HHS Public Access

Author manuscript

Curr Infect Dis Rep. Author manuscript; available in PMC 2019 July 31.

Published in final edited form as:

Curr Infect Dis Rep. ; 20(9): 36. doi:10.1007/s11908-018-0636-7.

Substance use and Adherence to Antiretroviral Therapy: What is known, and what is unknown

M. Eugenia Socías, MD, MSc[1,2] and **M-J Milloy, PhD**[1,2]

[1.]British Columbia Centre on Substance Use, 608-1081 Burrard Street, Vancouver, BC, Canada, V6Z 1Y6

[2.]Department of Medicine, University of British Columbia, 608-1081 Burrard Street, Vancouver, BC, Canada, V6Z 1Y6

Abstract

Purpose of review: People who use drugs face multiple challenges to achieve optimal HIV treatment outcomes. This review discusses the current knowledge in substance use and antiretroviral therapy adherence, highlighting recent findings and potential interventions.

Recent findings: Studies continue to demonstrate the negative impacts of substance use and related disorders on ART adherence, with the exception of cannabis. Evidence-based addiction treatment, in particular opioid agonist therapy appears to improve adherence levels. Most individual-level adherence specific interventions did not provide sustained effects, and no studies evaluating structural-level interventions were found.

Summary: Findings suggest the urgent need to scale-up opioid agonist therapy, as well as to simultaneously address multiple structural barriers to care to optimize HIV treatment outcomes among people who use drugs.

Keywords

adherence; antiretroviral therapy; people who use drugs; people who inject drugs; opioid agonist therapy; cannabis

Introduction

Antiretroviral therapy (ART) has dramatically modified the natural history of HIV infection. Timely initiation of ART is associated with reduced mortality, morbidity and transmission both at the individual and community level [1–5]. This scientific consensus had led to calls to scale-up access to HIV care and treatment worldwide as a central component of efforts control the HIV pandemic. However, challenges remain as early diagnosis, linkage to and

Send correspondence to: M-J Milloy, PhD. Research Scientist, B.C. Centre on Substance Use, University of British Columbia, St. Paul's Hospital. 608-1081 Burrard Street, Vancouver, B.C., V6Z 1Y6, Canada. bccsu-mjsm@cfenet.ubc.ca.

Disclosures

M-JM's institution has received an unstructured gift to support him from NG Biomed Ltd., a private firm seeking a government licence to produce medical cannabis.

retention in care, and long-term adherence to ART are critical for attaining these optimal clinical and public health outcomes [6, 7].

While impressive gains have made in terms of scaling-up access to ART in recent years, only 38% of the estimated 36.7 million people living with HIV (PLHIV) globally were virally suppressed in 2015. A key determinant of sustained viral suppression is consistent high levels of adherence to ART. Suboptimal adherence is a risk factor for virologic rebound, and subsequent increased likelihood of virologic failure, emergence of viral drug resistance, disease progression and onward viral transmission. Unfortunately, a substantial proportion of PLHIV do not achieve optimal levels of adherence [8, 9].

A number of reviews have examined barriers and facilitators to ART adherence across different populations and settings, and among them active substance use has been identified as one of the most common predictors of poor adherence [10–14]. Given the high prevalence of substance use and related disorders among PLHIV, as well as recent explosive outbreaks of HIV driven by parenteral transmission [15], understanding patterns of ART adherence among people who use drugs (PWUD), and ways to promote adequate and sustained levels of adherence will be critical to control the HIV pandemic.

This review focuses on studies published between 2012 and 2017, summarizing and discussing the current knowledge on the epidemiology of ART adherence among PWUD, potential interventions to improve adherence among this population, as well as current gaps and future directions for research.

