Participant Manual

Module 6

Managing ART in Injecting Drug Users

Treatment and Care for HIV-Positive Injecting Drug Users

asean
USAID FROM THE AMERICAN PEOPLE
World Health Organization
Regional Office for South-East Asia
fhi Family Health International

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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 7: Adherence counselling for injecting drug users: participant manual

Module 8: Drug interactions: participant manual

Module 9: Management of co-infections 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
ALT	alanine aminotransferase
APV	amprenavir
ART	antiretroviral therapy
ARV	antiretroviral
ASEAN	Association of Southeast Asian Nations
AST	aspartate aminotransferase
ATV/r	ritonavir-boosted atazanavir
ATZ	atazanavir
AUC	area under the curve
AZT	zidovudine (also ZDV)
BSL	blood sugar level
CAD	coronary artery disease
CBC	complete blood count
CCF	congestive cardiac failure
CDC	Centers for Disease Control and Prevention (US Government)
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinase
CSF	cerebrospinal fluid
CTL	cytotoxic T-lymphocyte
CXR	chest X-ray
d4T	stavudine
ddc	zalcitabine
ddI	didanosine
DOT	directly observed treatment
DU	drug user
EFV	efavirenz

ENT	ear, nose and throat
FBC	full blood count
FDA	Food and Drug Administration (US Government)
FDC	fixed-dose combination
FHI	Family Health International
FTC	emtricitabine
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
GGT	gamma-glutamyltransferase
GI	gastrointestinal
HAV	hepatitis A virus
HBC	home-based care
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HREZ	TB drug treatment regimen involving 4 drugs (H=isoniazid, R= rifampicin, E= ethambutol, Z= pyrazinamide)
IDU	injecting drug user
IDV	indinavir
INH	isoniazid
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function tests
LPV	lopinavir
MAC	*Mycobacterium avium* complex
MCV	mean corpuscular volume
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NVP	nevirapine
OGTT	oral glucose tolerance test

OI	opportunistic infection
OPC	outpatient clinic
OST	opioid substitution therapy
Pap	Papanicolaou
PCP	*Pneumocystis jiroveci* pneumonia
peg-INF	pegylated interferon
PI	protease inhibitor
PLWHA	people living with HIV and AIDS
PML	progressive multifocal leukoencephalopathy
PMTCT	prevention of mother-to-child transmission
PZA	pyrazinamide (TB drug)
RMP	rifampicin
RPR	rapid plasma reagin (syphilis test)
RTV	ritonavir
SAE	serious adverse event
SASO	Social Awareness Service Organization
SIV	simian immunodeficiency virus
SJS	Stevens–Johnson syndrome
STI	sexually transmitted infection
SQV	saquinavir
TAM	thymidine analogue mutation
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TDM	tetradecylmaltoside
TEN	toxic epidermal necrolysis
TG	triglyceride
TLC	total lymphocyte count
ULN	upper limit of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	United States Agency for International Development
VCT	voluntary counselling and testing
VL	viral load
VZV	varicella-zoster virus
WCC	white cell count
WHO	World Health Organization

Sub-module

6.1

IDU access to ART

OVERVIEW

Objectives:

By the end of the session participants will be able:

- To describe the current access of IDUs to ART programmes
- To explore personal beliefs and preconceptions about IDU access to ART
- To identify some of the barriers restricting access of IDUs to HIV care and treatment programmes including ART
- To understand and describe the evidence refuting some of the commonly held perceptions about IDUs and ART, which currently prevent IDUs from accessing ART programmes
- To begin to explore some of the successful models for providing quality ART to IDUs

Time to complete session:

1 hour 15 minutes

Session content:

- Epidemiology of HIV infection in IDUs
- Access of IDUs to ART programmes around the world
- Guidelines governing equitable access to ART
- Barriers to accessing ART for IDUs
- HIV Treatment efficacy data
- Adherence, resistance and injecting drug use
- Directly observed ART, IDUs and adherence
- Importance of the ART provider
- Some models that support ART for IDUs
- Recommendations for ART scale-up for IDUs in ASIA

Training materials:

- PowerPoint presentation 6.1: IDU access to ART
- Sub-module 6.1: IDU access to ART
- Exercise 6.1
- Blank flipcharts and pens (for co-facilitator to collate responses and summarize major issues about IDUs and ART)

EPIDEMIOLOGY OF HIV IN INJECTING DRUG USERS

While exact figures can be difficult to obtain, it is estimated that there are currently over 13 million injecting drug users (IDUs) in the world (XV International AIDS Conference Bangkok, 2004b). HIV epidemics in some western and many eastern European and central Asian countries are driven by injecting drug use, and the HIV prevalence related to injecting drug use has risen dramatically in China, Indonesia, Iran, Myanmar and Viet Nam. UNAIDS estimates that IDUs represent as much as 10% of global HIV infection, and outside of Africa IDUs account for one in three new HIV infections (International Harm Reduction Association and WHO, 2004).

ACCESS OF IDUs TO ART PROGRAMMES WORLDWIDE

While ARV therapy has been scaled up in many parts of the world and is now available for as little as US$300 a year, IDUs are often excluded from antiretroviral therapy (ART). For example, in Russia in 2002, IDUs represented 90% of HIV cases, yet no active IDUs were on ART. The situation in the Ukraine was reportedly similar, where IDUs make up 69% of HIV cases but only 20% are on triple combination ART (Open Society Institute, 2004). In France, Canada and the US, multiple studies have found that the majority of HIV-infected individuals not receiving ART are active IDUs (Wood et al. 2003). In some parts of the world ARVs may be "available" to IDUs but treatment is inadequate, most likely due to poor-quality service provision and inattention to issues such as adherence and lifestyle stability. A Swiss study demonstrated that IDUs outside a drug treatment programme had a significantly higher risk of inadequate treatment (Wood et al. 2003), and one study from Italy showed that ART was started later in IDUs compared with non-IDUs and that IDUs were less likely to be prescribed protease inhibitors (PIs) (Wood et al. 2003).

The situation in South-East Asia

The 2004 WHO and IHRA report, *Scaling up the provision of ARV to IDU and non-IDU in Asia*, made the following key findings:

1. Just 1–5% of IDUs in Asia access any drug prevention or treatment at all (including outreach, needle–syringe programmes, opioid substitution therapy [OST] or even information materials or primary health care). It is evident that ensuring access to ART for IDUs in this region will be a difficult task.
2. Despite some increases in epidemiological surveillance, the population of drug users (DUs) is still very much hidden, and the extent of the HIV epidemic among DUs and their social networks is relatively unknown.
3. Most organizations working with DUs need training materials in the local languages on most aspects of outreach, primary health care, advocacy and ART provision guidelines.
4. Most organizations lack the funding to adequately provide services to IDUs, including ART. The majority of organizations had not accessed or applied for funding from the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM).
5. Most countries in the region lack the required infrastructure to deliver ART to IDUs, including laboratory equipment and trained medical providers. There is a large and willing "human resource" that needs capacity building.
6. There are networks of PLWHA, but networks of DU organizations are underdeveloped. PLWHA groups are often involved in national policy workshops but DUs are not.

7. Many countries in the region are beginning to form joint action plans between law enforcement departments and public health organizations to tackle the dual epidemic of drug use and HIV (UNODC G22 Project, AUSAID Regional Harm Reduction Project).
8. Several small pilot programmes in the region are providing ART but DUs are often excluded.
9. Many organizations have access to detoxification centres and/or those in prison, and several organizations offer primary services to this group. This is significant, as providing services to IDUs in closed settings is a realistic environment for monitoring ART.

