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BEHAVIORAL BIO-MEDICAL INTERFACE (JL BROWN AND RJ DICLEMENTE, SECTION EDITORS)

Medications for Treatment of Opioid Use Disorder among Persons Living with HIV

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Abstract

Purpose of Review Recent HIV outbreaks have occurred as a result of the current US opioid epidemic. Providing medications for opioid use disorder (MOUD) with methadone, buprenorphine, and extended-release naltrexone is essential to achieving optimal HIV treatment outcomes including viral suppression and retention in treatment. This review describes the pharmacology of MOUD with specific attention to interactions with antiretroviral therapy, and to the effect of MOUD on HIV treatment outcomes.

Recent Findings Methadone and buprenorphine both improve HIV viral suppression, adherence to antiretroviral therapy, and overall mortality for persons with opioid use disorder (OUD). Extended-release naltrexone has been most extensively studied in persons with HIV leaving incarcerated settings, and improves HIV viral suppression in that context.

Summary Strategies that integrate MOUD and HIV treatment are crucial to optimize viral suppression. The differing pharmacokinetic and delivery characteristics of these MOUD offer diverse options. Given the chronic and relapsing nature of both HIV and OUD, long-term approaches are required.

Keywords Extended-release naltrexone · Methadone · Buprenorphine · HIV · Opioid use disorders · MAT · Medication for opioid use disorder · Opioid addiction

Introduction

The opioid epidemic is a national public health emergency. According to the most recent estimates, over 2.1 million US persons,12 years of age and older, have an opioid use disorder (OUD) [1], and more than 49,000 people died from a drug overdose attributed to opioids in 2017—a 4.1-fold increase since 2002 [2, 3]. Persons with OUD are at risk for HIV and viral hepatitis due to injection drug use as well as sexual risk behaviors. Several recent HIV outbreaks are the result of injection opioid use and have occurred in young, white, rural populations, reflecting the demographic most affected by the ongoing epidemic [4, 5]. Accordingly, a recent analysis predicted the US counties at highest risk of HIV and hepatitis C transmission due to the opioid epidemic are in rural Appalachia [6••]. A widely reported HIV outbreak in Scott County, Indiana, for example, was attributed to oxymorphone injection in a small, tightly networked rural community without access to syringe exchange services, nor robust OUD medication treatment [4, 7]. In addition, persons who use drugs and have HIV are less likely to receive and adhere to HIV care [8, 9].

Medications for opioid use disorder treatment (MOUD) are the most effective evidence-based treatment to prevent opioid craving, relapse, and overdose. There are three Food and Drug Administration (FDA)-approved medications for the treatment of OUD in the USA: methadone (a full mu opioid receptor agonist), buprenorphine (a partial mu opioid receptor agonist), and extended-release naltrexone (XR-NTX) (an opioid mu

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receptor antagonist). The differing pharmacokinetic and delivery characteristics of these MOUD offer diverse options for integrating MOUD for people living with OUD and HIV.

Providing MOUD with the opioid agonists methadone or buprenorphine can improve engagement and retention in care for persons living with HIV (PLH), receipt of antiretroviral therapy (ART), ART adherence, and HIV viral suppression [10•, 11, 12•]. MOUD also decreases illicit opioid use, HIV transmission [13], and mortality [14]. A meta-analysis of 32 studies, including in resource-limited settings, demonstrated that opioid agonist MOUD is associated with a 54% increase in the odds of antiretroviral coverage (odds ratio [OR] 1.54; 95% CI 1.17–2.03), with a 23% decrease in the odds of attrition (OR 0.77; 95% CI 0.63–0.95), and with a 45% increase in the odds of HIV viral suppression (OR 1.45; 95% CI 1.21–1.73) [10•]. Treating OUD in persons who inject drugs (PWID) decreases risky injection and sexual HIV transmission risk behaviors as well as opioid use [15, 16]. In a meta-analysis of 12 studies that examined the association between OAT and HIV incidence, opioid agonist MOUD reduced new HIV infections by 54% (rate ratio 0.45; 95% CI 0.32, 0.67) [13].