Recent trends in ART adherence among PWUD

Recent reviews continue to highlight active substance use as one of the major predictors of poor ART adherence among PLHIV [11, 13]. Sub-optimal levels of ART adherence have been observed among people who use injection, non-injection drugs or alcohol in low-, middle-, and high-income settings [16–18]. For example, a meta-analysis that included 15 studies of people with a history of injection drug use from seven low- and middle-income countries found a mean weighted adherence of 72% [18]. A long-term cohort study of HIV-positive PWUD in Canada showed substantial increase over time in the proportion of individuals with ≥95% adherence; however, in 2014, still only over half achieved this threshold [19]. In an analysis of the same cohort, periods of active injection drug use were associated with transitions out of optimal adherence and as barriers to becoming optimally adherent [20]. Another study conducted among 3,343 PLHIV in care across six countries from Latin America in 2012–2013 found that between 29% and 46% of people who used alcohol or illicit drugs reported missing ART doses in the prior week, compared to only 11% of individuals who did not report substance use [17].

Specific substances and ART adherence

Alcohol and problematic alcohol use are common among PLHIV, with some studies documenting up to 42% prevalence of heavy drinking [21]. A large body of research has documented negative impacts of alcohol use on HIV outcomes. A recent review examining the impacts of alcohol on the HIV cascade of care continuum published between 2010 and

2015 found an association between alcohol use and nonadherence, usually in a dose-response fashion, in most (n=16) of the 33 included studies focusing on the ART adherence step [22]. Other recent studies confirm this negative influence of alcohol on ART adherence in a variety of contexts [23, 17, 24, 25].

Recent research conducted in North America [24, 26–29] also confirms the links between heroin and cocaine use and suboptimal ART adherence found in previous reviews [14]. For example, a large study that pooled data from over 1,500 PLHIV across different sites in the United States, found independent and strong negative associations between recent heroin or cocaine use and objective measures of ART adherence (i.e., using electronic data monitoring) [27].

Of note, in many of these same studies [24, 26, 27, 25], cannabis use was not a risk for suboptimal ART adherence. This lack of association between cannabis use and ART adherence was also documented in other recent analyses [30–32]. Interestingly, in one of these studies, individuals with cannabis dependence had significantly lower rates of adherence than both non-dependent users and not users, suggesting that patterns of use may be an important factor in shaping adherence outcomes in this population [32]. In addition, these opposing findings between cannabis and other substances may relate to the fact that many PLHIV use cannabis therapeutically to address disease symptoms and medication side-effects which in turn may enhance adherence [33]. Alternatively, cannabis may be used as a substitute for other substances (e.g., alcohol, crack cocaine, opioid analgesics) with known detrimental effects on adherence [34, 35].

The literature around methamphetamine use and ART adherence is more limited, has mostly focused on men who have sex with men, and documented high rates of nonadherence among methamphetamine users [36]. Recent research continues to support this negative association [25, 37, 38]. Indeed, in one of these studies, ART non-adherence was more likely to occur in days where methamphetamine was also used [38].

Despite the high prevalence of prescription medication use (other than ART), including non-medical use, among PLHIV, we found only one study investigating the relationship between opioid analgesics and ART adherence. Among 258 marginalized PLHIV, opioid analgesic misuse, but not use, was associated with incomplete ART adherence, highlighting again that patterns of use and misuse, and associated contextual factors, rather than specific substances may be the critical factor shaping adherence behaviours [39].

Addiction treatment

Although PWUD are a heterogeneous population, accumulating evidence supports the role of evidence-based addiction treatment in improving ART outcomes among individuals with substance use disorders. To date, the largest body of evidence is for opioid agonist treatment ([OAT] e.g., methadone, buprenorphine). A recent systematic review found that engagement in OAT was associated with a two-fold increase in the likelihood of achieving optimal ART adherence [40]. Other recent studies echo this finding of OAT as a key facilitator of ART adherence [29, 41, 26, 20, 42]. Interestingly, in one study there was a positive dose-response

relationship between higher daily methadone dose and the likelihood of achieving ≥95% ART adherence, underlining the need for evidence-based dosing of OAT [42]. Regarding other addiction treatment modalities, the evidence is mixed. One study showed advantages of any treatment over no treatment [43] and other no effect [14]. These differences may relate to the fact that with the exception of opioid and alcohol use disorder for which effective pharmacotherapies exist, there are currently not such medications for other substance use disorders, and the evidence for other approaches is limited. Of note, no studies evaluating the impact of pharmacological therapies for alcohol use disorders on ART adherence were identified [22]. Collectively, these findings highlight the need to expand access to OAT to optimize ART outcomes among PLHIV with opioid use disorder, as well as for further research for evidence-based treatment for stimulant use disorder or other strategies to support this population in fully benefitting from ART.

