

Module 8

Drug Interactions

Treatment and Care for
HIV-Positive Injecting Drug Users



Module 8

Drug interactions

Participant Manual

2007



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Module 1: Drug use and HIV in Asia: participant manual

Module 2: Comprehensive services for injecting drug users – participant manual

Module 3: Initial patient assessment – participant manual

Module 4: Managing opioid dependence – participant manual

Module 5: Managing non-opioid drug dependence – participant manual

Module 6: Managing ART in injecting drug users – participant manual

Module 7: Adherence counselling for injecting drug users – participant manual

Module 9: Management of coinfections in HIV-positive injecting drug users – participant manual

Module 10: Managing pain in HIV-infected injecting drug users – participant manual

Module 11: Psychiatric illness, psychosocial care and sexual health – participant manual

Module 12: Continuing medical education – participant manual

Trainer manual: Treatment and care for HIV-positive injecting drug users

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Abbreviations and acronyms

3TC	lamivudine
ABC	abacavir
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
ASEAN	Association of Southeast Asian Nations
AZT	zidovudine (also ZDV)
CDC	Centers for Disease Control and Prevention (US Government)
CNS	central nervous system
CPK	creatine phosphokinase
CT	computed tomography scan
CYP	cytochrome P450
d4T	stavudine
ddC	zalcitabine
ddI	didanosine
dLV	delavirdine
EFV	efavirenz
FHI	Family Health International
FI	fusion inhibitors
fos-APV	fos-amprenavir
FTC	emtricitabine
GHB	gamma hydroxybutyrate
HIV	human immunodeficiency virus
IDUs	injecting drug users
IDV	indinavir
IRIS	immune reconstitution inflammatory syndrome
LFT	liver function test
LPV	lopinavir
MDMA	methylenedioxyamphetamine
MMT	methadone maintenance treatment
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors
NVP	nevirapine
OST	opioid substitution therapy
OTC	over the counter
PCP	<i>Pneumocystis jiroveci</i> pneumonia
PI	protease inhibitor
PLWHA	people living with HIV and AIDS
RTV	ritonavir
SQV	saquinavir
SSRI	selective serotonin reuptake inhibitors
T-20	enfuvirtide
TB	tuberculosis
TCA	tricyclic antidepressant
TDF	tenofovir
THC	tetrahydrocannabinol
USAID	United States Agency for International Development
WHO	World Health Organization
ZDV	zidovudine (also AZT)

Interactions between illicit drugs and ARVs

OVERVIEW



Objectives: By the end of the session participants will:

- Understand the mechanisms of drug interaction
- Be familiar with and able to use the standard table of interactions between illicit drugs and ARVs
- Be able to make clinical decisions using information on interactions between illicit drugs and ARVs



Time to complete session:

1 hour



Session content:

- Interactions between illicit drugs and ARVs
- Case study exercises to familiarize participants with the standard drug interaction tables



Training materials:

- PowerPoint presentation 8.1: Interactions between illicit drugs and ARVs
- Sub-module 8.1: Interactions between illicit drugs and ARVs
- Evaluation form

Table 1. Interactions between illicit drugs and ARVs

Drug	Interaction/effect	Recommendations
Amphetamines	↑ RTV levels, can increase toxicity	Do not prescribe RTV or RTV-containing regimens even in low doses if there is amphetamine use
Barbiturates	Barbiturates such as phenobarbital can induce CYP3A4 (i.e. more rapid drug clearance)	Consider avoiding other potent CYP3A4 inducers such as EFV or NVP in patients misusing barbiturates
Benzodiazepines (depending on the bdz used)	PIs can cause oversedation; NVP can cause withdrawal	Avoid concurrent use of alprazolam, midazolam and triazolam with all PIs, NVP and EFV
Cocaine	PIs and EFV ↑ levels – can cause overdose; NVP can cause hepatotoxic metabolite	Interactions can lead to increased hepatotoxicity; clinicians should monitor closely
Codeine	PIs can ↑ or ↓ metabolism and lead to: <ul style="list-style-type: none"> • possible overdose • possible loss of analgesia 	Interactions with ARVs are similar to those of methadone and other opioids; NNRTIs and some PIs may cause opiate withdrawal and loss of analgesia; clinicians should monitor closely
Heroin	NFV and RTV can cause withdrawal	Interactions with ARVs are similar to those of methadone and other opioids; NNRTIs and some PIs may cause opiate withdrawal and loss of analgesia; clinicians should monitor closely
MDMA (Ecstasy), GHB (gamma hydroxybutyrate)	RTV can ↑ drug levels and lead to toxicity	Clinicians should not prescribe PIs even in low doses if patients report MDMA or GHB use; MDMA/RTV use can be fatal
Morphine	NFV, RTV ⇒ withdrawal and loss of analgesia	Interactions with ARVs are similar to those of methadone and other opioids; NNRTIs and some PIs may cause opiate withdrawal and loss of analgesia; clinicians should monitor closely
Phencyclidine (PCP)	PIs and EFV can lead to toxicity	Use PIs cautiously and they may lead to PCP toxicity; clinicians should monitor closely
THC/marijuana	PIs may ↑ concentration; NNRTIs may ↓ concentration	No clinically significant interactions have been reported

Source: World Health Organization. *HIV/AIDS treatment and care for injecting drug users. Clinical protocol for the WHO European Region*. Copenhagen, Denmark, WHO 2006. (http://www.euro.who.int/document/SHA/WHO_Chapter_5_web.pdf).