Methadone

Methadone is a synthetic full-opioid agonist that has been a mainstay of treatment for OUD since the early 1960s in the form of methadone maintenance treatment (MMT). It is a long-acting, oral daily medication administered in federally licensed clinics. At low doses, it can alleviate pain and symptoms of opioid withdrawal, while the higher doses used in MMT block the effects of other opioids (e.g., heroin) and decrease opioid cravings. Copious evidence supports it as a safe, effective medication to decrease morbidity and mortality in persons with OUD [14, 17]. Achieving target therapeutic dosages, however, must occur slowly with careful monitoring as methadone prolongs the QTc interval, increasing risk for fatal ventricular arrhythmias, and has multiple drug-drug interactions due to its complex metabolism [18]. Methadone has high oral bioavailability, and undergoes *N*-demethylation via multiple CYP enzymes [19]. Methadone metabolism, therefore, may be altered by inhibitors and inducers of these multiple CYP enzymes. There are several clinically significant interactions between methadone and several ART medications. Patients on nevirapine, efavirenz, and ritonavir, as well as lopinavir/ritonavir and darunavir/ritonavir combinations may require higher methadone doses. There may also be significant effects on the metabolism of antiretrovirals by methadone, zidovudine in particular, potentially requiring dose-adjustment [19, 20]. Outside of ART, there are other commonly prescribed medications that interact with methadone. Patients receiving rifampin, carbamazepine, and phenytoin may require increased doses of methadone, and those receiving fluconazole, voriconazole, ciprofloxacin, fluoxetine, and quetiapine may require decreased doses of methadone due to QTc prolongation [21].

The provision of MMT is regulated at both the federal and state levels, which contributes to the gap in access. Federal regulations require methadone to be provided only by licensed opioid treatment programs (OTP), which typically do not provide medical treatment for other conditions (e.g., primary care). Over four decades of evidence demonstrate that MMT is both efficacious in clinical trials and effective in the community in promoting and sustaining abstinence and reducing risks associated with OUD [22, 23]. In a cohort of HIV-infected PWID in Vancouver, British Columbia, MMT was associated with greater ART adherence (AOR 1.52; 95% CI 1.16–2.00), HIV-1 RNA suppression (AOR 1.34; 95% CI 1.00–1.79), and CD4 cell count rise (AOR 1.58; 95% CI 1.26–1.99) over time [24].

Buprenorphine

In October 2002, buprenorphine, a semi-synthetic partial opioid mu receptor agonist and partial kappa receptor antagonist became available to treat OUD in the community by primary care physicians. The Drug Addiction Treatment Act of 2000 (DATA 2000) allowed qualified physicians to administer office-based treatment for OUD with FDA-approved medications. Buprenorphine is the only medication that falls into this category. It is available as a monoproduct and in combination with naloxone in tablet and film forms for sublingual administration, and more recently in a long-acting monthly injection [25] and a 6-month implant [26], with additional promising formulations in development [27]. The addition of naloxone to the sublingual products is intended as an abuse-deterrent because the naloxone is only bioavailable if the pill or film is injected, and then would cause precipitated withdrawal in the opioid-dependent individual. If the buprenorphine/naloxone (BUP/NX) tablet or film is taken sublingually, the naloxone is not meaningfully bioavailable. Buprenorphine binds tightly to the mu opioid receptor, which provides for clinical blockade of the effects of other opioids. As a partial-agonist, it has a ceiling of stimulation of the μ-opioid receptor, resulting in less respiratory suppression compared to full agonists.

In comparison to methadone, buprenorphine has few drug-drug interactions with ART or other medications, low overdose risk, and no requirement for daily observed dosing and avoids the administrative requirements of MMT, making it highly feasible for use in busy HIV clinics [28–30]. On a population level, it is less effective than methadone in retaining patients in treatment [31], but, like methadone, is associated with decreased overdose and all-cause mortality [14]. In a pilot trial ($n = 93$) of clinic-based buprenorphine vs. referral for methadone maintenance, HIV-infected participants randomized to clinic-based buprenorphine treatment were more likely to engage in treatment for opioid dependence compared to those referred for