GUIDELINES GOVERNING EQUITABLE ACCESS TO ART

Guidelines to govern equitable access to ARV exist. WHO states that:

> *Access to HIV treatment should not be artificially restricted due to political or social constraints. Specifically there should not be categorical exclusion of injection drug users from any level of care. All patients who meet eligibility criteria and want treatment should receive it, including IDUs, sex workers and other populations (WHO, 2005).*

The US Department of Health and Human Services states that:

> *No individual patient should automatically be excluded from consideration for ART simply because he or she exhibits a behaviour or other characteristic judged by some to lend itself to non-adherence (Workowski, 2002).*

BARRIERS TO ACCESSING ART FOR IDUs

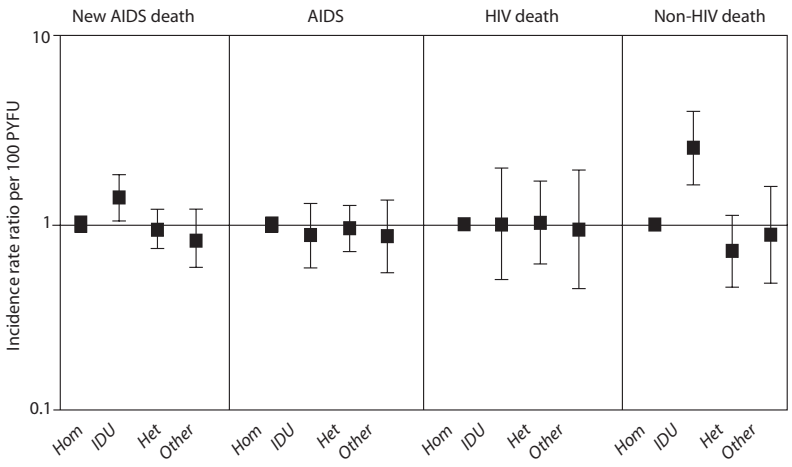
There are many barriers for IDUs to access ART. Some of these are related to the fact that injecting drugs is a criminal activity in many countries. IDUs are often poorly represented at many health service facilities and failure to access ART is part of that systemic failure. In addition, many health workers and policy-makers have misperceptions about the success of ARV therapy in IDU populations. These misperceptions include:

1. IDUs do not do as well on ART as non-IDUs.
2. Medical complications such as hepatitis B and C make HIV difficult to treat and less responsive to ART.
3. IDUs are poor candidates for ART due to poor adherence.
4. IDUs must be on opioid substitution therapy (OST) to access ART.

HIV TREATMENT EFFICACY DATA

Many early studies show that IDUs did not have good treatment outcomes on ART. Most of these results can be explained by: (1) selection bias; (2) poor adherence support; and (3) IDUs dying prematurely from non-HIV-related disease (*see* Figure 1). More recent evidence shows that when IDUs are similarly adherent to ART, they have similar outcomes to non-IDUs. In 1999, a large cohort study of 6645 patients on ART from 51 centres across Europe found no difference between IDUs and non-drug users in either CD4 counts or virological responses. In 2004, a Canadian study of 1522 IDUs and non-IDUs who adhered to ART experienced similar increases in CD4 counts. In a 2004 US study of clients of a mobile, needle and syringe exchange programme with peer support plus ART, at six months clients showed a 77% reduction in viral load to <400 copies/ml and 25% increase in CD4 count (XV International AIDS Conference Bangkok, 2004a).

Figure 1. Risk of AIDS and death by HIV exposure category

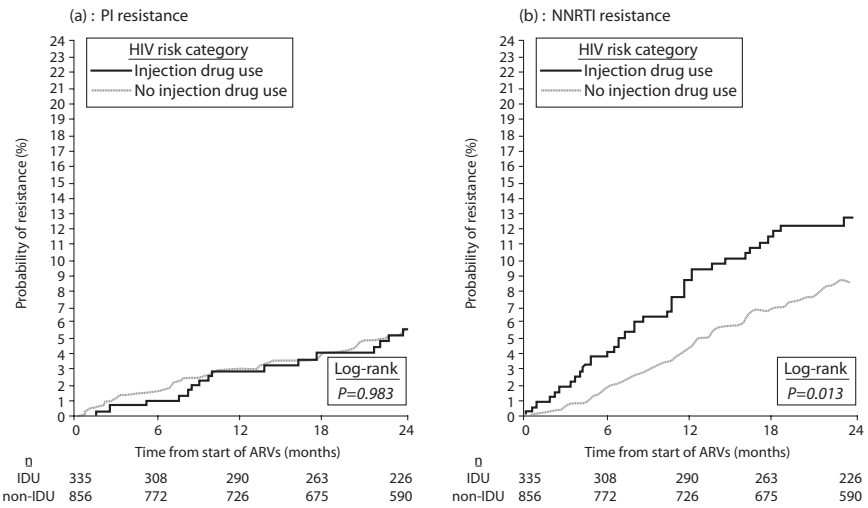


Source: Mocroft A et al.; for the EuroSIDA study group. *AIDS*, 2004.

ADHERENCE, RESISTANCE AND INJECTING DRUG USE

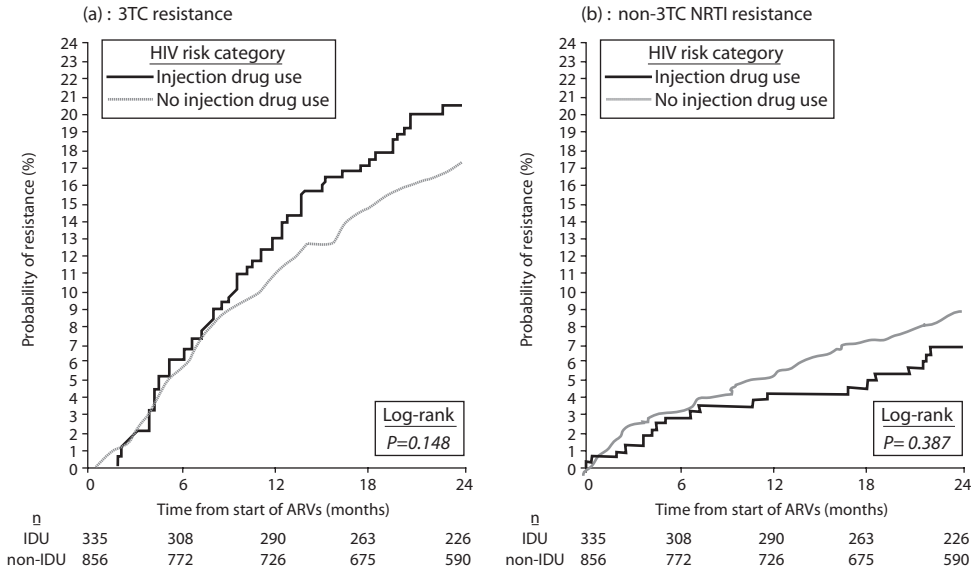
Experiences from many countries around the world have shown that IDUs can be adherent to ART, particularly (but not only) when drug treatment is associated with ARV treatment. A 2001 study in Brazil of 673 low-income patients in Sao Paulo showed overall adherence rates of 69% despite no use of OST. A 2000 French study of IDUs on buprenorphine and ART demonstrated 78% adherence. A 2002 study in Ireland where ART was offered at a methadone clinic demonstrated that 58% of individuals had a viral load of <50 copies/ml at 48 weeks. A 2004 study in Baltimore, USA of 286

Figure 2. Rates of ART resistance by IDU status



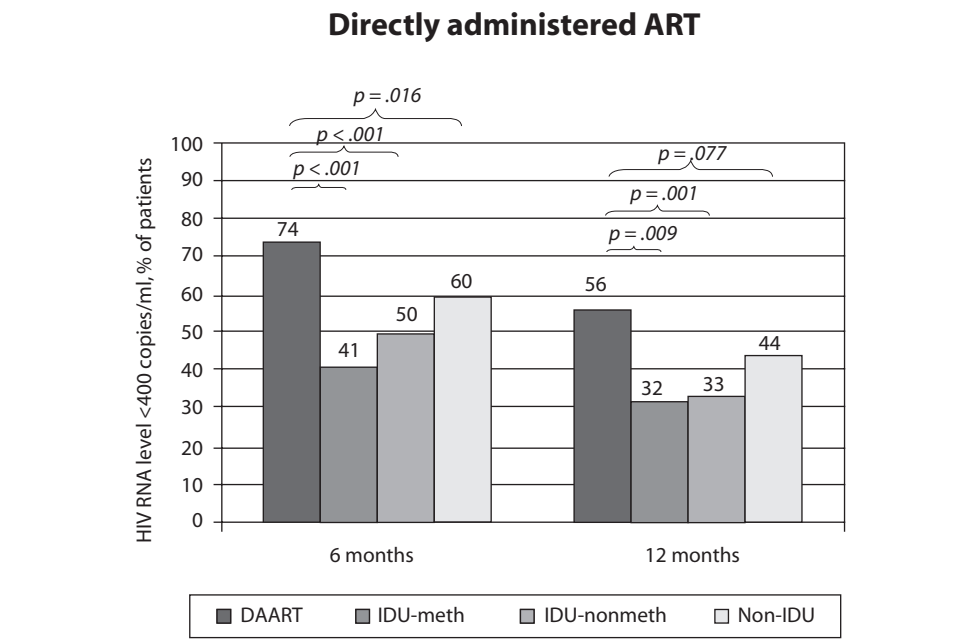
Source: Wood et al. *AIDS*, 2005.