Interactions between ARVs, opioid substitution therapy (OST) drugs and other medications commonly used to treat PLWHA

OVERVIEW



Objectives: By the end of the session the participants will:

- Be familiar with and able to use the standard table of interactions between ARVs and OST drugs
- Be familiar with and able to use the standard table of interactions between ARVs and other medications commonly used to treat PLWHA
- Be able to make clinical decisions using information on interactions between ARVs, OST drugs and other medications commonly used to treat PLWHA



Time to complete session:

1 hour 45 minutes



Session content:

- Interactions between ARVs and drugs used for OST
- Case study exercises to familiarize participants with the standard drug interaction tables
- Interactions between drugs commonly used to treat PLWHA and methadone and ARVs



Training materials:

- PowerPoint presentation 8.2: Interactions between ARVs, OST drugs and other medications commonly used to treat PLWHA
- Sub-module 8.2: Interactions between ARVs, OST drugs and other medications commonly used to treat PLWHA

Table 2. Interactions between ARVs and drugs used for opioid substitution therapy (OST)

Medication	Methadone		Buprenorphine	
	Effect on methadone	Effect on medication	Effect on buprenorphine	Effect on medication
NRTIs				
Abacavir (ABC)	↑ Methadone clearance	↑ Time to peak concentration; ↓ Peak concentration	Unknown, but interaction unlikely	Unknown, but interaction unlikely
Didanosine (ddl)	None reported	↓ ddl concentration by 57%, possible underdosing	Unknown, but interaction unlikely	Unknown, but interaction unlikely
Emtricitabine (FTC)	Not studied	Not studied	Unknown, but interaction unlikely	Unknown, but interaction unlikely
Lamivudine (3TC)	None	None	Unknown, but interaction unlikely	Unknown, but interaction unlikely
Stavudine (d4T)	None	↓ d4T concentration by 27%	Unknown, but interaction unlikely	Unknown, but interaction unlikely
Tenofovir (TDF)	None	None	Unknown, but interaction unlikely	Unknown, but interaction unlikely
Zalcitabine (ddC)	Not studied or reported	Not studied or reported	Unknown, but interaction unlikely	Unknown, but interaction unlikely
Zidovudine (AZT)	None	↑ AZT concentration by 43%, can precipitate AZT toxicity	No change in buprenorphine levels	No change in AZT levels
NNRTIs				
Delavirdine (dLV)	None	None	Potential ↑ in buprenorphine activity	No data, but change in dLV not expected
Efavirenz (EFV)	↓ Methadone levels by 52%; withdrawal symptoms; heroin use relapse; need for ↑ methadone	Not studied or reported	↓ buprenorphine concentrations	none
Nevirapine (NVP)	Methadone levels ↓ by 46%; withdrawal symptoms; need for ↑ methadone dose observed	Not studied or reported	Potential ↓ in buprenorphine activity	No data, but change in NVP not expected

Table 2 (contd.). Interactions between ARVs and drugs used for opioid substitution therapy (OST)

Medication	Methadone		Buprenorphine	
	Effect on methadone	Effect on medication	Effect on buprenorphine	Effect on medication
Protease inhibitors				
Ampranavir (APV)	↓ Active methadone levels by 13%, but no withdrawal symptoms observed	↓ APV concentration by 25%	Potential ↓ in buprenorphine activity	No data, but change in APV not expected
Atazanavir (ATV)	Not studied	Not studied	Not studied	No change expected
Fosamprenavir (fos-APV)	↓ Methadone levels by 13%, but no withdrawal symptoms observed	↓ APV concentration by 25%	Potential ↑ in buprenorphine activity	No data, but change in fos-APV not expected
Indinavir (IDV)	None	None	Potential ↑ in buprenorphine activity	No data, but change in IDV not expected
Lopinavir/ritonavir (LPV/r)	↓ Methadone levels reported; conflicting data – monitor for possible ↑ in methadone dose	Not studied or reported	Potential ↑ in buprenorphine activity	No data, but change in LPV/r not expected
Nelfinavir (NFV)	↓ Methadone levels, but conflict in data; monitor for need to ↑ methadone dose	None	Potential ↑ in buprenorphine activity	No data, but change in NFV not expected
Ritonavir (RTV)	Modest ↑ in methadone levels	None reported	Potential ↑ in buprenorphine activity	No data, but change in RTV not expected
Saquinavir (SQV)	Methadone R-isomer ↓ 32%; monitor for need to ↑ methadone dose	None reported	Potential ↑ in buprenorphine activity	No data, but change in SQV not expected
Fusion inhibitors (FI)				
Enfuvirtide (T-20)	Not studied; interaction unlikely	Not studied; interaction unlikely	Not studied; interaction unlikely	Not studied; interaction unlikely

Source: Copyright © New York State Department of Health AIDS Institute, 2000–2007 (<http://www.hivguidelines.org/Content.aspx?PageID=335&guideLineID=50&guideParent=&vType=&pGuideLineID=50>).