methadone (74% vs. 41%, $p < .001$); however, ART receipt, HIV RNA, and CD4 counts did not differ at 12 months [32]. Two US pilot studies of BUP/NX suggest it is safe and feasible and reduces opioid use in HIV care, but were limited by lack of a comparison group [28, 29], and small sample size [32]. In both studies, the majority of patients were already on ART with high baseline rates of viral suppression, limiting the capacity to assess the effect of BUP/NX on HIV outcomes. In the Buprenorphine HIV Evaluation and Support Collaborative (BHIVES), HIV-infected individuals with opioid dependence who received clinic-based buprenorphine/naloxone (BUP/NX) from an HIV clinic provider decreased opioid use [29], experienced higher quality of HIV care [30], and reported better quality of life [33]. A majority (60%) of BHIVES participants were already on ART at baseline. Participants initiating clinic-based BUP/NX ($N = 295$) were significantly more likely to initiate or remain on ART and improve CD4 counts over time compared with baseline. Retention on BUP/NX for three or more quarters was associated with increased likelihood of initiating ART ($\beta = 1.34$ [95% CI 1.18, 1.53]) and achieving viral suppression ($\beta = 1.25$ [95% CI 1.10, 1.42]) among the 64 of 119 (54%) participants not on ART at baseline compared with the 55 participants not retained on buprenorphine [28].

In addition, a non-randomized prospective trial of 98 PLH with OUD released from prison were initiated on BUP/NX at time of release to evaluate opioid relapse as well as to evaluate the ability to maintain viral suppression at 6 months post-release to the community. This study notably was conducted soon after the FDA approval of buprenorphine in the community and the subjects had been thus unfamiliar with buprenorphine. The results showed that there was high satisfaction with BUP/NX and reductions in craving and reductions in opioid use by urine toxicology [11]. Multivariate regression analyses revealed that retention in buprenorphine treatment had an AOR of 5.37 (95% CI 1.14–25.1) of predicting viral suppression at < 50 copies/ML at 6 months [34].

Naltrexone

Naltrexone is a μ-opioid receptor antagonist that blocks the action of full- or partial-agonist opioids and removes the rewarding effects of using opioids. Naltrexone is available in an oral formulation and an extended-release formulation that was FDA-approved in the USA for opioid dependence in 2011. Data on the effect of naltrexone on opioid cravings are mixed [35, 36]. A 2011 Cochrane review of 13 studies [37] showed that oral naltrexone did not perform better than either placebo or other pharmacological treatments. Therefore, oral naltrexone should generally be reserved for the most highly motivated patients [37] and/or where monitoring adherence is part of the treatment (e.g., impaired professionals). The extended release formulation is more effective than the oral, and has recently been compared to buprenorphine in two large studies that suggest they are comparable for individuals who have previously undergone detoxification and are able to initiate XR-NTX [38, 39]. Nevertheless, both formulations of naltrexone have low patient and provider uptake.

Daily oral naltrexone has been used to treat opioid and alcohol use disorders in HIV-infected persons. Tetrault et al. assessed changes in liver enzymes and HIV biomarkers in 114 HIV-infected US veterans 365 days before, during, and 365 days after treatment with oral naltrexone [40]. Comorbidities common among the participating veterans were opioid dependence (32%), alcohol dependence (89%), and hepatitis C (53%). About half (52%) received antiretroviral therapy during naltrexone treatment. Participants were prescribed naltrexone for a median 49 days (interquartile range 30–83 days). Mean AST and ALT levels decreased during and after naltrexone treatment. Two of 114 participants (1.8%) experienced mild liver enzyme elevations during naltrexone treatment, less than five times the upper limit of normal, which resolved upon treatment discontinuation. Mean HIV RNA levels decreased after naltrexone treatment and mean CD4 count remained stable throughout. This study suggests the risk of hepatotoxicity is minimal in HIV-infected participants treated with naltrexone, and that there are no adverse immunologic or virologic effects of treatment. The safety of extended-released naltrexone (XR-NTX) is further demonstrated in PLH randomized to XR-NTX following release from prison, who experienced no change in hepatic enzymes compared to those receiving placebo in two double-blind, placebo-controlled randomized trials in PLH with alcohol use disorders and those with opioid use disorders [41], nor in the completed trials themselves [12, 42, 43]. HIV/HCV co-infection has no effect on XR-NTX hepatic safety [44].