Figure 3. Rates of ART resistance by IDU status



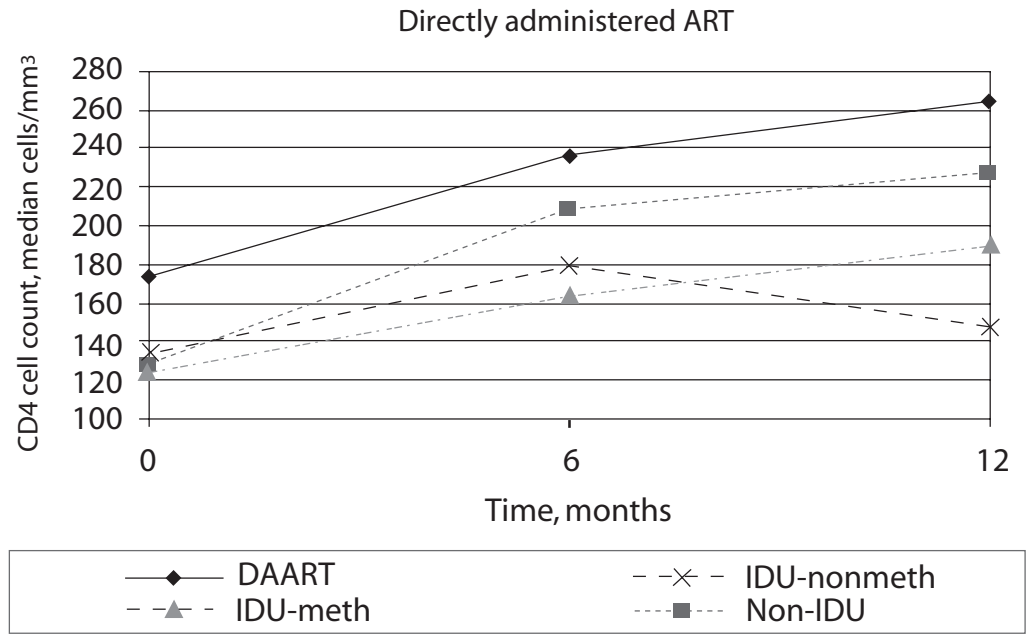
Source: Wood et al. *AIDS*, 2005.

Figure 4. Viral suppression at 6 and 12 months



Source: Lucas G et al. *Clinical Infectious Diseases*, 2006.

Figure 5. Median CD4 count at 6 months and 12 months



Source: Lucas G et al. *Clinical Infectious Diseases*, 2006.

patients, demonstrated that 58% of those who received ART at a methadone clinic achieved a viral load of <50 copies/ml at 48 weeks compared with 39% of non-drug users self-administering ART (XV International AIDS Conference Bangkok, 2004a; Centre for Research on Drugs and Health Behaviour, 2003; Lucas et al. 2006).

In 2005 a group of Canadian researchers demonstrated that ART resistance rates were no different across all ARV classes between IDUs and non-IDUs (Wood et al. 2005).

DIRECTLY OBSERVED ART, IDUs AND ADHERENCE

Some recent studies documenting the experiences of directly administered ART have shown very successful outcomes (Lucas et al. 2006).

Despite this promising evidence there are many limitations to directly administered ART including:

- Many regimens are twice daily.
- ART is lifelong.
- Regimens are resource intensive and difficult to sustain.
- They have a negative impact on individual freedom.

The authors of this study recommended the need for randomized controlled trials examining directly administered ART and also recommended that the cost-effectiveness of this model be further evaluated.

Do IDUs have to be on OST to take ART successfully?

There is little doubt that continuing drug use is one of the major behavioural features that impact negatively on adherence. Some studies have shown that active injectors have lower rates of

adherence compared with non-users or non-injectors (Centre for Research on Drugs and Health Behaviour, 2003). However, there are studies that refute this. In 2001, a Baltimore study of 796 patients found that active IDUs achieved an adherence of 66% without any special support. A 2004 US study of mobile needle and syringe exchange showed that among those who received peer support plus ART adherence counselling, rates reached 85% after six months (even though 35% were homeless and 74% deeply depressed) (XV International AIDS Conference Bangkok, 2004a). Several studies have also noted that former IDUs had higher levels of adherence (83%) than those who had never used drugs at all (76%). In Brazil (mostly cocaine users who cannot be treated with OST) the success of the ART programme indicates that adherence is related to social and community support rather than just to OST(Centre for Research on Drugs and Health Behaviour, 2003). Some authors report that the regular and stable attendance at a clinic is more important than OST itself. Therefore, while OST is very useful in improving adherence, it is not absolutely essential.

IMPORTANCE OF THE ART PROVIDER

As a potential ART provider you have a very important role. Satisfaction with one's physician has been associated with higher levels of adherence, and willingness to start ART has been associated with patient trust in the physician. It has been demonstrated that IDUs being treated by a physician with experience in HIV have an increased ART uptake. Surveys of physicians have shown that a physician's judgement of patient adherence is critical for prescribing ART (Wood et al. 2003). This is very worrying as physicians have been shown to be consistently poor at predicting those who can be "adherent" (Wood et al. 2003).

SOME MODELS THAT SUPPORT ART FOR IDUs

(This will be covered in more detail in the sessions on adherence.)

1. *Provision of drug treatment services* has consistently been shown to improve adherence and retention in HIV treatment (Wood et al. 2003).
2. *Offering ARV daily at OST clinics*. This can be directly observed treatment (once-daily dosing) or partial directly observed treatment ([DOT] morning DOT with evening take-away ARVs and self-administration).
3. *Offering social support services* in addition to health services at a single site helps in retaining IDUs on treatment (e.g. food, transport) (XV International AIDS Conference Bangkok, 2004a).
4. *Offering intensive adherence education and support* has been shown to improve adherence among those who have previously failed therapy (XV International AIDS Conference Bangkok, 2004a).

RECOMMENDATIONS FOR ART SCALE-UP FOR IDUs IN ASIA

The 2004 WHO and International Harm Reduction Association report recommended "scaling up the provision of ART to IDUs and non-IDUs in Asia" and made the following key recommendations:

1. As outreach (especially when it is linked to sterile injecting equipment and peer education) is known to be a highly effective way to reach IDUs/DUs, the scale-up of outreach needs to be the first step in potentially providing ART to this group.
2. As OST has been highly effective in reducing the incidence of injecting drug use among opiate users and also in keeping them in regular contact with the health services, these too must be rapidly expanded.

3. PLWHA networks have been highly successful in providing services and support to other PLWHA. The specific needs of IDUs/DUs with HIV may be different. Supporting networks of this group of patients is likely to result in the delivery of better services to them (e.g. SASO in Manipur, India).
4. ARV education and provision, adherence monitoring and provision of other services for HIV-positive DUs/IDUs should be implemented through the processes mentioned above.
5. Training tools, information and best practice guidelines about existing ART provision and services to IDUs/DUs (e.g. WHO advocacy document for IDU programmes) need to be adapted to local conditions and made available in local languages and disseminated through the various networks without delay.
6. Supporting local organizations through technical support in grant application writing would greatly increase the funding available for ARVs and services to IDUs/DUs.
7. Regional networks in conjunction with technical assistance organizations should have ongoing roles in all aspects of scaling up ART to IDUs/DUs including implementation, monitoring and advocacy.

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EXERCISE 6.1

Write your response below each question.