Social-structural exposures

Despite the growing acknowledgement on the importance of social-structural factors as drivers of health outcomes, particularly among marginalized populations, comparatively less research has examined the influence of structural vulnerability on ART adherence. The few existing studies, mostly for the North American setting suggest that unstable housing (e.g., homelessness, residential eviction), incarceration and prohibited income generation activities are important structural barriers to optimal ART outcomes, and mostly mediated by lower levels of adherence [44–47].

Interventions to improve adherence among PWUD

A previous systematic review comprehensively reviewed the evidence of interventions to improve ART adherence among PWUD [48]. Among the fifteen randomized clinical trials (RCTs) included in this review, the strongest evidence was for directly administered antiretroviral therapy (DAART). RCTs evaluating contingency management and multi-component, nurse delivered interventions also demonstrated improvements in short-term ART adherence. However, these benefits waned rapidly after the interventions were discontinued [48]. Given the need for lifelong ART adherence, these results suggest the need to further explore how to sustain the effects of these interventions.

Since the publication of this review, a number of other RCTs evaluating adherence interventions for PWUD were published. Lucas *et al.* evaluated the efficacy of a DAART intervention embedded within an OAT program [49]. In this study, rates of ART adherence and viral suppression at 12 months were overall low, with no differences between participants in the DAART and self-administered arm, contradicting previous RCTs in this area. However, most previous studies assessed shorter interventions periods and the sustained benefits after intervention cessation were equivocal [48], raising the question about the real-world effectiveness of this intervention.

Although no recent studies evaluating contingency management to promote ART adherence among PWUD were found, we identified two studies that targeted viral suppression. The first one by Farber *et al*—a pilot study that used a within-subject design, found a 12% (from

57% to 69%) increase in the proportion of undetectable viral loads after the introduction of cash incentives ($100) rewarding reductions in viral load (or maintaining viral suppression) [50]. In the second study, 120 ART-naïve HIV-positive PWUD were randomized to receive or not voucher incentives for achieving specific steps along the continuum of HIV care [51]. Although the voucher incentive arm was associated with improved ART initiation and monthly medication refill rates compared to the control arm, no differences were observed in viral suppression. The opposing findings in these studies may relate to differences in study design, setting (U.S. vs. India) populations (e.g., only half of the study sample in the Farber *et al.* study were PWUD), different types and size of incentive or other unmeasured factors. Both studies were also limited by small sample sizes.

More recently, Project HOPE went one step further and evaluated a combination approach of patient navigation with or without financial incentives to promote engagement in HIV and addiction care [52]. In this large RCT that was conducted in 11 sites across the U.S., 801 inpatient HIV-positive PWUD with detectable viral load were randomized to one of three arms: 1) usual care, 2) six months of patient navigation, or 3) six months of patient navigation plus financial incentives targeting behaviors aimed at reducing substance use and improving engagement in HIV care. At 12 months, no differences were found in viral suppression, death, or other key secondary outcomes, including ART adherence, substance use or engagement in addiction care. Possible explanations for these results may include the short duration of the intervention, the lack of addiction care options in many settings, the high proportion of participants with stimulant use disorders (70%) for which no effective treatment exists, and competing interests that were not addressed in the context of a highly marginalized population. Collectively, findings from these three studies do not support the use of financial incentives (alone) to improve progression along the HIV continuum of care among PWUD.