XR-NTX has been shown to be feasible and acceptable for HIV clinic-based treatment. The NIDA Clinical Trials Network (CTN)-0055 CHOICES pilot study randomized 51 participants with HIV and opioid and/or alcohol use disorder (16 with OUD, 27 with AUD, 8 with both) to receive XR-NTX or treatment as usual (TAU) [45]. Two-thirds (68%) of participants assigned to XR-NTX initiated treatment, and 88% of these were retained on XR-NTX at 16 weeks. In comparison, 96% of TAU participants initiated treatment, but only 50% were retained on medication at 16 weeks. Mean days of opioid use in past 30 days decreased from 17.3 to 4.1 for TAU and from 20.3 to 7.7 for XR-NTX. Mean heavy drinking days decreased from 15.6 to 5.7 for TAU and 12.5 to 2.8 for XR-NTX. Among those with OUD, HIV suppression improved from 67 to 80% for XR-NTX and 58 to 75% for TAU. XR-NTX was well-tolerated, with no precipitated withdrawals and one serious injection site reaction. The currently enrolling CTN-0067 CHOICES Scale-up study will assess the effect of XR-NTX versus TAU for OUD on HIV outcomes [46].

Two recently completed double-blind randomized controlled trials among PLH being released from prison and jail in the USA with AUD and OUD, respectively, found that XR-NTX

improved or maintained viral suppression at < 50 copies/mL 6 months after release [12, 42]. The first study among those with HIV and AUD had 100 participants randomized in a 2:1 fashion to receive XR-NTX or matched placebo injection starting 1 week prior to release from an incarcerated setting then five subsequent injections in the community. Those who received XR-NTX were more likely to maintain or improve to viral suppression at 6 months (31 to 56.7%, $p = 0.001$) as compared to those who received placebo (42 to 30.3%, $p = 0.292$). The 6-month between-group analysis also demonstrated that those who received XR-NTX had a greater proportion with viral suppression (56.7%) as compared to the placebo group (30.3%, $p = 0.015$), and receipt of XR-NTX was associated with viral suppression at 6 months in multivariate regression analysis (AOR 4.54 (95% CI, 1.43–14.43, $p = 0.009$) [12•]. The other double-blind, placebo-controlled trial of XR-NTX among PLH with OUD released from prison and jail had 98 participants also randomized in 2:1 fashion (XR-NTX: placebo) with the same design as the previously mentioned study. This study also found that those who received XR-NTX were more likely to have maintained or achieved viral suppression from baseline to 6 months (37.9 to 60.6%, $p = 0.002$) as compared to the placebo group (55.6 to 40.7%, $p = 0.294$), and multivariate regression analysis found the only predictor of viral suppression at 6 months was receiving XR-NTX (OR 2.77, 1.013–7.562, $p = 0.047$) [42].

Naltrexone is metabolized through both hepatic glucuronidation and minor extra-hepatic metabolism. When taken orally, it undergoes extensive first-pass metabolism, with reduction of naltrexone to the active metabolite 6-beta-naltrexol by dihydrodiol dehydrogenase. 6-Beta-naltrexol levels are much lower with injectable extended-release naltrexone [47–49]. Elimination of conjugated naltrexone and 6-beta-naltrexol is through renal excretion. Naltrexone has no effect on Cytochrome P450 metabolism. It is thus unlikely to have clinically significant drug-drug interactions with antiretroviral medications. There are theoretical interactions possible between naltrexone and antiretrovirals that undergo glucuronidation, such as raltegravir (a substrate of UDP-glucuronosyltransferase [UGT] 1A1) and zidovudine (a substrate of UGT 2B7); however, there is no evidence to change ART dosage or medications. A pharmacokinetic study of oral zidovudine administered to 15 participants taking oral naltrexone revealed no change in area under the curve (AUC) for zidovudine compared to controls [50].

Conclusions/Recommendations

Strategies that integrate OUD and HIV are crucial to optimize HIV viral suppression. Given the chronic and relapsing nature of both HIV and OUD, long-term approaches are required. The International Association of Providers of AIDS Care guidelines recommend scale-up of evidence-based treatments for substance use disorders for optimizing the HIV care continuum [51]. The HIV Cascade of Care is an effective organizing framework to define quality outcome measures for agencies and healthcare systems to scale-up and target interventions to improve HIV care [52]. An analogous OUD Treatment Cascade has been proposed to help guide the US response to the opioid crisis, which includes five stages: diagnosis of OUD, linkage to care, medication initiation, retention in treatment for at least 6 months, and continuous remission from illicit opioid use among those retained [53, 54]. Applying the OUD Treatment Cascade within the HIV Cascade of Care to optimize HIV and OUD treatment outcomes, clinics and systems can integrate standard, ongoing screening protocols for OUD and other substance use disorders (e.g., NIDA Quick Screen, NIDA Modified-ASSIST) [55], provide linkage to care and medication initiation via integrated primary care models as described in this review and elsewhere [56] as well as through licensed opioid treatment programs, and include retention in OUD treatment as part of an ongoing clinical quality management program. Areas of opportunity for further research include the role of extended-release formulations of buprenorphine in the care of persons with HIV and OUD, as well as consideration of novel care models and payment structures that increase the number of PLH able to access MOUD.

