

POLICY AND PROGRAMMING IMPLICATIONS

Educate drug users about interactions between opioid drugs and ARVs. Key points are:

- Efavirenz and Nevirapine reduce levels of heroin, so people may experience withdrawal
- Ritonavir, Efavirenz and nevirapine reduce levels of methadone.
- It may be unsafe to mix Ecstasy / methamphetamines with Ritonavir
- Methadone doubles the levels of AZT in the body
- Stopping ARVs or not adhering to the ARV regime can lead to symptoms of overdose

Support safer drug use:

In most cases, problems arise because ARV drugs stop the liver processing recreational drugs in the normal way. This means that illicit drugs stay in the body for longer periods of time and/or at higher levels. Recommend that people take a lesser dose of the recreational drug and take it less often.²⁰

Support drug users to talk frankly with medical professionals

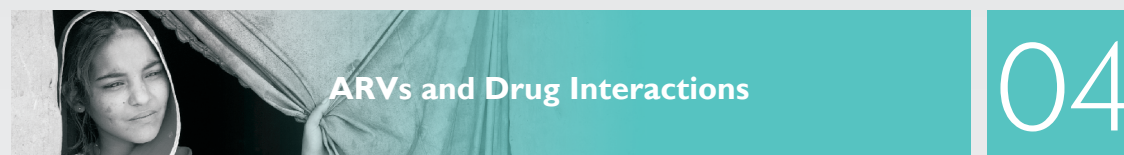
who prescribe ARVs about their drug use.

Stay informed through internet resources:

Good sources are

- www.HIV-druginteractions.org
- www.HIVpharmacology.com
- www.AIDSinfo.nih.gov

²⁰ARVs and recreational drug interactions: street drugs, 21 May 2009 <http://i-base.info/tffa/7-drug-users-and-hiv/7-7-arvs-and-recreational-drug-interactions-street-drugs>



BACKGROUND

Drug interactions have been identified between antiretroviral drugs (ARVs) and a number of recreational drugs as well as between ARVs and opioids. Although clinicians and researchers have identified these interactions for over a decade, research on the interaction between legally prescribed opioids such as methadone, and ARVs, remains underdeveloped, and there is no hard data on the interaction between illicit substances such as heroin, and ARVs. The available data shows that most ARVs tend to decrease the level of opioids in the body, so that people using opioids may experience withdrawal when they initiate antiretroviral treatment. The information brief provides basic information on the interaction between ARVs and common recreational drugs as well as between ARVs and methadone. It requires a qualified medical professional to treat drug interactions.

WHAT ARE THE ISSUES?

Research on the interaction between ARVs and other drugs—both prescribed drugs and illicit drugs—is inadequate. Most of the guidelines on possible interactions are 'informed guesswork' based on the way the drugs in question are metabolised by liver enzymes. Many warnings and recommendations concerning interactions with illegal drugs are based on case reports, rather than prospective or controlled studies. Drug companies and governments do not want to be seen as condoning illegal drug use and that has hampered research on this subject.¹

Opioids

It is difficult to predict the interaction between ARVs and heroin:

Although there is no research on the way in which starting ARV treatment can impact a person who uses heroin, some researchers have stated that interactions of heroin with ARVs is similar to those of methadone and other opioids.² Others, however, have argued that interactions between ARVs and methadone do not always match real interactions between ARVs and heroin in people, for a number of reasons:

- Because heroine is illegal, predicted interactions are not based on studies in humans but on theory, experiments in test tubes (in vitro) or tests on animals.
- Illegal drugs like heroin are seldom pure. Street drugs are often contaminated by other substances. It is

therefore difficult to predict how a street drug will interact with ARVs.

- Illegal drugs rarely have standard doses. What could be a relatively minor interaction at one dose could be serious at another.³

AZT and methadone:

Methadone doubles the levels of AZT in the body.⁴

NNRTIs and methadone:

The NNRTIs efavirenz and nevirapine speed up methadone metabolism and this can result in substantially decreased levels of methadone: Both efavirenz and nevirapine reduce levels of heroin and methadone and this can lead to withdraw symptoms. A study among patients in Dublin reported that nevirapine reduced methadone levels by 46 percent within two to three weeks of starting the NNRTI, and patients began to report opioid withdrawal symptoms eight to ten days after starting nevirapine. Within 24 hours of taking efavirenz, systemic exposure to methadone is reduced by about 60 percent.⁵ Another study found that when the NNRTIs nevirapine or efavirenz were given to patients receiving methadone maintenance therapy, methadone concentrations were decreased by 50 percent to 60 percent and some patients experienced withdrawal symptoms.⁶



UNODC

United Nations Office on Drugs and Crime
Country Office Pakistan

For more information on the
UNODC Country Office, Pakistan
Plot No. 5-11, Diplomatic Enclave, G-4, Islamabad
www.unodc.org/pakistan

¹AIDS MAP, Interactions with Recreational Drugs. <http://www.aidsmap.com/Interactions-with-recreational-drugs/page/1280663/>