1. Do you personally think that active IDUs can take ART successfully?

2. What are the reasons you think active IDUs can or cannot successfully take ART?

Sub-module

6.2

General HIV care for IDUs

OVERVIEW

Objectives:

By the end of the session participants will be able:

- To outline the health problems common to HIV-positive IDUs and the essential components of healthcare service delivery for HIV-positive IDUs
- To describe the common non-HIV related infections and medical conditions of HIV-positive IDUs including their management
- To describe common opportunistic infections (OIs) and their management
- To outline the difference between primary and secondary OI prophylaxis
- To perform an initial evaluation of an HIV-positive IDU at the HIV clinic

Time to complete session:

3 hours and 15 minutes

Session content:

- Looking after IDUs with HIV
- Common health problems in HIV-positive IDUs
- Comprehensive care models for HIV-positive IDUs
- Initial evaluation of the HIV-positive IDU
- WHO clinical staging system for HIV-infected adults and adolescents
- Management of common health problems in IDUs
- Overdose
- Diagnosis and management of OIs
- Prevention of OIs
- Follow-up visits

Training materials:

- PowerPoint presentation 6.2: General HIV care for IDUs
- Sub-module 6.2: General HIV care for IDUs
- Blank flipchart paper and pens
- Exercise 6.2.1: WHO clinical staging exercise
- Exercise 6.2.2: Role-play: Initial clinical evaluation
- Annex 1: Outpatient chart
- Annex 2: Facilitator's checklist
- Annex 3: Clinical staging system of HIV infection in adults and adolescents

LOOKING AFTER IDUs WITH HIV

- IDUs with HIV present with clinical and psychosocial difficulties related both to HIV and to injecting drug use.
- IDUs often have poly-substance use.
- IDUs may have difficulty in dealing with health professionals (and vice versa).
- Special care is needed to ensure they get the best service available and keep using the services.
- Injecting drug use is usually illegal and IDUs are anxious about any contact with authorities and institutions.

COMMON HEALTH PROBLEMS AMONG HIV-POSITIVE IDUS

- OIs characteristic of HIV
- Infection with other bloodborne viruses (hepatitis B and hepatitis C) leading to liver disease
- Drug-related hepatitis
- Increased risk of tuberculosis
- Other bacterial infections—soft tissue infections, pneumonia and endocarditis
- Traumatic injuries
- Sexually transmitted infections (STIs)
- Overdose
- Psychiatric co-morbidity
- Poly-substance use

COMPREHENSIVE CARE MODELS FOR HIV-POSITIVE IDUs

A major challenge in delivering care to IDUs is their need for multiple services that concurrently address both biomedical and psychosocial issues. Different models of care that address both HIV and opioid substitution therapy (OST) and counselling include the following:

1. One site that provides both HIV care and treatment, and substance dependence treatment
2. Close proximity between separate clinics for HIV care and treatment, and substance dependence treatment
3. Primary care practitioners offering both HIV care and treatment, and substance dependence treatment

Medical care for HIV-positive IDUs requires a multidisciplinary team who have experience with both HIV infection and injecting drug use. Staff should be friendly and have a non-judgemental and unbiased attitude toward both IDUs and PLWHA. HIV services should be linked with harm reduction services so that care for HIV infection as well as OST and drug counselling services are provided. They should also be linked with social services and community and home-based support. Such services should provide ARV therapy and adherence support, involve peer educators, provide education and promote active participation in health. Services must be accessible to the client and should be free of charge.

INITIAL EVALUATION OF THE HIV-POSITIVE IDU

- Establish a relationship.
- Carry out a psychosocial assessment – including drug and alcohol use.
- Carry out clinical and laboratory assessment – including WHO staging.
- Prioritize immediate needs.
- Make a management plan.

1. Reception and triage

- Greet the patient and explain the process and what they should expect to happen.
- Register the patient if new, confirm HIV status (if patient does not have confirmed status, refer to VCT after medical review), provide ID code and document care supporter details.
- Register address, phone number or other means to contact/trace the patient in case of need.
- Weigh the patient (IT IS IMPORTANT TO WEIGH THE PATIENT AT EVERY VISIT). Take vital signs (temperature, respiratory rate, pulse rate and blood pressure).
- Determine the reason for the visit. Take a brief history, assess if the patient is really unwell and needs to see the doctor urgently.
- All clients should be assessed by a doctor at the first visit.

2. History

Brief psychosocial history and risk assessment:

- Marital status
- Employment status
- Education status
- Living situation
- Family situation – names of family members and, if HIV-positive where they receive treatment
- Disclosure
- Date first tested for HIV
- Injecting drug and alcohol use
- Sexual risk behaviour

Medical history:

- Past medical history – including detailed history of tuberculosis (TB) (where treated, with what, for how long)
- Detailed history of ART – treated with what, where, for how long, any side-effects, adherence
- Other medications including traditional medicine
- Drug allergies
- Smoking/alcohol/drug use in the past and at present
- Symptoms of OIs – cough >2 weeks, night sweats, fever, diarrhoea, weight loss, enlarged nodes, pain, nausea and vomiting
- Current functional status – normal, ambulatory, bed-bound
- Women – pregnancy history, method of contraception, date of last menstrual period
- Past and recent hospital admissions

A full psychosocial assessment may be done by a drug counsellor, a general counsellor or a case manager. Assessment should include the following (*see* session evaluating drug dependence):

- Sociodemographic history
- Employment/education
- Living situation
- Full drug use assessment – past, present, safe practices, etc.
- Financial resources – ability to meet basics needs (food, clothing, shelter)
- Parenting/child needs (including guardianship plans) – are there children/dependents who need support?
- Ability to arrange transport for clinic visits?
- Is there adequate emotional support from friends or family?
- HIV knowledge and acceptance/fear of having the infection and prognosis/future, what lies ahead
- Mental health assessment – are there any symptoms of anxiety, depression, insomnia, forgetfulness, suicidal thoughts or social isolation?
- Client's knowledge, attitude and beliefs about HIV and transmission
- Nutrition
- Activities of daily living
- Has the client been sexually active in the past 12 months/since last visit? Does client practice safe sex? Does client need further information on reducing risk/safe sex practices?

3. Examination

Check weight and vital signs—temperature, pulse rate and blood pressure (should have been taken at triage but need to make sure they have been done)

A full assessment is necessary on the first visit:

- General psychological state (mood assessment)
- Nutritional status
- General skin condition including jaundice, herpes zoster scars
- Conjunctiva for anaemia
- Mouth for general oral hygiene, thrush and oral hairy leukoplakia
- Lymphadenopathy
- Abdomen for hepatosplenomegaly
- Chest and cardiovascular system
- Ear, nose, throat (ENT) and eyes
- Neurological and mental state examination

4. Assess and document WHO clinical stage for HIV infection, including reasons for stage

5. Make a provisional diagnosis and formulate and document a treatment plan

- Diagnosis and treatment for OIs and other conditions, whether HIV-related or not
- Prophylaxis required or not (e.g. if WHO clinical stage 3 or 4 – co-trimoxazole)

- Blood tests
- Screening for TB (all potential ART clients plus any PLWHA with clinical suspicion of TB) – *see* Module 9.2
- Other medical referral – infectious diseases, maternal health, STIs, etc.
- Referral for counselling, home-based care, PLWHA support group

6. Laboratory assessment

- CD4 count (or total lymphocyte count if unable to access CD4 count)

Plus tests that are clinically indicated:

- Screening for TB if there are symptoms/signs of TB – cough >2 weeks, fever, weight loss, night sweats, chest signs
- LFT if jaundiced
- FBC if clinically anaemic

Record tests that are done.

At this initial visit you should let the client know that blood tests are needed to see how HIV has affected their immune system. Combined with the clinical assessment and WHO staging, the blood tests help to determine how much the immune system has been damaged by HIV, probable outcome and prognosis, what treatment is needed, and whether ARVs are needed at this stage. If ARVs are needed, the patient should be informed that further tests will be required, including a pregnancy test for women.

7. Always provide information and support to the patient at the first and every other visit

- About HIV, OIs, ART and follow-up care
- About self-care to both clients and supporters
- Access to community support and PLWHA support groups
- Access to home-based care and what services are available
- Orient the client on client flow
- Special support (e.g. nutrition, financial, psychosocial)
- Reaffirm safe behaviour and contraception

WHO CLINICAL STAGING SYSTEM FOR HIV-INFECTED ADULTS AND ADOLESCENTS

Clinical stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy
- And/or performance scale normal

Clinical stage 2

- Weight loss <10% of body weight
- Minor mucocutaneous manifestations

- Herpes zoster in past five years
- Recurrent upper respiratory tract infections
- And/or performance scale – symptomatic, but normal activity

Clinical stage 3

- Weight loss >10% of body weight
- Unexplained diarrhoea >1 month
- Unexplained fever >1 month
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary TB in past year
- Recurrent bacterial infections (e.g. pneumonia, pyomyositis)
- And/or performance scale – bedridden <50% of the day for the past month

Clinical stage 4

- HIV wasting syndrome
- *Pneumocystis jiroveci* pneumonia (PCP)
- Mucocutaneous herpes simplex >1 month
- Extrapulmonary TB or atypical TB (*Mycobacterium avium* complex [MAC])
- Kaposi sarcoma
- Candidiasis of the oesophagus
- Toxoplasmosis of the brain
- Extrapulmonary cryptococcosis
- Disseminated mycosis (histoplasmosis and penicilliosis)
- Non-typhoid *Salmonella* septicaemia
- Lymphoma
- Cryptosporidiosis with diarrhoea >1 month
- Cytomegalovirus infection outside liver
- HIV encephalopathy
- Progressive multifocal leukoencephalopathy
- And/or performance scale – bedridden >50% of the day during the past month

Note: Both presumptive and definitive diagnoses are acceptable, as definitive diagnoses of many stage 4 conditions are rare in resource-poor settings.