Finally, two pilot studies evaluated mobile health (mHealth) interventions to improve ART adherence among PWUD. The iTAB study examined the effect of personalized ART reminder text messages (in addition to daily short message service [SMS] assessing methamphetamine use) among HIV-positive methamphetamine users in San Diego, U.S. [53]. A 30-day evaluation showed preliminary evidence of the acceptability and feasibility of this intervention among this populations, with 70% response-rate to adherence reminders, 80% self-reported adherence, and high overall satisfaction with the program. The TxText intervention involved automated bidirectional daily SMS assessing mood, substance use and ART adherence for HIV-positive ART non-adherent PWUD, and subsequent personalized intervention SMS based on participant' responses [54]. A three-month evaluation of this intervention showed consistent engagement with the tool over the study period, with responses rates between 64% and 69% to each of the categories. While preliminary feasibility and acceptability evaluations of these mHealth interventions are promising, full results of these studies are yet not available, and thus the efficacy of mHealth technology on promoting and sustaining ART adherence among PWUD remains unknown.

Conclusions

The review of current literature continues to demonstrate the negative impacts of substance use and related disorders on ART adherence, particularly when left untreated. The use of cannabis appears to be an exemption to this detrimental association, potentially due to some of its suggested therapeutic uses, though evidence in this area is limited and inconsistent, and deserves further research. Another avenue of future research relates to what level of adherence may be sufficient to achieve optimal treatment outcomes among PWUD with newer ART formulations. Indeed, while recent research has suggested that improved ART regimens with higher genetic barrier may allow for lower levels of consistent adherence than those historically required (≥95%) to achieve viral suppression, the evidence for PWUD is scant and inconclusive [55, 56]. In addition, emerging studies also suggest that these sub-optimal levels of adherence may result in higher levels of immune activation and inflammation and increased non-AIDS related morbidity [57]. Our review also points to the lack of long-term benefits of any of the individual-level adherence interventions, and the absence of studies evaluating structural-level interventions. Although there is continued need for the development and testing novel adherence strategies tailored to PWUD, these findings also highlight the urgent need to implement and scale-up interventions with proven individual and community-level benefits, particularly opioid agonist therapy. Similarly, in the context of a marginalized population with multiple structural barriers to care, findings from this review also underscore the need to simultaneously address to achieve optimal treatment outcomes and reduced health inequities faced by PWUD.

Acknowledgments

MES is supported by Michael Smith Foundation for Health Research (MSFHR) and Canadian Institutes of Health Research (CIHR) fellowship awards. M-JM is supported in part by NIH (U01-DA021525), a Scholar Award from MSFHR and a New Investigator award from the Canadian Institutes of Health Research (CIHR).

References

1. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365(6):493–505. doi: 10.1056/NEJMoa1105243. [PubMed: 21767103]
2. Grinsztejn B, Hosseinipour MC, Ribaudo HJ, Swindells S, Eron J, Chen YQ et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. Lancet Infect Dis 2014;14(4):281–90. doi: 10.1016/S1473-3099(13)70692-3. [PubMed: 24602844]
3. Insight Start Study Group, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med 2015;373(9):795–807. doi:10.1056/NEJMoa1506816. [PubMed: 26192873]
4. Temprano Anrs Study Group, Danel C, Moh R, Gabillard D, Badje A, Le Carrou J et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med 2015;373(9):808–22. doi:10.1056/NEJMoa1507198. [PubMed: 26193126]
5. •• Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, van Lunzen J et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. JAMA 2016;316(2):171–81. doi:10.1001/jama.2016.5148. [PubMed: 27404185] (This study provides among the first estimates of HIV transmission in condomless sex in the context of suppressive ART)