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Compliance with Ethical Standards

Conflict of Interest Dr. Korthuis serves as principal investigator for NIH-funded clinical trials that receive donated study medication from Alkermes (extended-release naltrexone) and Inidivior (buprenorphine/naloxone). Dr. Fanucchi has nothing to disclose.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Center for Behavioral Health Statistics and Quality. Results from the 2016 National Survey on Drug Use and Health: Detailed Tables. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2017.
2. Centers for Disease Control and Prevention. Increases in Drug and Opioid Overdose Deaths - United States, 2000-2014. Morb Mortal Wkly Rep. 2016;64(50):1378–82.

3. Centers for Disease Control and Prevention. Provisional Drug Overdose Death Counts, in Vital Statistics Rapid Release, N.C.f.H. Statistics, Editor. 2018.
4. Strathdee SA, Beyrer C. Threading the needle–how to stop the HIV outbreak in rural Indiana. N Engl J Med. 2015;373(5):397–9.
5. Schumaker E. Opioids have sparked an HIV outbreak in Massachusetts, in Huffington Post. 2018.
6.•• Van Handel MM, et al. County-level vulnerability assessment for rapid dissemination of HIV or HCV infections among persons who inject drugs, United States. J Acquir Immune Defic Syndr. 2016;73(3):323–31. **This study is an evaluation of the US counties at highest risk of an HIV outbreak associated with injection drug use**.
7. Conrad C, Bradley HM, Broz D, Buddha S, Chapman EL, Galang RR, et al. Community outbreak of HIV infection linked to injection drug use of oxymorphone–Indiana, 2015. MMWR Morb Mortal Wkly Rep. 2015;64(16):443–4.
8. Azar P, Wood E, Nguyen P, Luma M, Montaner J, Kerr T, et al. Drug use patterns associated with risk of non-adherence to antiretroviral therapy among HIV-positive illicit drug users in a Canadian setting: a longitudinal analysis. BMC Infect Dis. 2015;15:193.
9. Zhang Y, Wilson TE, Adedimeji A, Merenstein D, Milam J, Cohen J, et al. The impact of substance use on adherence to antiretroviral therapy among HIV-infected women in the United States. AIDS Behav. 2018;22(3):896–908.
10.• Low AJ, et al. Impact of opioid substitution therapy on antiretroviral therapy outcomes: a systematic review and meta-analysis. Clin Infect Dis. 2016;63(8):1094–104. **This study is a review and meta-analysis of the impact of treatment with methadone and buprenorphine on HIV treatment outcomes**.
11. Springer SA, Chen S, Altice FL. Improved HIV and substance abuse treatment outcomes for released HIV-infected prisoners: the impact of buprenorphine treatment. J Urban Health. 2010;87(4):592–602.
12.• Springer SA, et al. Extended-release naltrexone improves viral suppression among incarcerated persons living with HIV with opioid use disorders transitioning to the community: results of a double-blind, placebo-controlled randomized trial. J Acquir Immune Defic Syndr. 2018;78(1):43–53. **This study demonstrates improved viral suppression with extended-release naltrexone compared to placebo in persons living with HIV leaving incarceration**.
13. MacArthur GJ, Minozzi S, Martin N, Vickerman P, Deren S, Bruneau J, et al. Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. BMJ. 2012;345:e5945.
14. Sordo L, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ. 2017;357:j1550.
15. Metzger DS, Woody GE, McLellan A, O'Brien CP, Druley P, Navaline H, et al. Human immunodeficiency virus seroconversion among intravenous drug users in- and out-of-treatment: an 18-month prospective follow-up. J Acquir Immune Defic Syndr. 1993;6(9):1049–56.