Table 3. Interactions between drugs commonly used to treat PLWHA and methadone and ARVs

Medication	Actions/uses	Interaction with methadone	Interaction with ARV medications
Psychotropic medications			
Alprazolam (benzodiazepine)	Sedative	May result in unpredictable interaction Additive CNS depression and possible excessive sedation	Alprazolam clearance decreased by 41%; Clinicians should avoid concurrent use of certain benzodiazepines (alprazolam, midazolam and triazolam) with all PIs and EFV
Desipramine	Tricyclic antidepressant (TCA)	May result in unpredictable interaction Possible increased TCA toxicity Associated with cardiac rhythm disturbances and should be used cautiously with methadone	Desipramine clearance decreased by 59%
Fluoxetine (SSRI)	Treatment of depression and compulsive disorders	Decreased methadone levels reported in preclinical studies Associated with cardiac rhythm disturbances and should be used cautiously with methadone	Ritonavir increased by 19%
Fluvoxamine (SSRI)	Treatment of depression and compulsive disorders	Increased methadone levels reported	No effect reported in preclinical study
Sertraline (SSRI)	Treatment of depression and compulsive disorders	Increases methadone levels by 26%, without increase in side-effects Associated with cardiac rhythm disturbances, caution when used with methadone	Not studied or reported
St John's wort (herb)	Antidepressant	Significant decrease in methadone levels reported and may cause withdrawal	IDV decreased by 57%; do not co-administer to patients taking PIs or NNRTIs
Valproic acid	Anticonvulsant	None reported	AZT increased in preclinical studies

Table 3 (contd.). Interactions between drugs commonly used to treat PLWHA and methadone and ARVs

Medication	Actions/uses	Interaction with methadone	Interaction with ARV medications
Other medications			
Carbamazepine	Anticonvulsant	Decreased methadone levels May cause opioid withdrawal Methadone dose increase may be required Consider using valproic acid as an alternative	Some interactions (see <i>Clinical protocol on use of antiretrovirals in HIV-infected adults and adolescents</i>). Monitor for toxicities and dose adjustments.
Fluconazole	Antifungal antibiotic	Increased methadone levels (35%) Clinical significance unknown, although cases requiring dose reduction reported No signs of methadone toxicity reported Other azole antifungal antibiotics may potentially influence opioid toxicity (e.g. itraconazole, ketoconazole, voriconazole)	Potential for bidirectional inhibition between some azole antifungal antibiotics and PIs. Monitor for toxicities and dose adjustments. Toxicity and antifungal outcomes observed with NNRTIs. Refer to <i>Clinical protocol on use of antiretrovirals in HIV-infected adults and adolescents</i> .
Phenobarbital (barbiturate)	Anticonvulsant barbiturate sedative	Decreases methadone levels, often sharply May cause withdrawal Methadone dose increase may be required	Barbiturates such as phenobarbital are potent inducers of CYP3A4. Clinicians should consider avoiding concurrent administration of other potent inducers (e.g. EFV and NVP) in patients misusing barbiturates
Phenytoin	Anticonvulsant Control of seizures	Decreases methadone levels, often sharply May cause withdrawal Methadone dose increase may be required	Some interactions (see <i>Clinical protocol on use of antiretrovirals in HIV-infected adults and adolescents</i>). Monitor for toxicities and dose adjustments.
Interferon-alfa + ribavirin	Anti-hepatitis C treatment	Side-effects can mimic opioid withdrawal symptoms and methadone dose is often increased	Hepatitis C infection can aggravate the potential hepatotoxicity of several ARV regimens (refer to <i>Clinical protocol on hepatitis C and HIV coinfection; section 3.3.1 Interactions between anti-HIV and anti-HCV drugs</i>).

Table 3 (contd.). Interactions between drugs commonly used to treat PLWHAs and methadone and ARVs

Medication	Actions/uses	Interaction with methadone	Interaction with ARV medications
Rifabutin	Treatment of pulmonary TB	No change in methadone levels Mild narcotic withdrawal symptoms	Some interactions (see <i>Clinical protocol on use of antiretrovirals in HIV-infected adults and adolescents</i>) but rifabutin may be a preferred option for the treatment of pulmonary TB as an alternative to rifampicin. Monitor for toxicities and dose adjustments.
Rifampicin (Rifampin)	Treatment of pulmonary TB	Possibly severe decrease in methadone levels (33–68%) May induce methadone withdrawal Methadone dose increase may be required	Methadone dosage may need to be increased PIs contraindicated Rifampicin should not be co-administered with LPV, NFV, SQV Rifabutin may be a potential alternative (see above)
Sildenafil	Erectile dysfunction agent	Not reported	No effect of sildenafil on PI Ritonavir increases sildenafil level 10-fold Saquinavir increases sildenafil level 3-fold Use cautiously (lowest dose every 48 hours) and monitor for adverse effects

Source: World Health Organization. *HIV/AIDS treatment and care for injecting drug users. Clinical protocol for the WHO European Region*. Copenhagen, Denmark, WHO, 2006. (http://www.euro.who.int/document/SHA/WHO_Chapter_5_web.pdf).