6. Mayer KH. Introduction: Linkage, engagement, and retention in HIV care: essential for optimal individual- and community-level outcomes in the era of highly active antiretroviral therapy. Clin Infect Dis 2011;52 Suppl 2:S205–7. doi:10.1093/cid/ciq043.
7. Mugavero MJ, Norton WE, Saag MS. Health care system and policy factors influencing engagement in HIV medical care: piecing together the fragments of a fractured health care delivery system. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2011;52 Suppl 2:S238–46. doi:10.1093/cid/ciq048. [PubMed: 21342913]
8. Bezabhe WM, Chalmers L, Bereznicki LR, Peterson GM. Adherence to Antiretroviral Therapy and Virologic Failure: A Meta-Analysis. Medicine (Baltimore) 2016;95(15):e3361. doi:10.1097/MD.0000000000003361. [PubMed: 27082595]
9. Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA 2006;296(6):679–90. doi:10.1001/jama.296.6.679. [PubMed: 16896111]
10. Mills EJ, Nachega JB, Bangsberg DR, Singh S, Rachlis B, Wu P et al. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. PLoS Med 2006;3(11):e438. doi:10.1371/journal.pmed.0030438. [PubMed: 17121449]
11. Langebeek N, Gisolf EH, Reiss P, Vervoort SC, Hafsteinsdottir TB, Richter C et al. Predictors and correlates of adherence to combination antiretroviral therapy (ART) for chronic HIV infection: a meta-analysis. BMC Med 2014;12:142. doi:10.1186/PREACCEPT-1453408941291432. [PubMed: 25145556]
12. Malta M, Magnanini MM, Strathdee SA, Bastos FI. Adherence to antiretroviral therapy among HIV-infected drug users: a meta-analysis. AIDS Behav 2010;14(4):731–47. doi:10.1007/s10461-008-9489-7. [PubMed: 19020970]
13. •• Mannheimer S, Hirsch-Moverman Y. What we know and what we do not know about factors associated with and interventions to promote antiretroviral adherence. Curr Infect Dis Rep 2015;17(4):466. doi:10.1007/s11908-015-0466-9. [PubMed: 25860778] (A systematic review of interventions to improve antiretroviral adherence).
14. Gonzalez A, Barinas J, O'Cleirigh C. Substance use: impact on adherence and HIV medical treatment. Curr HIV/AIDS Rep 2011;8(4):223–34. doi:10.1007/s11904-011-0093-5. [PubMed: 21858414]
15. Des Jarlais DC, Kerr T, Carrieri P, Feelemyer J, Arasteh K. HIV infection among persons who inject drugs: ending old epidemics and addressing new outbreaks. AIDS 2016;30(6):815–26. doi:10.1097/QAD.0000000000001039. [PubMed: 26836787]
16. Beer L, Skarbinski J. Adherence to antiretroviral therapy among HIV-infected adults in the United States. AIDS Educ Prev 2014;26(6):521–37. doi:10.1521/aeap.2014.26.6.521. [PubMed: 25490733]
17. De Boni RB, Shepherd BE, Grinsztejn B, Cesar C, Cortes C, Padgett D et al. Substance Use and Adherence Among People Living with HIV/AIDS Receiving cART in Latin America. AIDS Behav 2016;20(11):2692–9. doi:10.1007/s10461-016-1398-6. [PubMed: 27091028]
18. • Feelemyer J, Des Jarlais D, Arasteh K, Uuskula A. Adherence to antiretroviral medications among persons who inject drugs in transitional, low and middle income countries: an international systematic review. AIDS Behav 2015;19(4):575–83. doi:10.1007/s10461-014-0928-3. [PubMed: 25331268] (A systematic review of ART adherence among people who inject drugs in transitional-, low- and middle-income countries).
19. Milloy MJ, Wood E, Kerr T, Hogg B, Guillemi S, Harrigan PR et al. Increased Prevalence of Controlled Viremia and Decreased Rates of HIV Drug Resistance Among HIV-Positive People Who Use Illicit Drugs During a Community-wide Treatment-as-Prevention Initiative. Clin Infect Dis 2016;62(5):640–7. doi:10.1093/cid/civ929. [PubMed: 26553011]
20. Joseph B, Kerr T, Puskas CM, Montaner J, Wood E, Milloy MJ. Factors linked to transitions in adherence to antiretroviral therapy among HIV-infected illicit drug users in a Canadian setting. AIDS Care 2015;27(9):1128–36. doi:10.1080/09540121.2015.1032205. [PubMed: 25915438]
21. Williams EC, Hahn JA, Saitz R, Bryant K, Lira MC, Samet JH. Alcohol Use and Human Immunodeficiency Virus (HIV) Infection: Current Knowledge, Implications, and Future Directions. Alcohol Clin Exp Res 2016;40(10):2056–72. doi:10.1111/acer.13204. [PubMed: 27696523]