16. Sullivan LE, Moore BA, Chawarski MC, Pantalon MV, Barry D, O'Connor PG, et al. Buprenorphine/naloxone treatment in primary care is associated with decreased human immunodeficiency virus risk behaviors. J Subst Abus Treat. 2008;35(1):87–92.
17. Mattick RP, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2008;2:CD002207.
18. Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. Arch Intern Med. 2007;167(22):2469–75.
19. Volpe DA, et al. Methadone metabolism and drug-drug interactions: in vitro and in vivo literature review. J Pharm Sci. 2018.
20. McCance-Katz EF. Treatment of opioid dependence and coinfection with HIV and hepatitis C virus in opioid-dependent patients: the importance of drug interactions between opioids and antiretroviral agents. Clin Infect Dis. 2005;41(Suppl 1):S89–95.
21. McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. Am J Addict. 2010;19(1):4–16.
22. Mathers BM, Degenhardt L, Phillips B, Wiessing L, Hickman M, Strathdee SA, et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. Lancet. 2008;372(9651):1733–45.
23. Kreek MJ, Borg L, Ducat E, Ray B. Pharmacotherapy in the treatment of addiction: methadone. J Addict Dis. 2010;29(2):200–16.
24. Palepu A, Tyndall MW, Joy R, Kerr T, Wood E, Press N, 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. 2006;84(2):188–94.
25. Once-monthly subcutaneous buprenorphine (Sublocade) for opioid use disorder. Med Lett Drugs Ther. 2018;60(1541):35–37.
26. Rosenthal RN, Lofwall MR, Kim S, Chen M, Beebe KL, Vocci FJ, et al. Effect of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine: a randomized clinical trial. JAMA. 2016;316(3):282–90.
27. Lofwall MR, Walsh SL, Nunes EV, Bailey GL, Sigmon SC, Kampman KM, et al. Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder: a randomized clinical trial. JAMA Intern Med. 2018;178(6):764–73.
28. Altice FL, Bruce RD, Lucas GM, Lum PJ, Korthuis PT, Flanigan TP, et al. HIV treatment outcomes among HIV-infected, opioid-dependent patients receiving buprenorphine/naloxone treatment within HIV clinical care settings: results from a multisite study. J Acquir Immune Defic Syndr. 2011;56(Suppl 1):S22–32.
29. Fiellin DA, Weiss L, Botsko M, Egan JE, Altice FL, Bazerman LB, et al. Drug treatment outcomes among HIV-infected opioid-dependent patients receiving buprenorphine/naloxone. J Acquir Immune Defic Syndr. 2011;56(Suppl 1):S33–8.
30. Korthuis PT, Fiellin DA, Fu R, Lum PJ, Altice FL, Sohler N, et al. Improving adherence to HIV quality of care indicators in persons with opioid dependence: the role of buprenorphine. J Acquir Immune Defic Syndr. 2011;56(Suppl 1):S83–90.
31. Potter JS, Marino EN, Hillhouse MP, Nielsen S, Wiest K, Canamar CP, et al. Buprenorphine/naloxone and methadone maintenance treatment outcomes for opioid analgesic, heroin, and combined users: findings from starting treatment with agonist replacement therapies (START). J Stud Alcohol Drugs. 2013;74(4):605–13.
32. Lucas GM, et al. Clinic-based treatment of opioid-dependent HIV-infected patients versus referral to an opioid treatment program: a randomized trial. Ann Intern Med. 2010;152(11):704–11.
33. Korthuis PT, Tozzi MJ, Nandi V, Fiellin DA, Weiss L, Egan JE, et al. Improved quality of life for opioid-dependent patients receiving buprenorphine treatment in HIV clinics. J Acquir Immune Defic Syndr. 2011;56(Suppl 1):S39–45.
34. Springer SA, Qiu J, Saber-Tehrani AS, Altice FL. Retention on buprenorphine is associated with high levels of maximal viral suppression among HIV-infected opioid dependent released prisoners. PLoS One. 2012;7(5):e38335.
35. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011;377(9776):1506–13.
36. Dijkstra BA, et al. Does naltrexone affect craving in abstinent opioid-dependent patients? Addict Biol. 2007;12(2):176–82.