Some notes on laboratory staging

CD4 count

Do not rely on the CD4 count as the sole predictor of immunodeficiency—it is much more important to have made an independent assessment of the clinical state and to then correlate the laboratory findings with the clinical condition. Consider hyposplenism/splenectomy as a cause of falsely elevated CD4 counts. Other factors that influence CD4 counts include:

- Use of steroids
- Intercurrent illness
- Laboratory error
- Seasonal and diurnal variation
- Analytical variation

Total lymphocyte count

The total lymphocyte count (TLC) can be used to roughly estimate the level of immunosuppression; however, it should be correlated with the presence of symptoms and WHO staging. A TLC <1200 and symptoms of AIDS correlates well with a CD4 count of <200 cells/mm^3. However, when the TLC is <1200 and there are no symptoms of the AIDS, it is not a good predictor of CD4 count. Remember that a patient in WHO stage 3 or 4 and TLC >1200 should still be considered immunosuppressed.

MANAGEMENT OF COMMON HEALTH PROBLEMS IN IDUs

Viral hepatitis

All HIV-infected patients should be tested at baseline for evidence of hepatic injury, especially substance users who are at high risk for infection with hepatitis viruses A, B and C (HAV, HBV and HCV).

Hepatitis B is primarily transmitted by sexual contact and injection drug use, and hepatitis C by injection drug use. Hepatitis A is transmitted by the faecal–oral route and in most resource-limited settings, asymptomatic HAV infection (and thus antibody protection) is acquired in childhood; thus, it has less relevance in this setting.

Chronic hepatitis B and C contribute substantially to morbidity and mortality among IDUs. IDUs may transmit hepatitis to both substance-using contacts and to non-substance-using sexual, household and other close contacts. It is particularly important to prevent viral hepatitis among HIV-infected substance users because HBV and HCV coinfection can have additional implications for HIV-infected patients. Furthermore, bidirectional interactions between HIV and hepatitis viruses may complicate disease progression and treatment of both viruses.

Where there is no serological evidence of prior exposure, clinicians should offer hepatitis B vaccination to HIV-infected substance users to prevent infection. Ideally, hepatitis B vaccine should be administered early in the course of HIV disease before severe immune suppression has occurred. However, advanced immune suppression is not a contraindication to vaccination, and vaccination of susceptible persons should not be deferred or delayed because of advanced immune suppression or in anticipation of expected immune recovery due to the effect of ART.

Clinicians should perform baseline HCV screening for all HIV-infected substance users, particularly before starting ARV therapy. Hepatitis C infection should be considered in any HIV-infected substance user who develops clinical hepatitis or abnormal LFT.

Substance-sharing contacts should be advised to undergo medical evaluation. As part of this medical evaluation, all contacts should be offered testing for HIV and hepatitis C.

Clinicians should advise HIV/HCV coinfected patients and patients infected with HCV alone to discontinue consumption of alcohol.

STIs in HIV-infected substance users

High rates of STI are seen among both IDUs and non-injection substance users, such as crack cocaine users. STIs have been shown to be independent risk factors for the sexual transmission of HIV.

Primary care clinicians play an important role in reinforcing behavioural risk-reduction measures. Among substance users in the US, incidence rates for early syphilis range from 2.9 per 1000 person years to 1 per 100 person years, which is substantially higher than that in the general population. Outbreaks of primary and secondary syphilis have been associated with the use of crack cocaine and the exchange of sex for money or drugs.

The presence of genital ulcer disease has been associated with HIV transmission. Genital ulcers directly increase the likelihood of genital secretions containing an infectious amount of HIV-1 and the potential for contact between HIV-1 in genital secretions and genital mucosal cells receptive to HIV-1 infection. Smoking crack cocaine may cause blisters and sores on the lips and oral mucosa, which may also facilitate the transmission of infectious pathogens.

It is recommended that STI screening is undertaken annually for HIV-infected substance users (and if symptoms arise). STI services need to be integrated into existing HIV or drug treatment programmes to ensure that they are accessible and appropriate for the populations served.

- Clinicians should screen HIV-infected substance users for syphilis.
- Clinicians should screen HIV-infected substance users annually for gonorrhoea and chlamydia.
- Female HIV-infected substance users should have annual Papanicolaou (Pap) smears.

Soft tissue disorders

Abscesses are common among IDUs (prevalence of up to 32% in some settings). The most common organisms are skin and oral flora, including *Staphylococcus aureus*, facultative Gram-negative bacteria and mixed anaerobic bacteria. This suggests that contamination is usually related to injection practices and not the drugs used. However, drugs or injection equipment may be contaminated with environmental organisms, such as *Clostridium tetani or C. botulinum,* and may cause tetanus or wound botulism.

Abscess formation is associated with not cleaning the skin prior to injection, use of dirty syringes, injecting subcutaneously and injecting cocaine. HIV does not appear to be a consistent risk factor for abscess formation.

Soft tissue infections can be reduced by:

- Cleaning the skin thoroughly before each injection
- Using a sterile syringe or at least a sterile needle for every injection
- Rotating injection sites
- Keeping tetanus vaccinations up-to-date
- Avoiding intramuscular injection of cocaine

Pus-filled abscesses usually need to be drained and packed. Culture and sensitivity testing should be performed when pus can be obtained safely, because antimicrobial-resistant organisms, including methicillin-resistant *Staphylococcus aureus,* are becoming increasingly common among injectors. The clinician should be aware that subcutaneous injection may cause inflammation and swelling that is not infected and will resolve on its own. IDUs may also develop necrotizing skin and soft tissue infections.

OVERDOSE

Clinicians should counsel substance-using patients about the risk of overdose and how it may be prevented.

Opioid substitution therapy has been demonstrated to be an effective preventative measure for overdose. Heroin use is associated with a significant increase in mortality, approximately half of which is due to overdose. The risk of overdose may be as high as 2% per year. Heroin overdose is characterized by respiratory depression primarily due to reduction in brainstem sensitivity to carbon dioxide, which may lead to death. Death usually occurs 1–3 hours after injection rather than suddenly. In many cases of overdose, opioids are taken along with alcohol or benzodiazepines.

Risk factors for heroin overdose include:

- Age: late 20s or early 30s
- Using heroin for 5–10 years
- Recent release from detoxification or correctional facility
- Using heroin outdoors
- Using heroin alone
- Mixing heroin with alcohol or benzodiazepines
- Concurrent serious medical conditions, particularly pulmonary and hepatic dysfunction.

Patients should be taught the following:

- The risks of mixing depressants with heroin
- The risk of reinitiating heroin use after a period of abstinence
- To recognize the signs of a possible heroin overdose in another user and to immediately call for medical help (many people who overdose are not alone).

It has been suggested that heroin users may benefit from training in resuscitation and the provision of naloxone, which can be administered to companions should they overdose.

Cocaine overdose

Cocaine overdose is much more difficult to describe and quantify than heroin overdose. It may be more accurate to refer to it as "cocaine-related mortality" because there does not seem to be a direct relationship between dose, tolerance and mortality. Potentially lethal reactions to cocaine include seizures, myocardial infarction, hypertensive crisis, cerebral haemorrhage, aortic dissection and hyperthermia. It has been noted that more deaths are attributed to cocaine during hot weather when hyperthermia becomes more likely. Dysrhythmias may occur but are likely to be lethal only in the presence of previous myocardial damage.

DIAGNOSIS AND MANAGEMENT OF OIs

Opportunistic infections are the major cause of morbidity and mortality in persons with HIV/AIDS. The frequency and clinical manifestations of OIs depend on the degree of immunodeficiency of the patient. It is therefore always useful to know a patient's CD4 count or WHO stage when trying to identify clinical problems.

One of the most common OIs in South-East Asia is TB. Other common OIs include cryptococcosis, oropharyngeal and oesophageal candidiasis, chronic diarrhoea and wasting, and PCP.