Presentation 8.1: Interactions between illicit drugs and ARVs

Interactions between illicit drugs and ARVs

Session objectives

- Understand the mechanisms of drug interaction
- Be familiar with and able to use the standard table of interactions between illicit drugs and ARVs
- Be able to make clinical decisions using information on interactions between illicit drugs and ARVs

Internet sources for drug interactions

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

Why are drug interactions important?

Drug interactions can lead to:

- Suboptimal ART
- Toxicity

Always ask your patient about other medications including over-the-counter (OTC) and herbal medicines.

Source: From David Burger. *Drug interactions in the treatment of HIV*.

Mechanisms of drug interactions

- Absorption
- Distribution
- Metabolism
- Excretion

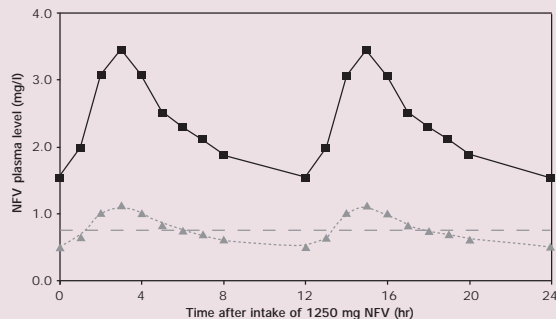
Source: From David Burger. *Drug interactions in the treatment of HIV*.

Absorption

- A number of ARVs need a low pH in the stomach to get dissolved and be absorbed:
 - ◆ IDV
 - ◆ ATV
- Substances that reduce stomach acid may reduce absorption of IDV, ATV:
 - ◆ Antacids
 - ◆ H₂-receptor antagonists (e.g. ranitidine)
 - ◆ Proton pump inhibitors (e.g. omeprazole)
 - ◆ ddl chewable tablets (buffered)
- Food increases stomach acid

Source: From David Burger. *Drug interactions in the treatment of HIV*.

The influence of food on the pharmacokinetics of NFV



Source: Trubetskoy O. Are humans really are what they eat? Complexity of human drug metabolism. <http://sprrott.physics.wisc.edu/Chaos-Complexity/olga.ppt#287,1>, Are humans really are what they eat?

Metabolism

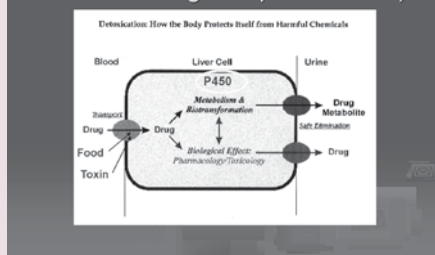
A family of liver enzymes

- Cytochrome P450 (CYP) are a family of liver enzymes that break down drugs
- Six sub-families:
 - ◆ CYP1A, CYP2A, CYP2C, CYP2D, CYP2E, CYP3A
- CYP 3A: breaks down 50% of drugs
 - ◆ All PIs and NNRTIs
 - ◆ Methadone and buprenorphine
 - ◆ Midazolam
 - ◆ Cocaine
- CYP2D: breaks down amphetamines

Source: Trubetskoy O. Are humans really are what they eat? Complexity of human drug metabolism. <http://sprrott.physics.wisc.edu/Chaos-Complexity/olga.ppt#287,1>, Are humans really are what they eat?

Drug metabolism

Drug metabolism process (defense mechanism against plants' toxins)



Source: Trubetskoy O. Are humans really are what they eat? Complexity of human drug metabolism. <http://sprrott.physics.wisc.edu/Chaos-Complexity/olga.ppt#287,1>, Are humans really are what they eat?

Inducing and inhibiting drug metabolism

Drugs that induce CYP3A – faster metabolism of other drugs → ↓ blood levels

- NVP & EFV → ↑CYP3A → faster metabolism of methadone → withdrawal
 - Rifampin, carbamazepine, phenytoin, barbiturates
- Drugs that inhibit CYP3A → slower metabolism of other drugs → ↑ blood levels
- Ketoconazole → ↓CYP3A → slower metabolism of ARVs → ↑ blood levels
→ slower metabolism of midazolam → ↑ blood levels
 - Itraconazole, isoniazid

PIs can induce or inhibit CYP3A

What is the danger?

- Drug interactions – protease inhibitors (PIs) and commonly used NNRTIs, such as efavirenz (EFV) and nevirapine (NVP), either INDUCE or INHIBIT the cytochrome P450 system of the liver, the system responsible for the metabolism of illicit drugs.

Interactions between illicit drugs and ARVs

Please refer to the table in this module – Table 1: Interactions between illicit drugs and ARVs. Take note of the key interactions and use the case studies to familiarize yourself with the use of the table.

Which illicit drugs should be of concern?

Benzodiazepines

- Midazolam
- Triazolam
- Alprazolam
- Flunitrazepam

Opioids

- Heroin
- Methadone
- Codeine
- Morphine
- Hydrocodone
- Oxycontin and other analgesics

Which illicit drugs should be of concern?