37. Minozzi S, et al. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev. 2011;4:CD001333.
38. Lee JD, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet. 2017.
39. Tanum L, Solli KK, Latif ZEH, Benth JŠ, Opheim A, Sharma-Haase K, et al. Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. JAMA Psychiatry. 2017;74(12):1197–205.
40. Tetrault JM, Tate JP, McGinnis KA, Goulet JL, Sullivan LE, Bryant K, et al. Hepatic safety and antiretroviral effectiveness in HIV-infected patients receiving naltrexone. Alcohol Clin Exp Res. 2012;36(2):318–24.
41. Vagenas P, di Paola A, Herme M, Lincoln T, Skiest DJ, Altice FL, et al. An evaluation of hepatic enzyme elevations among HIV-infected released prisoners enrolled in two randomized placebo-controlled trials of extended release naltrexone. J Subst Abus Treat. 2014;47(1):35–40.
42. Springer SA, di Paola A, Barbour R, Azar MM, Altice FL. Extended-release naltrexone improves viral suppression among incarcerated persons living with HIV and alcohol use disorders transitioning to the community: results from a double-blind, placebo-controlled trial. J Acquir Immune Defic Syndr. 2018;79(1):92–100.
43. Springer SA, di Paola A, Azar MM, Barbour R, Krishnan A, Altice FL. Extended-release naltrexone reduces alcohol consumption among released prisoners with HIV disease as they transition to the community. Drug Alcohol Depend. 2017;174:158–70.
44. Mitchell MC, Memisoglu A, Silverman BL. Hepatic safety of injectable extended-release naltrexone in patients with chronic hepatitis C and HIV infection. J Stud Alcohol Drugs. 2012;73(6):991–7.
45. Korthuis PT, Lum PJ, Vergara-Rodriguez P, Ahamad K, Wood E, Kunkel LE, et al. Feasibility and safety of extended-release naltrexone treatment of opioid and alcohol use disorder in HIV clinics: a pilot/feasibility randomized trial. Addiction. 2017;112(6):1036–44.
46. Clinical Trials Network-0067 Comparing Treatments for HIV-Infected Opioid Users in an Integrated Care Effectiveness Study (CHOICES) Scale-Up.
47. Dunbar JL, Turncliff RZ, Dong Q, Silverman BL, Ehrich EW, Lasseter KC. Single- and multiple-dose pharmacokinetics of long-acting injectable naltrexone. Alcohol Clin Exp Res. 2006;30(3):480–90.
48. Alkermes Inc., Vivitrol package insert. 2010.
49. Saber-Tehrani AS, Bruce RD, Altice FL. Pharmacokinetic drug interactions and adverse consequences between psychotropic medications and pharmacotherapy for the treatment of opioid dependence. Am J Drug Alcohol Abuse. 2011;37(1):1–11.
50. McCance-Katz EF, Rainey PM, Friedland G, Kosten TR, Jatlow P. Effect of opioid dependence pharmacotherapies on zidovudine disposition. Am J Addict. 2001;10(4):296–307.
51. International Advisory Panel on HIV Care Continuum Optimization. IAPAC Guidelines for Optimizing the HIV Care Continuum for Adults and Adolescents. J Int Assoc Provid AIDS Care. 2015:1–32.
52. Gardner EM, McLees MP, Steiner JF, del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis. 2011;52(6):793–800.
53. Williams AR, Nunes E, Olfson M. To battle the opioid overdose epidemic, deploy the 'Cascade of Care' model. Health Affairs Blog. 2017. https://doi.org/10.1377/hblog20170313.059163.
54. Socias ME, Volkow N, Wood E. Adopting the 'cascade of care' framework: an opportunity to close the implementation gap in addiction care? Addiction. 2016;111(12):2079–81.
55. National Institute on Drug Abuse. Chart of Evidence-Based Screening Tools and Assessments for Adults and Adolescents. Revised June 2018. https://www.drugabuse.gov/nidamed-medical-health-professionals/tool-resources-your-practice/screening-assessment-drug-testing-resources/chart-evidence-based-screening-tools. Accessed 3 January 2019.
56. Korthuis PT, McCarty D, Weimer M, Bougatsos C, Blazina I, Zakher B, et al. Primary care-based models for the treatment of opioid use disorder: a scoping review. Ann Intern Med. 2017;166(4):268–78.