Prevalence of OIs among persons with AIDS, Thailand (2 series)

(Chariyalertsak, 2001; Amornkul, 1999)

Tuberculosis	29–37%
Cryptococcosis	19–38%
Wasting syndrome	8–28%
Pneumocystis jiroveci pneumonia	5–20%
Bacterial pneumonia	4%
Oesophageal candidiasis	3–6%
Penicillium marneffei infection	3%
Toxoplasmosis	2–3%
Cryptosporidiosis	1–2%

Other conditions that may be present are HIV-related malignancies, which include lymphoma, cervical carcinoma and Kaposi sarcoma.

TB and HIV coinfection (*see also* Sub-module 9.2)

TB can occur at any stage of HIV infection and the clinical features will depend on the level of immunodeficiency.

In the HIV-infected:

- TB is common.
- TB is often the first presentation of HIV (e.g. in Viet Nam 10% of people diagnosed with TB have HIV infection).
- Voluntary counselling and testing (VCT) should be offered to patients with TB; if HIV is identified, this allows entry into HIV care early with the benefits of general care, support, nutrition, co-trimoxazole prophylaxis, treatment of OIs and access to ART if required.

TB can present in atypical ways; in addition, smear-negative pulmonary disease and extrapulmonary disease are common, particularly with advanced HIV disease and immune suppression. Early in HIV disease, TB presents as in the non-HIV-infected population.

Pulmonary tuberculosis

In the early stages of HIV infection when the immune status is still good, clients present with typical TB – fever, cough, fatigue, weight loss, night sweats. Chest x-ray (CXR) appearances are typical of TB and the sputum smear is usually positive.

In the late stages of HIV infection with immunosuppression, TB can be harder to recognize and patients may just have fever and weight loss – sometimes severe wasting syndrome plus diarrhoea and anaemia. CXR often does not suggest TB – there may be no cavities and often no upper lobe disease. Miliary disease is common and X-ray may even be normal, because an inflammatory response cannot be mounted. Pleural effusion and pericardial effusion are common. The smear will often be negative.

Extrapulmonary TB

Extrapulmonary TB is much more common in PLWHA, particularly with advanced disease and low CD4 counts. It can present as:

- TB lymphadenitis: the affected lymph nodes are often firm, symmetrical and persist for a long time, but can appear abruptly, with asymmetry, fluctuation and discharge. Always perform an X-ray and sputum smear, because these might provide the diagnosis and allow easy access to care. Otherwise, referral for aspiration and biopsy may be required. Abdominal nodes are less accessible and an ultrasound may assist in the diagnosis).
- TB meningitis: this presents with subacute onset of headache and fever; meningeal signs, mental disturbances and focal neurological deficits if the disease has been prolonged. Appropriate referral is required.
- TB peritonitis: this can present with abdominal pain, ascites, diarrhoea and palpable lymphadenopathy.
- Gastrointestinal TB: it presents with abdominal pain, diarrhoea or ileus, bloody stool and often ascites or a palpable mass in the abdomen.
- Miliary TB: usually a patient is unwell and presents with fever, fatigue, dyspnoea, hepatosplenomegaly, weight loss. Respiratory symptoms may be minimal and there may be signs and symptoms due to the involvement of other organs such as the gastrointestinal tract, central nervous system and anaemia. The smear may be positive – if negative, a review by the TB services is required.
- Bone/joint disease requires referral.

Special considerations in the treatment of TB for HIV-infected persons

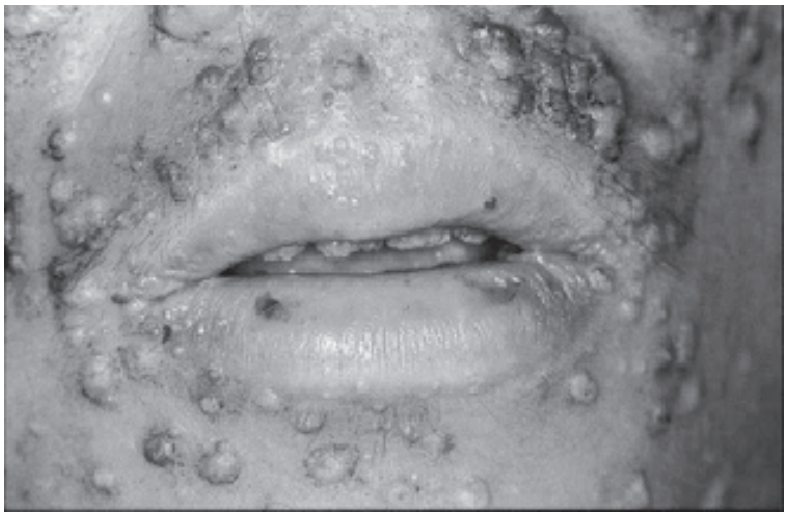
Treatment of TB in HIV infected patients is generally no different from that in non-immunosuppressed patients. However:

- Streptomycin is not recommended in settings with poor sterilization facilities or where sterile needles or syringes are not easily available to avoid HIV transmission through contaminated needles and syringes.
- The duration of TB treatment may need to be longer in those who are extremely immunosuppressed (CD4 <100 cells/mm^3) or in those with severe extrapulmonary or disseminated disease such as miliary TB, meningitis, and bone and joint disease.
- TB treatment does not obviate the need for all other HIV care, but decisions about ART and TB treatment need careful consideration and combined management. Because of the pill burden, confusion is likely if side-effects and drug toxicities/interactions occur (*see* Sub-module 9.2).
- Special care needs to be taken with regard to infection control in the PLWHA setting, particularly in the clinic, during social contact and at home. Other family members should be screened and so should their children, regardless of HIV status.

Penicilliosis

Penicilliosis is caused by the organism *Penicillium marneffei*. On clinical examination, there are skin lesions typical of penicilliosis plus systemic symptoms of fever (>38°C), hepatomegaly, splenomegaly and weight loss.

Figure 6. Penicilliosis



Source: Viet Nam CDC Harvard Medical School AIDS Partnership. *Clinical training*. Ho Chi Minh City, Viet Nam, 2006.

Diagnosis is made by:

- Blood culture (positive)
- Microscopic examination of skin lesions

Localized penicilliosis is treated with itraconazole 8 mg/kg/day for 6–8 weeks (200 mg bid). Treatment of systemic penicilliosis is with amphotericin B, 1.0 mg/kg/day for 6–8 weeks or itraconazole 200 mg bid for 2 months and then 200 mg once/day for 4 months or amphotericin B 1.0 mg/kg/day for 2 weeks followed by itraconazole 200 mg once/day for 10 weeks.

Cryptococcal meningitis

This presents with slow onset of headache, fever, fatigue, mental disorders, meningeal and other uncommon neurological abnormal signs. The CSF opening pressure is high and the CD4 count is <100 cells/mm^3.

Diagnosis is made by:

- Cryptococcal antigen in the CSF and/or in blood (may not be available in all countries)
- India-ink stain
- CSF culture

Treatment of cryptococcal meningitis

Induction phase:

- Amphotericin B 0.7 mg/kg/day plus flucytosine (if available) 100 mg/kg/day for 2 weeks

Consolidation therapy:

- Fluconazole 400–800 mg for 8–10 weeks

If cryptococcal meningitis is mild, oral fluconazole alone can be used from the beginning.

Pneumocystis jiroveci pneumonia

Clinical manifestations:

- Gradual onset of shortness of breath, dry cough, fever

- Lung sounds: may be faint crackles
- Hypoxia is common
- CD4 count <200 cells/mm^3 (though occasionally higher)

CXR:

1. Typical: bilateral diffuse infiltration
2. Atypical: normal or lateral infiltration
   - Pneumothorax is suggestive of PCP.

Treatment of PCP:

- Trimethoprim–sulfamethoxazole (co-trimoxazole). The dose is based on trimethoprim 15 mg/kg/day in three–four divided doses; usually 2 double-strength tablets or 4 single-strength tablets are given every 8 hours for two–three weeks. Co-trimoxazole can be given IV if available.
- For severe cases, add prednisone 40 mg bid for 5 days then 40 mg qd for 5 days followed by 20 mg/day for 11 days (21 days total).

PREVENTION OF OIs

It is important to understand the difference between primary prevention of OIs and secondary prevention of OIs:

- Primary prevention means giving medication to prevent an OI from occurring.
- Secondary prevention means giving medication after an OI has already occurred to prevent it from recurring.