- Cocaine
- Amphetamines
- MDMA (Ecstasy)
- Gamma hydroxybutyrate (GHB)
- Ketamine (K, special K)
- Phencyclidine (PCP)

Benzodiazepines and PIs-1

- When used with PIs, metabolism of certain benzodiazepines is INHIBITED.
- Over dosage, somnolence, drowsiness and build-up of metabolites can occur.
- Does not occur with all benzodiazepines, but particularly with triazolam, midazolam, alprazolam and flunitrazepam.

Benzodiazepines and PIs-2

- If a patient complains of sleep disorder, anxiety or asks for sleeping pills – consider benzodiazepines. DUs often will not volunteer the name of the medication they are using.
- When prescribing PIs to these suspected patients, be aware of increased drowsiness and confusion.

Benzodiazepines and NVP-1

- NVP is a cytochrome P450 INDUCER and will increase the clearance of certain benzodiazepines: triazolam, midazolam, alprazolam and flunitrazepam.
- Can facilitate withdrawal and dangerous dose escalation by the patient.

Benzodiazepines and NVP-2

- If a patient complains of sleep disorder, anxiety or asks for sleeping pills – consider benzodiazepines. DUs often will not volunteer the name of the medication they are using.
- When prescribing NVP to these suspected patients, be aware of increased agitation and withdrawal symptoms, even seizures from increased clearance of the benzodiazepine.

Cocaine and ARVs

- Cocaine is used either as a single drug or in conjunction with others, such as heroin.
- PIs INHIBIT cytochrome P450 action and can lead to slower cocaine metabolism and overdose / toxicity.
- NVP INDUCES cytochrome P450 action and can cause an excess of possibly hepatotoxic metabolites.

Amphetamines, MDMA (Ecstasy) and ARVs

- Interactions with PIs may cause INHIBITION and slower metabolism of these drugs and therefore toxicity.

Heroin, illicit opioids and ARVs

- Expect to see similar reactions as between methadone and ARVs
- NNRTIs (EFV and NVP) and PI (ritonavir-containing drugs) can cause significantly more rapid withdrawal
- The result can be increased, dangerous self-use of higher doses of opioids and overdose, toxicity and death

THC (cannabis) and ARVs

- Thus far, there are no reports of drug-to-drug interaction between ARVs and marijuana.
- Still, we must be aware of cannabis and possible issues such as complacency, memory loss and compliance.

Case study 1

A 31-year-old man has recently started on second-line ART. In his medical history he states that he has always been an anxious person, but he claims he has had his anxiety under control for several years now. He denies recreational drug use.

Case study 1 (cont.)

He is started on second-line ART with ddl, abacavir (ABC) and LPV/r. One week later he comes to his first follow-up appointment. He seems quite relaxed, in fact, inappropriately so. He says he has been 100% adherent, but he sleeps almost all day now, and he thinks it is a side-effect of the ARVs. He comes in two weeks later for an emergency appointment and is brought in by a friend because he is lethargic and confused.

Case study 1 (cont.)

His friend has brought in all the medications as well, and there is an extra bottle of pills, but they are unlabelled.

- What do you suspect has occurred?
 - ◆ ARV toxicity?
 - ◆ CNS event or infection?
 - ◆ Immune reconstitution inflammatory syndrome (IRIS)?
 - ◆ Illicit drug use?
- If illicit drug use, what type of drug?

Case study 1 – discussion

ARV toxicity: somnolence is not a typical early side-effect of ddi/ABC/LPV-r

CNS event or infection: unlikely with CD4 count over 200 cells, but certainly should be considered in the differential diagnosis

CNS IRIS: possible but a little early (only day 7)

Case study 1 – discussion

Illicit drug use:

We have evidence of an unmarked medication and a history and behaviour that should have raised suspicion in the prescribing physician, if not at the initial visit, then at the second one.

Case study 1 – discussion (cont.)

Extremely anxious patients should be questioned in a strong, but caring and trust-inspiring way to be truthful about every medication or drug that they ingest. They should be warned that drug interactions with ARVs are very common and very dangerous.

Case study 1 – discussion (cont.)

What type of drug do you suspect?

- Somnolence is a side-effect of opioids and benzodiazepines. You check for old and new track marks. There are none.
- You examine the extra bottle of pills.
- They are consistent with alprazolam (Xanax), an anxiolytic drug readily obtainable over-the-counter in many countries, as well as through the internet.

Case study 1 – discussion (cont.)

What is your line of management?

- Check a urine drug screen to rule out the concomitant use of other illicit drugs. Benzodiazepines are often used to counter the stimulant effects of cocaine and amphetamines. Result: +++ benzodiazepine, negative for cocaine, amphetamine or opioids

Case study 1 – discussion (cont.)

What is your line of management?

- Close inpatient observation of the patient is warranted as he is weaned off of alprazolam. He is physically stable so no drug reversal is needed (e.g. romazicon injection).

Case study 1 – discussion (cont.)

What is your line of management?

- An alternative benzodiazepine should be substituted and slowly removed (along with drug counselling) to prevent withdrawal effects and possible seizures. A drug that does not interact with ARV medications is preferable.
- Avoid using: midazolam, triazolam or flunitrazepam

Case study 1 – discussion (cont.)

What is your line of management?

- His physician continued his ART under close observation and used a slowly lessening dose of diazepam to manage withdrawal and prevent seizure. There was no interruption in ART which could have caused possible HIV mutation and drug resistance.