²USAID, WHO, FHI. 2007. Drug Interactions: Treatment and Care for HIV-Positive Injecting Drug Users, Module 8, Participant Manual. Module_8_Treatment_Care_for_HIV_Positive_IDU.pdf

³ARVs and recreational drug interactions: overview, 21 April 2009 <http://i-base.info/tffa/7-drug-users-and-hiv/7-5-arvs-and-recreational-drug-interactions-overview>

⁴ARVs and recreational drug interactions: methadone, 21 May 2009 <http://i-base.info/tffa/7-drug-users-and-hiv/7-8-arvs-and-recreational-drug-interactions-methadone>

⁵AIDS MAP, Interactions with Recreational Drugs. <http://www.aidsmap.com/Interactions-with-recreational-drugs/page/1280663/>

⁶Clarke SM, Mulcahy FM, Tjia J, et al., Pharmacokinetic interactions of nevirapine and methadone and guidelines for use of nevirapine to treat injection drug users. Clin Infect Dis. 2001;33:1595-1597; and Clarke SM, Mulcahy FM, Tjia J, et al. The pharmacokinetics of methadone in HIV-positive patients receiving the non-nucleoside reverse transcriptase inhibitor efavirenz. Br J Clin Pharmacol. 2001;51:213-217; and Interactions Between Heroin and Antiretrovirals? Michael L. Lim, Pharm D; Angela D.M. Kashuba, BScPhm, PharmD, DABCP Posted: 04/17/2002 <http://www.medscape.com/viewarticle/431745>

ARVs and Drug Interactions

Protease Inhibitors and methadone:

Some protease inhibitors have effects in real life opposite to those predicted in the test tube. There have been cases of decreases in methadone levels in people when test tube experiments predicted an increase.⁷ Protease inhibitors (lopinavir/ritonavir, ritonavir/saquinavir, and nelfinavir) have been reported to decrease methadone concentrations, but research is not conclusive.⁸

- Nelfinavir (Viracept) and methadone may have pharmacokinetic interactions that require dose adjustments of methadone. Theoretically, this interaction should result in reduced methadone levels, but studies have found that only a minority of patients experience opioid withdrawal when initiating Nelfinavir.
- Ritonavir reduces blood levels of both methadone and heroin; ritonavir-boosted protease inhibitors have shown widely varying effects on methadone levels. However, a study of methadone and ritonavir in humans did show a decrease in methadone levels of 36 percent.⁹

PMTCT and methadone:

For pregnant women already on or starting ART, drug interactions may be a concern. Drug interactions can potentially result in decreased methadone levels or in increased ARV levels, increasing the risk of ARV-related side-effects. NNRTIs significantly decrease the methadone level and can precipitate withdrawal symptoms.

Ecstasy

Combining even a small dose of ecstasy with the protease inhibitor Ritonavir has increased and prolonged the effects of ecstasy. In one report, a man died after drinking beer

and taking ecstasy after he began taking ritonavir.¹⁰ An autopsy found that he had unusually high levels of ecstasy in his blood. It was reported that the man had taken no more than 2.5 ecstasy tablets, yet at post-mortem, he had blood levels equivalent to taking 22 tablets.¹¹

Methamphetamine

As in the case of ecstasy, combining methamphetamine with Ritonavir can lead to overdose and death. In 2000, Australian doctors reported what they believed to be a fatal interaction between ritonavir and methamphetamine, commonly known as 'crystal' or 'crystal meth'. A 49-year-old Melbourne man taking ritonavir, soft gel saquinavir, and d4T (stavudine, Zerit) was found dead the morning after injecting methamphetamine and sniffing amyl nitrite (poppers). A toxicology analysis showed that the dead man had methamphetamine levels of 0.5mg/l in his blood, a level seen in many overdose cases.¹²

Benzodiazepines

Several common benzodiazepines available on the street can have toxic effects when combined with protease inhibitors. These include alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium), and flunitrazepam (Rohypnol). Protease inhibitors cause the levels of these drugs to rise, and can result in toxicities such as oversedation. For example, ritonavir has been shown to increase effects of alprazolam.¹³ Conversely, when protease inhibitors are stopped, patients may have benzodiazepine withdrawal symptoms.

EVIDENCE: GOOD PRACTICES

AZT:

Because methadone increases the levels of AZT by roughly twofold, people taking both drugs need only take half the standard dose of AZT to get the same anti-HIV effect.¹⁴

Patients on **nevirapine** may experience opioid withdrawal symptoms but should not increase their opioid at the same time as starting nevirapine. Instead, it may be better to monitor withdrawal symptoms and increase the methadone dose if withdrawal does begin to occur.¹⁵

Patients on **efavirenz**, should not increase their dosage of opioids immediately because the neurological side-effects of efavirenz may be mistaken for opioid withdrawal. In the case of methadone, monitoring methadone levels closely and increasing methadone dosing in 10mg increments as needed is recommended for patients initiating an NNRTI-based regimen.¹⁶

Ritonavir has shown widely varying effects on methadone levels, so the best advice is to monitor carefully for methadone withdrawal and increase the dose accordingly.