OIs that can be prevented include:

- PCP
- Cerebral toxoplasmosis
- TB
- Fungal infection – cryptococcosis and penicilliosis
- MAC

Co-trimoxazole prophylaxis for PCP

One of the most important OIs that can be prevented is PCP. This can be prevented by using co-trimoxazole, which is usually taken once a day or three times a week. It has been shown to decrease the morbidity and mortality from PCP. It is inexpensive, generally well-tolerated and can be a good way to prepare a patient to take medications on a daily basis and improve adherence prior to beginning ARVs.

In a study of 509 PLWHA in Uganda on daily co-trimoxazole prophylaxis (Mermin et al. 2004), it was found that:

- In those with CD4 counts <200 cells/mm^3 or stage 3 or 4, death rate was 46% lower
- Incidence of diarrhoea fell by 35%.
- Hospital admissions fell by 15–30%.
- Co-trimoxazole was well-tolerated and treatment adherence was high.
- The CD4+ cell count decline was slowed from 203 cells/mm^3 per year to 77 cells/mm^3 per year.

In addition to preventing PCP, co-trimoxazole prophylaxis also prevents:

- Cerebral toxoplasmosis
- *Streptococcus pneumoniae* pneumonia
- Non-typhoid salmonellosis
- Nocardiosis
- Isosporiasis

According to the WHO guidelines, co-trimoxazole prophylaxis is recommended for:

- All symptomatic people with mild, advanced or severe disease
- WHO clinical stage 2, 3 or 4
- Anyone on TB treatment
- Any WHO clinical stage and CD4 <350 cells/mm^3
- Dose: 960 mg/day (one double-strength tablet or two single-strength tablets once daily: 160 mg trimethoprim/800 mg sulfamethoxazole)

Isoniazid preventive therapy (IPT) for prevention of TB

Isoniazid prophylaxis is currently not recommended in some countries in Asia due to concerns about promoting isoniazid resistance, but it is generally regarded as international "best practice". If skin testing is available, IPT may be reserved for persons with a positive tuberculin skin test (≥ 5 mm induration). Otherwise, IPT is suggested for all HIV-positive patients living in countries with a high prevalence of TB. IPT is also suggested for HIV-positive persons exposed to cases of active TB.

The dose of isoniazid (INH) is 300 mg per day for 9 months.

Note: It is critical to exclude active TB before starting isoniazid.

When is it safe to stop primary and secondary prophylaxis?

- PCP: if CD4 count ≥200 cells/mm^3 for six or more months, it is safe to discontinue primary and secondary prophylaxis.
- Toxoplasmosis: discontinue if CD4 count ≥200 cells/mm^3 for six months and there are no signs of toxoplasmosis.
- MAC: discontinue primary prophylaxis if CD4 count is >100 cells/mm^3 for >three months; secondary prophylaxis can be stopped when CD4 count is >100 cells/mm^3 for >6 months, 12 months of treatment have been completed and patient is asymptomatic.

FOLLOW-UP VISITS

Important steps:

1. Triage

- Greet the patient.
- Retrieve records.
- Weigh the patient (IT IS IMPORTANT TO WEIGH THE PATIENT AT EVERY VISIT).
- Take vital signs (temperature, respiratory rate, pulse rate and blood pressure).
- Ensure that the results of investigations are in the client file.
- Determine reason for visit – assess if the patient is really unwell and needs to see the doctor urgently.

- Decide if patient needs to see the health worker on this visit and which health worker they should see.

2. History

- Medical history since last visit – new medication, new diagnoses, hospitalization
- Drug use – consideration of substitution therapy, progress with drug counsellor
- Follow up and document results of investigations taken at the last visit
- New symptoms or complaints
- Always ask about cough
- List all medications patient has been taking and assess adherence to co-trimoxazole, etc.
- If on ARVs, ask about side-effects and missed doses/adherence (a full adherence assessment should be done by adherence counsellor – *see* section on adherence but it is also useful to assess and emphasize the importance of adherence)
- Check nutrition and performance status
- Check for sexual activity and injecting drug use and related activity.

3. Examination

- Record weight.
- Conduct examination according to clinical symptoms.
- Always check the mouth.

4. Record change in clinical staging

5. Provisional diagnosis and management plan

- Arrange tests if necessary for acute care.
- Screen for TB if necessary.
- Treat OIs as needed.
- Refer to drug substitution therapy or to drug counsellor.
- Refer to other medical services, as required.
- Refer for adherence counselling if on ART.
- Refer for counselling, home-based care (HBC), PLWHA support.
- Arrange follow-up appointment.

6. Provide information and support at every visit

- Provide information on HIV, OIs, ARV treatment and follow-up care.
- Check on self-care with both client and supporter.
- Assess access to community support and PLWHA support groups.
- Assess access to HBC.
- Ask about special support (e.g. nutrition, hygiene, psychosocial, financial).
- Always ask the client if they have any questions about any aspect of care.

Record any new developments, information, abnormal results and the plan, treatment and follow up.

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EXERCISE 6.2.1

WHO clinical staging exercise

Case study 1: Huong

Huong is a 43-year-old man who had a positive HIV test at VCT three months ago.

He is complaining of fever and today he weighs 45 kg. He used to be 49 kg. He tells you that he is having trouble with mouth ulcers and painful cuts at the edges of his mouth but he is otherwise well.

Case study 2: Thuy

Thuy is a 28-year-old woman, a spouse of an IDU who was admitted to the provincial hospital with meningitis. She found out in hospital that she was HIV positive. She tells you that the doctors thought it was caused by some kind of fungus. She weighs 38 kg and she used to weigh 45 kg three months ago.

Case study 3: Ha

Ha is a 31-year-old woman. She has bad oral candidiasis and you have just diagnosed her with pulmonary TB. Last month she could only get out of bed two days a week on average.

Case study 4: Giang

Giang is a 23-year-old IDU. He has come to your clinic for the first time today. He has no symptoms except an upset stomach two days ago. On examination he is completely well.

EXERCISE 6.2.2

ROLE-PLAY

Client: Hoa

You are a 24-year-old woman who is visiting your health service for the first time. Your husband died from TB and HIV four months ago. He also had hepatitis C. Two weeks ago you went to the VCT centre for your first HIV test. You got the result last week. You are HIV positive. You are very scared and have not told anyone about the result as yet. You have not used any drugs since your husband died but before that you used to inject heroin 2–3 times a day. You smoke 20 cigarettes a day and do not take any alcohol or other drugs. You have no children and you now live with your mother since your husband died. She does not know that you or your husband ever used drugs or that he died of HIV. You are not working at the moment (you used to do sex work to support your and your husband's drug habits) and don't have much money to look after yourself.

You are very shy and it has taken a lot of courage for you to go to the health service. You are feeling unwell and are having trouble swallowing food. You have lost quite a bit of weight and feel weak and tired. You are worried you could be pregnant as you have not had a period since your husband died.

You do not know much about HIV and are worried about hepatitis C as well. You think that you may as well start injecting drugs again because your situation feels so hopeless. As you do not have much money you think that you might have to start sex work again.

ANNEX 1

OUTPATIENT CHART

Department of health: ……

Hospital/Outpatient care:……

OUTPATIENT CHART

Registration ID ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Full name: ……

Year of birth : ……..……

Address : …… ……..……

Ward/Commune :……...……

District……..

Province/city…….

Year enrolled in care:_____

PATIENT CARD

PHOTO

Hospital/Outpatient care: _____

Registration ID No.: ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

I. ADMINISTRATION INFORMATION

1. Patient name (in capital): ..... 2. Date of birth: ...../...../.....

3. Sex: ..... 4. Occupation: ..... 5. Ethnicity: .....

6. Address: ..... District .....

City/Province: ..... Telephone: Home: ..... Mobile: .....

7. Name and address of treatment supporter: .....

..... Telephone: .....

8. Date of registration: ...../...../.....

9. Referred from ☐ PMTCT ☐ VCT ☐ Outpatient care ☐ HBC ☐ Self-referred
☐ TB Clinic ☐ Private Clinic ☐ Provincial Hospital ☐ Other

(specify name of site) _____

II. REASON FOR PRESENTATION (e.g. check-up, acute symptoms, requesting ART)

.....

.....

.....

III. CURRENT SYMPTOMS (in past month cough, fever, weight loss, pain, diarrhoea, painful swallowing, rash)

.....

.....

.....

.....

IV. MEDICAL HISTORY

(dates)	(general medical history including history of OIs)
...../...../.....	.....
...../...../.....	.....
...../...../.....	.....