Case study 1 – resolution

- Illicit drug use and HIV infection are common and these situations need to be considered in every patient.
- Have a strong index of suspicion regarding your patient's history. Use a firm but caring approach.
- If at all possible and safe, attempt to manage the situation without disrupting ART compliance, as in many instances, second-line ARVs may not be available.

Case study 2

- A 23-year-old woman with a history of injecting heroin presents to the clinic for management of HIV infection. Her CD4 count is 157 cells/mm³. She admits to previous heroin use, but claims that she is now drug-free.

Case study 2 (cont.)

- She admits she has relapsed on and off heroin for a year, but she is now in counselling and a peer support group and ready to take charge of her life, including getting treatment for HIV. She claims that she contracted HIV through injecting drug use at least five years ago. She has not tried OST with methadone or buprenorphine. She wants to be drug-free entirely.

Case study 2 (cont.)

- An ART work-up is performed, as well as a urine drug screen. The drug screen is negative for illicit drugs. Her other laboratory tests are normal and she is prescribed d4T/3TC/EFV combination. She is accurately counselled against becoming pregnant while on EFV.

Case study 2 (cont.)

- She seems to do well for three months on treatment and then reports to her physician that she has relapsed and begun using heroin again. Now she is using heroin daily, and admits it is heavy use.
- She has been, however, 100% compliant with ART.

Case study 2 (cont.)

- Her physician feels she is no longer capable of compliance and stops her ART.
- He tells her he will consider starting again when she is clean and sober.

Case study 2 (cont.)

- Three days later she is brought into the clinic nearly unresponsive, clearly overdosed. She is revived with naloxone and admitted for supportive care.

Questions:

- **What may have precipitated an overdose?**
- **How might this situation have been better handled?**

Case study 2 (cont.)

What may have precipitated the drug overdose?

- Desperate behaviour?
- The use of other illicit drugs with heroin (commonly cocaine)
- Stoppage of a drug interaction with the discontinuation of ART

What may have precipitated the drug overdose?

- While desperate behaviour and concomitant illicit drugs have to be taken into consideration, there is an important drug interaction here between **EFV** and opioids (including heroin).
- **EFV** significantly enhances the clearance and thus decreases the concentration of opioids in the body. While she was taking **EFV** she required larger doses of heroin to get the same feeling of being intoxicated.

What may have precipitated the drug overdose?

- When EFV was discontinued, clearance of the heroin was slowed to normal and no longer enhanced. It took only a few days to build up and reach toxic, overdose levels.

How might this situation have been better handled?

- Because of HIV mutation and potential drug resistance (as well as the resultant unforeseen drug interaction), great effort should be made to maintain compliance and not discontinue an effective ARV regimen. In many countries there is no effective second-line treatment.
- Illicit drug use is not an absolute reason to discontinue an ARV regimen. Non-compliance is.

How might this situation have been better handled?

- Each case must be judged by its facts. Potentially, this patient could have accepted her addiction and been placed on OST (methadone or buprenorphine, with note of their interactions with EFV).

How might this situation have been better handled?

- If she had been showing reckless behaviour, trying to conceal her use, not showing up at appointments or showing signs of non-compliance, THEN a planned discontinuation with knowledge of her heroin use could have been done.

How might this situation have been better handled?

- Do not use illicit drug use as an absolute indicator of non-compliant behaviour. Many IDUs maintain both their dangerous illicit drug use AND a compliant ART schedule.
- Taking care to evaluate their behaviour will help you decide if they are candidates for ART.

Knowledge of the patient's illicit drug use will help you choose potential ARVs with the least possibility of drug interactions.

Providing a firm but caring and trusting, approach will give the physician more information about a patient's habits and allow for better choices in prescribing ART.

Presentation 8.2: Interactions between ARVs, OST drugs and other medications commonly used to treat PLWHA

Interactions between ARVs, opioid substitution therapy (OST) drugs and other medications commonly used to treat PLWHA

Session objectives

- Be familiar with and able to use the standard table of interactions between methadone and buprenorphine and ARVs
- Be familiar with and able to use the standard table on interactions between other key drugs used to treat PLWHA and ARVs
- Be able to make clinical decisions using information on interactions between ARVs, OST drugs and medications commonly used to treat PLWHA

For this session refer to the two standardized tables accompanying sub-module 8.2:

Table 2: Interactions between ARVs and opioid substitution therapy (OST) medications

Table 3: Drug interactions between medicines commonly used to treat PLWHA and methadone and ARVs

Please note the key interactions and use the case studies to become familiar with the use of the tables.