It can be difficult to distinguish between ARV side effects and symptoms of opioid withdrawal such as nausea and vomiting. Symptoms that develop within 2-3 days are probably from ARV toxicity. Symptoms that develop after 6 days are more likely to be from withdrawal.¹⁷

Drug interactions vary greatly from person to person:

Drug users are often falsely reassured by the reactions of other people they are using drugs with, and service providers should advise patients that interactions between street drugs and medications can be unpredictable and sometimes dangerous.¹⁸

If a person taking opioids experiences toxicity

(methadone toxicity or symptoms of opioid overdose) this may be because they have stopped taking their ARVs or are not adhering to the ARV regime. For example, efavirenz can cause dizziness, somnolence, insomnia, or confusion. If patients decrease or stop their ARV medication to avoid these side effects, they may be at risk for opioid toxicity. Methadone patients who have had their dose increased to when they are on efavirenz or nevirapine need to be monitored closely for possible methadone toxicity in case they go off these medications unexpectedly.¹⁹

PMTCT:

For drug-using pregnant women living with HIV who are not yet eligible for ART, the same ARV prophylactic regimens for PMTCT are recommended as for women who are not IDUs. If a pregnant woman receives NNRTI-based ART, the dose of methadone may need to be increased. Withdrawal symptoms generally occur 4-8 days following the start of NVP-based ART.

⁷ARVs and recreational drug interactions: overview, 21 April 2009

<http://i-base.info/ttfa/7-drug-users-and-hiv/7-5-arvs-and-recreational-drug-interactions-overview>

⁸Kaletra (lopinavir/ritonavir) product information. Abbott Laboratories, Abbott Park, Ill; October 2000; and Gerber JG, Rosenkranz S, Segal Y, et al. Effect of ritonavir/saquinavir on stereo selective pharmacokinetics of methadone: results of AIDS Clinical Trials Group (ACTG) 401. J Acquir Immune Defic Syndr. 2001;27:153-160; and Interactions Between Heroin and Antiretrovirals? Michael L. Lim, PharmD; Angela D.M. Kashuba, BScPhm, PharmD, DABCP

Posted: 04/17/2002, <http://www.medscape.com/viewarticle/431745>; and Valerie A. Gruber & Elinore F. McCance-Katz, Methadone, Buprenorphine, and Street Drug Interactions with Antiretroviral Medications, Curr HIV/AIDS Rep (2010) 7:152-160

⁹ARVs and recreational drug interactions: methadone, 21 May 2009

<http://i-base.info/ttfa/7-drug-users-and-hiv/7-8-arvs-and-recreational-drug-interactions-methadone>

¹⁰Henry JA, Hill IR. 1998. Fatal interaction between ritonavir and MDMA. Lancet 352:1751-1752, cited in Valerie A. Gruber & Elinore F. McCance-Katz, 2010. Methadone, Buprenorphine, and Street Drug Interactions with Antiretroviral Medications, Curr HIV/AIDS Rep 7:152-160 Published online: 8 June 2010

¹¹AIDS MAP, Interactions with Recreational Drugs, <http://www.aidsmap.com/Interactions-with-recreational-drugs/page/1280663/>

¹²AIDS MAP, Interactions with Recreational Drugs, <http://www.aidsmap.com/Interactions-with-recreational-drugs/page/1280663/>

¹³Greenblatt DJ, von Moltke LL, Harmatz JS, et al.: Alprazolam- ritonavir interaction: Implications for product labeling. Clin Pharmacol Ther 2000, 67:335-341 cited in Valerie A. Gruber & Elinore F. McCance-Katz, 2010. Methadone, Buprenorphine, and Street Drug Interactions with Antiretroviral Medications, Curr HIV/AIDS Rep 7:152-160 Published online: 8 June 2010

¹⁴ARVs and recreational drug interactions: methadone, 21 May 2009

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¹⁵AIDS MAP, Interactions with Recreational Drugs, <http://www.aidsmap.com/Interactions-with-recreational-drugs/page/1280663/>

¹⁶AIDS MAP, Interactions with Recreational Drugs, <http://www.aidsmap.com/Interactions-with-recreational-drugs/page/1280663/>

¹⁷ARVs and recreational drug interactions: methadone, 21 May 2009

<http://i-base.info/ttfa/7-drug-users-and-hiv/7-8-arvs-and-recreational-drug-interactions-methadone>

¹⁸Hamington RD, Woodward JA, Hooton TM, Horn JR. 1999. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and gamma-hydroxybutyrate. Arch Intern Med 159:2221-2224.

¹⁹Valerie A. Gruber & Elinore F. McCance-Katz, 2010. Methadone, Buprenorphine, and Street Drug Interactions with Antiretroviral Medications, Curr HIV/AIDS Rep 7:152-160 Published online: 8 June 2010