22. •• Vagenas P, Azar MM, Copenhaver MM, Springer SA, Molina PE, Altice FL. The Impact of Alcohol Use and Related Disorders on the HIV Continuum of Care: a Systematic Review : Alcohol and the HIV Continuum of Care. Curr HIV/AIDS Rep 2015;12(4):421–36. doi:10.1007/s11904-015-0285-5. [PubMed: 26412084] (A systematic review of the impact of alcohol use and related disorders on engagement in the HIV continuum of care).
23. Gonzalez-Alvarez S, Madoz-Gurpide A, Parro-Torres C, Hernandez-Huerta D, Ochoa Mangado E. Relationship between alcohol consumption, whether linked to other substance use or not, and antiretroviral treatment adherence in HIV+ patients. Adicciones 2017;0(0):916. doi:10.20882/adicciones.916.
24. Nolan S, Walley AY, Heeren TC, Patts GJ, Ventura AS, Sullivan MM et al. HIV-infected individuals who use alcohol and other drugs, and virologic suppression. AIDS Care 2017;29(9):1129–36. doi:10.1080/09540121.2017.1327646. [PubMed: 28513200]
25. Shuper PA, Joharchi N, Irving H, Fletcher D, Kovacs C, Loutfy M et al. Differential predictors of ART adherence among HIV-monoinfected versus HIV/HCV-coinfected individuals. AIDS Care 2016;28(8):954–62. doi:10.1080/09540121.2016.1158396. [PubMed: 26971360]
26. 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. doi:10.1186/s12879-015-0913-0. [PubMed: 25927573]
27. •• Rosen MI, Black AC, Arnsten JH, Goggin K, Remien RH, Simoni JM et al. Association between use of specific drugs and antiretroviral adherence: findings from MACH 14. AIDS Behav 2013;17(1):142–7. doi:10.1007/s10461-011-0124-7. [PubMed: 22246513] (This study using a large dataset of studies conducted in the United States indicated an association between use of most substances and sub-optimal adherence, with the exception of cannabis).
28. Gonzalez A, Mimiaga MJ, Israel J, Andres Bedoya C, Safren SA. Substance use predictors of poor medication adherence: the role of substance use coping among HIV-infected patients in opioid dependence treatment. AIDS Behav 2013;17(1):168–73. doi:10.1007/s10461-012-0319-6. [PubMed: 23008124]
29. Hayashi K, Wood E, Kerr T, Dong H, Nguyen P, Puskas CM et al. Factors associated with optimal pharmacy refill adherence for antiretroviral medications and plasma HIV RNA non-detectability among HIV-positive crack cocaine users: a prospective cohort study. BMC Infect Dis 2016;16(1):455. doi:10.1186/s12879-016-1749-y. [PubMed: 27568002]
30. Slawson G, Milloy MJ, Balneaves L, Simo A, Guillemi S, Hogg R et al. High-intensity cannabis use and adherence to antiretroviral therapy among people who use illicit drugs in a Canadian setting. AIDS Behav 2015;19(1):120–7. doi:10.1007/s10461-014-0847-3. [PubMed: 25012624]
31. Vidot DC, Lerner B, Gonzalez R. Cannabis Use, Medication Management and Adherence Among Persons Living with HIV. AIDS Behav 2017;21(7):2005–13. doi:10.1007/s10461-017-1782-x. [PubMed: 28456895]
32. Bonn-Miller MO, Oser ML, Bucossi MM, Trafton JA. Cannabis use and HIV antiretroviral therapy adherence and HIV-related symptoms. J Behav Med 2014;37(1):1–10. doi:10.1007/s10865-012-9458-5. [PubMed: 23054178]
33. de Jong BC, Prentiss D, McFarland W, Machekano R, Israelski DM. Marijuana use and its association with adherence to antiretroviral therapy among HIV-infected persons with moderate to severe nausea. J Acquir Immune Defic Syndr 2005;38(1):43–6. [PubMed: 15608523]
34. Socias ME, Kerr T, Wood E, Dong H, Lake S, Hayashi K et al. Intentional cannabis use to reduce crack cocaine use in a Canadian setting: A longitudinal analysis. Addict Behav 2017;72:138–43. doi:10.1016/j.addbeh.2017.04.006. [PubMed: 28399488]
35. Lucas P, Walsh Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. Int J Drug Policy 2017;42:30–5. doi:10.1016/j.drugpo.2017.01.011. [PubMed: 28189912]
36. Rajasingham R, Mimiaga MJ, White JM, Pinkston MM, Baden RP, Mitty JA. A systematic review of behavioral and treatment outcome studies among HIV-infected men who have sex with men who abuse crystal methamphetamine. AIDS Patient Care STDS 2012;26(1):36–52. doi:10.1089/apc.2011.0153. [PubMed: 22070609]