Interactions between ARVs and methadone and buprenorphine

Methadone and buprenorphine

Methadone and buprenorphine:

- ◆ Are the most common drugs prescribed for OST
- ◆ Significant interactions with some of the most commonly used ARVs

Refer to Table 2 in Sub-module 8.2

- ◆ Use the table to check for drug interactions
- ◆ Additional information is available on web sites

AZT and methadone

- AZT does not change methadone levels in the bloodstream
- Methadone significantly increases the blood concentration of AZT (43%)
- Watch for possible increases in AZT toxicity: anaemia, myalgia, bone marrow suppression, fatigue, headache and vomiting

EFV and methadone

- Efavirenz (EFV) can significantly decrease the concentration of methadone in the blood by 60%
- Can cause methadone withdrawal
- Withdrawal can be delayed and possibly not seen until 2–3 weeks after starting the EFV
- May require a methadone dose increase of 50%

NVP and methadone

- Nevirapine (NVP) can significantly decrease the blood concentration of methadone (46%)
- Methadone withdrawal common
- Withdrawal can be delayed and possibly not seen until 2–3 weeks after starting NVP
- May need a methadone dose increase of approximately 15%

PIs and methadone

- Remember: PIs can induce or inhibit CYP3A
- PIs can induce CYP3A → faster metabolism of other drugs → ↓ blood levels
- PI → ↑CYP3A → faster metabolism of methadone → withdrawal

PIs can inhibit CYP3A → slower metabolism of other drugs → ↑ blood levels

- PI → ↓ CYP3A → slower metabolism of methadone → toxicity

Ritonavir and methadone

- Ritonavir (RTV) can significantly decrease methadone levels in the blood by 26–53%
- Can cause methadone withdrawal
- Withdrawal symptoms can be delayed by 2–3 weeks
- Side-effects of RTV may mimic withdrawal symptoms

Case study 1

- Refer to the case study in the following slides
- Discuss in pairs for 10 minutes
- Use Table 2 in Sub-module 8.2
- Answer each question
- Report answers back to session trainer

Case study 1 (cont.)

- 28-year-old woman with HIV
- IDU for 12 years
- Methadone maintenance – 50 mg/day for one year
- Peer support group for addiction
- HIV test positive five years ago
- CD4 count of 105 cells/mm³
- Previously fearful of ART but now willing

Case study 1 (cont.)

- Baseline tests
- Strong counselling on adherence
- Started on:
 - ◆ AZT+3TC twice daily
 - ◆ NVP once daily for two weeks
- Follow-up appointment at two weeks (with plan to increase NVP to twice a day)

Case study 1 (cont.)

At two-week follow-up appointment:

- Looks thinner
- Complains of feeling a bit weak and nauseated, but able to get through her days even though tired
- Increased muscle pains in her legs
- Sleep is not quite normal
- She thinks she just has to get used to the medication
- Reports adherence has been 100%

Case study 1 questions

- What drug-to-drug interactions are you concerned about?
- Is this a classic picture of side-effects of AZT?
- Do you make any changes to her medication regimen?
- What else needs to be considered in her case?

What drug–drug interactions are you concerned about?

- Methadone can greatly increase AZT levels in her blood
- AZT toxicity – nausea, vomiting, weakness, headache
- AZT does not affect methadone levels
- NVP can decrease methadone levels; methadone withdrawal – chills, sweating, nausea, diarrhoea, stomach cramps, muscle aches, anxiety
- Methadone: no reported effect on NVP

Is this a classic picture of AZT toxicity?

- AZT toxicity can cause clinically significant muscle aches, nausea, fatigue and anaemia
- BUT two weeks' use is probably a little early for a full AZT toxicity profile

Do you make any changes to her medication regimen?

- Due for NVP dose
- Will worsen the methadone / NVP drug interaction and cause early withdrawal symptoms
- Consider a modest increase in methadone dose – 5 to 10 mg per day
- Follow closely for improvement in symptoms
- Probably too early to discontinue AZT unless there is severe anaemia or evidence of aberrant muscle breakdown (high increase in creatine phosphokinase [CPK])

What else needs to be considered in her case?

- As with all patients with CD4 count < 200 cells/mm³, she may be having symptoms of a developing OI.
- She has not yet been started on co-trimoxazole for *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis. She should be.
- Was she already anaemic when she started AZT? It needs to be considered.
- Is she taking any other drugs or supplements that she has not mentioned? Many “natural” and prescribed remedies can also interact with ARVs and OST.

Case study 2

- 25-year-old woman with HIV
- CD4 count of 220 cells/mm³
- On d4T/3TC/EFV one year
- Diagnosed with pulmonary TB
- Treated with four-drug TB regimen including rifampicin
- Long-term daily heroin injector
- Despite heroin use, clinical indicators show she is adherent with both her TB and HIV medications

Case study 2 (cont.)

At about two months into TB treatment:

- Wants to stop using heroin
- Receiving psychological counselling
 - ◆ Wants to improve her life
 - ◆ Thinking about having children one day
- Requests methadone maintenance treatment (MMT)

Case study 2 (cont.)

- Started on standard methadone initiation dose of 30 mg per day
- Seems to experience severe withdrawal symptoms
- She says that if she knew she would feel this bad, she would never have quit heroin and if it does not get better, she will have to start using it again

Case study 2: questions

- What drug–drug interactions are occurring here?
- How can this scenario be avoided?
- Do you make any changes to her medication regimen?
- What important points should be considered at her follow-up appointments?

Case study 2: questions (cont.)

What drug–drug interactions are occurring here?

- Methadone and rifampicin

Rifampicin, used in nearly all TB treatment regimens, can severely decrease methadone levels (33–68%).

This patient’s methadone dose may need to be increased due to this interaction.

