Jack C, Lalloo U. Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. J Antimicrob Chemother. Dec; 2006 58(6):1299–1302. [PubMed: 17032686]
52. WHO Stop TB Strategy. http://www.stopTB.org
53. World Health Organization. Department ST. Policy Guidelines for Collaborative TB and HIV Services for Injecting and Other Drug Users: An Integrated Approach. Geneva: 2008.
54. Sylla L, Bruce RD, Kamarulzaman A, Altice FL. Integration and co-location of HIV/AIDS, tuberculosis and drug treatment services. Int J Drug Policy. Aug; 2007 18(4):306–312. [PubMed: 17689379]