37. Moore DJ, Blackstone K, Woods SP, Ellis RJ, Atkinson JH, Heaton RK et al. Methamphetamine use and neuropsychiatric factors are associated with antiretroviral non-adherence. AIDS Care 2012;24(12):1504–13. doi:10.1080/09540121.2012.672718. [PubMed: 22530794]

38. Parsons JT, Kowalczyk WJ, Botsko M, Tomassilli J, Golub SA. Aggregate versus day level association between methamphetamine use and HIV medication non-adherence among gay and bisexual men. AIDS Behav 2013;17(4):1478–87. doi:10.1007/s10461-013-0463-7. [PubMed: 23553345]

39. Jeevanjee S, Penko J, Guzman D, Miaskowski C, Bangsberg DR, Kushel MB. Opioid analgesic misuse is associated with incomplete antiretroviral adherence in a cohort of HIV-infected indigent adults in San Francisco. AIDS Behav 2014;18(7):1352–8. doi:10.1007/s10461-013-0619-5. [PubMed: 24077929]

40. •• Low AJ, Mburu G, Welton NJ, May MT, Davies CF, French C 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. doi:10.1093/cid/ciw416. [PubMed: 27343545] (This systematic review and meta-analysis demonstrated the positive impacts of opioid agonist therapy to improve engagement in each step of the HIV continuum of care).

41. Nosyk B, Min JE, Colley G, Lima VD, Yip B, Milloy MJ et al. The causal effect of opioid substitution treatment on HAART medication refill adherence. AIDS 2015;29(8):965–73. doi: 10.1097/QAD.0000000000000642. [PubMed: 25915170]

42. Lappalainen L, Nolan S, Dobrer S, Puscas C, Montaner J, Ahamad K et al. Dose-response relationship between methadone dose and adherence to antiretroviral therapy among HIV-positive people who use illicit opioids. Addiction 2015;110(8):1330–9. doi:10.1111/add.12970. [PubMed: 25940906]

43. Rosen MI, Black AC, Arnsten JH, Simoni JM, Wagner GJ, Goggin K et al. ART adherence changes among patients in community substance use treatment: a preliminary analysis from MACH14. AIDS Res Ther 2012;9(1):30. doi:10.1186/1742-6405-9-30. [PubMed: 23057423]

44. Richardson LA, Kerr TH, Dobrer S, Puskas CM, Guillemi SA, Montaner JS et al. Socioeconomic marginalization and plasma HIV-1 RNA nondetectability among individuals who use illicit drugs in a Canadian setting. AIDS 2015;29(18):2487–95. doi:10.1097/QAD.0000000000000853. [PubMed: 26558546]

45. Kennedy MC, Kerr T, McNeil R, Parashar S, Montaner J, Wood E et al. Residential Eviction and Risk of Detectable Plasma HIV-1 RNA Viral Load Among HIV-Positive People Who Use Drugs. AIDS Behav 2017;21(3):678–87. doi:10.1007/s10461-016-1315-z. [PubMed: 26906022]

46. Milloy MJ, Montaner JS, Wood E. Incarceration of people living with HIV/AIDS: implications for treatment-as-prevention. Curr HIV/AIDS Rep 2014;11(3):308–16. doi:10.1007/s11904-014-0214-z. [PubMed: 24962285]