Case study 2: questions (cont.)

What drug–drug interactions are occurring here?

- Methadone and efavirenz (EFV)

EFV (and most NNRTIs) can severely decrease levels of methadone (up to 60%).

This patient's methadone dose may need to be increased due to this interaction (and may need up to a 50% dose increase at times!).

How can this scenario be avoided?

- We must try to foresee drug interactions when HIV, TB and opioid dependence are being treated together. This is a COMMON situation:
 - ◆ HIV and TB are common coinfections
 - ◆ Injecting drug use and TB are common co-occurrences
 - ◆ HIV and Injecting drug use are common co-occurrences

How can this scenario be avoided? (cont.)

Failure to anticipate drug–drug reactions with injecting drug use and coinfection treatment can result in:

- Poor compliance
- Undertreatment of all coinfections
- Patient's loss of confidence in your treatment
- Reversion to injecting drug use due to poor control of the withdrawal symptoms

Do you make any changes to her medication regimen?

- Gradual increase of methadone (5–10 mg) every 1–2 days until withdrawal symptoms are controlled.
- This must be closely monitored to assure compliance and prevent accidental overdosing of methadone.

Do you make any changes to her medication regimen?

- Rifabutin can be substituted for rifampicin.
- Rifabutin WILL NOT affect the dosing of methadone.
- Eventually TB treatment will be discontinued (6–9 months), so you must anticipate a possible dose decrease in methadone when rifampicin is discontinued.

Do you make any changes to her medication regimen?

If she wants to proceed with plans for pregnancy, EFV will have to be discontinued and replaced most likely with NVP. NVP interactions with methadone also need to be considered in any change in ARV.

Case study 3

- A 28-year-old HIV-positive man comes to the clinic for management of severe oral / oesophageal candidiasis. He also is positive for cryptococcal antigen. His CD4 count is 75 cells/mm³. He is a former IDU, but he has been on OST successfully for six months. He is not yet on ART.

Case study 3 (cont.)

He is prescribed fluconazole 200 mg per day. He also currently is under consideration for ART and is awaiting evaluation of his LFT and renal function. He is placed on co-trimoxazole for PCP prophylaxis. One week later he begins to show mental status changes, sedation and inability to focus.

Case study 3: questions

- What is the potential cause of the changes in his mental status?
- What changes in his medication, if any, are needed?
- Can ART still be prescribed in this situation?

What is the potential cause of the changes in his mental status?

- Cryptococcal meningitis or possible other CNS opportunistic infection (CD4 count <85 cells/mm³)
- Concomitant use of another sedative (prescribed or illicit drug)
- **Interaction between fluconazole and methadone**

What is the potential cause of the changes in his mental status?

Lumbar puncture and CT are performed. They are both negative. Urine drug screen is performed. Only positive for methadone. This is a clear case of methadone potentiation by fluconazole.

Fluconazole and methadone interaction

- Fluconazole can increase methadone levels up to 35%.
- Fluconazole is VERY commonly used in addition to ARVs.

What changes are needed in his medications?

- Approximately a week after starting fluconazole a reduction in methadone dose may be needed. Methadone is a long-acting opioid and clinical signs may thus lag behind. Be prepared to follow the patient closely after initiating fluconazole therapy.

What changes are needed in his medications?

- Changing to a different azole antifungal medication will not make a difference. Methadone interacts similarly with other antifungals: itraconazole, ketoconazole and voriconazole.

Can ARVs still be prescribed in this situation?

- Certainly.
- But be aware of further interactions if ARVs such as AZT, NVP or EFV are used.
- Attempt to use regimens that will be effective but produce the least amount of drug–drug interaction.

Buprenorphine and ARVs

- Buprenorphine is now being used instead of methadone for OST in some countries.
- It is a shorter-acting opioid with both agonist and antagonist properties.
- Buprenorphine may cause less drug–drug interactions with ARVs than methadone.

Buprenorphine and ARVs

- Not as well studied as methadone and ARVs
- Probably has similar interactions and should be used with close observation when using EFV, NVP as with methadone
- Does not seem to interact with ZDV
- May have an interaction with RTV
- Watch closely when using buprenorphine with the following drugs: fluconazole, rifampicin, phenytoin, carbamazepine and benzodiazepines

Treatment and Care for HIV-Positive Injecting Drug Users

The “Treatment and Care for HIV-Positive Injecting Drug Users” training curriculum is designed for clinicians who provide treatment and care, including ART, for HIV-positive injecting drug users. The training curriculum consists of a trainer manual, 12 participant manuals, and a CD-ROM with PowerPoint presentations and reference articles. Topics covered in the curriculum include:

Module 1: Drug use and HIV in Asia

Module 2: Comprehensive services for injecting drug users

Module 3: Initial patient assessment

Module 4: Managing opioid dependence

Module 5: Managing non-opioid drug dependence

Module 6: Managing ART in injecting drug users

Module 7: Adherence counselling for injecting drug users

Module 8: Drug interactions

Module 9: Management of coinfections in HIV-positive injecting drug users

Module 10: Managing pain in HIV-infected injecting drug users

Module 11: Psychiatric illness, psychosocial care and sexual health

Module 12: Continuing medical education

Trainer manual

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