47. Milloy MJ, Kerr T, Bangsberg DR, Buxton J, Parashar S, Guillemi S et al. Homelessness as a structural barrier to effective antiretroviral therapy among HIV-seropositive illicit drug users in a Canadian setting. AIDS Patient Care STDS 2012;26(1):60–7. doi:10.1089/apc.2011.0169. [PubMed: 22107040]

48. Binford MC, Kahana SY, Altice FL. A systematic review of antiretroviral adherence interventions for HIV-infected people who use drugs. Curr HIV/AIDS Rep 2012;9(4):287–312. doi:10.1007/s11904-012-0134-8. [PubMed: 22936463]

49. Lucas GM, Mullen BA, Galai N, Moore RD, Cook K, McCaul ME et al. Directly administered antiretroviral therapy for HIV-infected individuals in opioid treatment programs: results from a randomized clinical trial. PLoS One 2013;8(7):e68286. doi:10.1371/journal.pone.0068286. [PubMed: 23874575]

50. Farber S, Tate J, Frank C, Ardito D, Kozal M, Justice AC et al. A study of financial incentives to reduce plasma HIV RNA among patients in care. AIDS Behav 2013;17(7):2293–300. doi:10.1007/s10461-013-0416-1. [PubMed: 23404097]

51. Solomon SS, Srikrishnan AK, Vasudevan CK, Anand S, Kumar MS, Balakrishnan P et al. Voucher incentives improve linkage to and retention in care among HIV-infected drug users in Chennai, India. Clin Infect Dis 2014;59(4):589–95. doi:10.1093/cid/ciu324. [PubMed: 24803381]

52. • Metsch LR, Feaster DJ, Gooden L, Matheson T, Stitzer M, Das M et al. Effect of Patient Navigation With or Without Financial Incentives on Viral Suppression Among Hospitalized

Patients With HIV Infection and Substance Use: A Randomized Clinical Trial. JAMA 2016;316(2):156–70. doi:10.1001/jama.2016.8914. [PubMed: 27404184] (This randomized clinical trial among hospitalized patients with HIV and substance use found no beneficial effect of patient navigation with or without financial incentives to improve HIV treatment adherence and viral suppression).

53. Moore DJ, Montoya JL, Blackstone K, Rooney A, Gouaux B, Georges S et al. Preliminary Evidence for Feasibility, Use, and Acceptability of Individualized Texting for Adherence Building for Antiretroviral Adherence and Substance Use Assessment among HIV-Infected Methamphetamine Users. AIDS Res Treat 2013;2013:585143. doi:10.1155/2013/585143. [PubMed: 24078868]
54. Ingersoll K, Dillingham R, Reynolds G, Hettema J, Freeman J, Hosseinbor S et al. Development of a personalized bidirectional text messaging tool for HIV adherence assessment and intervention among substance abusers. J Subst Abuse Treat 2014;46(1):66–73. doi:10.1016/j.jsat.2013.08.002. [PubMed: 24029625]
55. • Viswanathan S, Detels R, Mehta SH, Macatangay BJ, Kirk GD, Jacobson LP. Level of adherence and HIV RNA suppression in the current era of highly active antiretroviral therapy (HAART). AIDS Behav 2015;19(4):601–11. doi:10.1007/s10461-014-0927-4. [PubMed: 25342151] (This study estimated the minimum adherence needed to achieve viral suppression with newer antiretroviral regimens in large cohorts of men who have sex with men and people who inject drugs).
56. Viswanathan S, Justice AC, Alexander GC, Brown TT, Gandhi NR, McNicholl IR et al. Adherence and HIV RNA Suppression in the Current Era of Highly Active Antiretroviral Therapy. J Acquir Immune Defic Syndr 2015;69(4):493–8. doi:10.1097/QAI.0000000000000643. [PubMed: 25886923]
57. Castillo-Mancilla JR, Brown TT, Erlandson KM, Palella FJ, Jr., Gardner EM, Macatangay BJ et al. Suboptimal Adherence to Combination Antiretroviral Therapy Is Associated With Higher Levels of Inflammation Despite HIV Suppression. Clin Infect Dis 2016;63(12):1661–7. doi:10.1093/cid/ciw650. [PubMed: 27660234]