Ever treated for TB? **Diagnosis:** Pulmonary Extrapulmonary

Where treated? _____ **AFB** Positive Negative Not tested

Treatment:	Regimen	Start (mo/year)	Duration (mo)		Result
	_____	_____	_____	Completed	Other: _____
	_____	_____	_____	Completed	Other: _____

On co-trimoxazole prophylaxis?.....

History of medication allergy: (specify names of medication and type of reaction): .....

.....

Ever taken ARVs: ☐ Yes ☐ No If Yes ☐ PMTCT ☐ PEP ☐ ARV treatment

Specify specific regimen, date, duration of treatment, why treatment stopped and percentage adherence

.....

.....

IDU .....: ☐ Yes ☐ Date of first injecting drug use ..... Other substance use .....

Currently injects (what/amt per day) ..... Shares equipment with .....

Ever been on drug substitution ..... Drug rehabiliation/detox .....

2. History of family members and sex partners (both HIV-positive and -negative):

Names of family members and sex partners	HIV status	Age	ARV regimen	Treatment site

INITIAL VISIT

Date: ……/……./200…….

1. **Overall evaluation** (nutrition, overall physical condition, acutely unwell, psychological condition)

.....

.....

.....

Vital signs: Weight: ..... kg **Temperature:** ..... °C **Blood pressure:** ..... /mmHg

Pulse rate: ..... time/minute **Respiratory rate:** ..... time/minute **Height:** ..... cm

2. **Physical examination** (skin and mucous membranes, lymph nodes, respiratory, gastrointestinal, eyes/ENT, genitourinary, teeth/facial, neurological, markers of substance use)

Psychoneurological:.....

Skin/mucous membranes:.....

Lymph nodes:.....

Eye:.....

ENT:.....

Lung:.....

Heart:.....

Gastrointestinal:.....

Hepatosplenomegaly:.....

Genitourinary:.....

Muscle, joint and bone:.....

3. **Functional status:** ☐ Work ☐ Ambulatory ☐ Bed bound

4. **Lab evaluation results (if any)**

CD4 count (% and absolute number): .....Total lymphocyte count .....

Hb: ..... g/L ALT/AST...../..... Hep B:..... Sputum: 1st..... 2nd..... 3rd .....

: LN biopsy .....

Chest X ray

Ultrasound ..... **Hep. C .....**

Urea: ..... Creat: ..... Elec .....

Other tests:.....

.....

5. **Diagnosis**

☐ TB suspect

☐ HIV clinical stage: ☐ 1 ☐ 2 ☐ 3 ☐ 4

OIs and other illnesses

.....

.....

.....

6. **Treatment**

☐ Refer OST/drug counsellor
☐ Not eligible for ARV treatment
☐ Eligible for ARV treatment
☐ Referral to specialization clinic
☐ TB ☐ STI/Derm
☐ Eyes ☐ Paediatric ☐ Gastro
☐ Other.....
☐ Hospitalization

☐ Co-trimoxazole prophylaxis
☐ Other treatment.....

.....

.....

.....

Date of appointment: ...../...../200.....

Treatment doctor: .....

SUMMARY OF TREATMENT

Day/month/year	
/ /	HIV (+) confirmation at facility:
/ /	Date of registration for care services
	ART
/ /	Clinical eligibility: ☐ WHO Stage:……. ☐ CD4 ……..…… ☐ Total lymphocyte count:……
/ /	Screened for ☐ CXR ☐ Sputum x 3
/ /	Attended all individual adherence counselling and group education sessions
/ /	Transferred from: _____ Transferred with medical records ☐ Yes ☐ No Started ART :…./……/…….. Name regime……..……
/ /	Name first-line regime proposed (or second-line if eligible):……
	Health status when starting ART: Weight:…….....Functional status…… Clinical stage: ☐ 1 ☐ 2 ☐ 3 ☐ 4
/ /	Start date ARV treatment:……./……/20….
	Substitution within first-line regimen
/ /	New regimen Reason
/ /	New regimen Reason
/ /	New regimen Reason
/ /	New regimen Reason
	Switch to second-line regimen
/ /	New regimen Reason
/ /	New regimen Reason
/ /	New regimen Reason
/ /	New regimen Reason
	Treatment monitoring (pre-ART or ART duration)
/ /	☐ Died ☐ Reason:……..……
/ /	Referral to facility:……
/ /	☐ Lost follow up:……

ARV treatment interruption

Date of stop treatment	Reason	Date of retreatment
/ /		/ /
/ /		/ /
/ /		/ /
/ /		/ /

Codes for reason for treatment interruption:

1. Side-effects	*4. Poor adherence*	*7. Do not have money*
2. Pregnancy	*5. Hospitalization*	*8. Patient decision*
3. Treatment failure	*6. Stock-out*	*9. Other*

Reason for switching to other ARVs (codes)

1. Side-effects
2. Pregnancy
3. Initiation of TB treatment
4. New ARVs
5. Stock out
6. Other reasons (specify)

Reason for switching to 2nd-line regimens (codes)

1. Clinical failure
2. Immunological failure
3. Virological failure

* Lost to follow up (stop treatment): > 3 months during ARV treatment; > 6 months during pre-ART

FOLLOW-UP VISITS

Date and type of visit (code: routine follow-up or acute care)	Weight (every visit) plus height (for children)	Preg ☐ Yes ☐ No Family planning ☐ Yes ☐ No Specify method	Functional status	WHO stage	Vital signs - *Temp.* - *BP* - *Pulse rate* - *Resp. rate*	Clinical history and examination: 1: Clinical history since last visit – hospital admissions (diagnosis/ days admitted) + new medication prescribed 2: History of presenting complaint if acute care visit (side-effects, symptoms of new OI) 3: Review of symptoms (opportunistic infections) 4: Physical examination 5: Diagnosis	Code for diagnosis **HA** Hospital admission since last visit **R** routine **NOI** New OI **SE** ARV side-effects **IRIS immune reconstitution inflammatory syndrome**

Functional status:
Work (L)
Ambulatory (D)
Bed bound (N)

New OIs
Suspected pulmonary TB
Suspected extrapulmonary TB
Confirmed pulmonary TB
Confirmed extrapulmonary TB
Oral candidiasis
Suspected oesophageal candidiasis
Cryptococcal meningitis
Herpes zoster
Cytomegalovirus

TREATMENT

Treatment prescribed			Test results					Management plan and/or referral	Date next appointment	Doctors signature
Current ART regimen Estimate % adherence	Other medication (ongoing and new today) e.g. OI Rx	IDU substitution Rx ☐ Yes ☐ No (*Specify what*)	CD4 or Total lymphocyte count	Hb g/l	ALT/ AST	TB code	Other			

Non-adherence reason codes:

1. Side-effects
2. Forgot
3. Feeling better
4. Unable to get to clinic
5. Unable to pay for medicines
6. Shared/selling ARVs
7. Too busy
8. Afraid others will know
9. Ran out of drugs
10. Feeling too sick
11. Drank alcohol
12. Travelled - forgot to take ART
13. Didn't want to take any more
14. Too many tablets

Adherence evaluation (co-trimoxazole and ART)

Adherence estimate	%	Forgot times/ month
Good	≥95	≤3 times
Normal	85–94%	4–8 times
Bad	<85%	≥9 times

TB status coding

Adherence estimate
1. No signs
2. TB referral
3. TB Rx
4. Sputum/CXR sent

ANNEX 2

FACILITATOR'S CHECKLIST

Instructions to facilitators:

Please use this checklist as a guide to assess how the initial clinical evaluation is going.

Do not expect the participants to do everything perfectly.

After approximately 20 minutes stop the exercise and use this checklist as a guide to ask the group whether there is anything else that needs to be done or anything that they would do differently.

Give POSITIVE FEEDBACK before you make any suggestions/recommendations.

Important issues	Comments
Establish a good relationship with the client	
Psychosocial assessment – enough to get to know Hoa a little better	
Ask about current and past injecting drug use – plus other substance abuse	
Ask about past medical history including whether she had been on ARVs	
Enquire about symptoms of OI, particularly TB, PCP and thrush	
Ask about functional status	
Do an examination of Hoa (including weight)	
Assess WHO stage	
Prescribe any treatment for Hoa – was this treatment appropriate	
Refer Hoa to other services – social worker, drug counsellor	
Explain the different tests that were taken and when Hoa should come back for a follow-up appointment	
Ask Hoa if she has any questions or concerns	

ANNEX 3

WHO clinical staging system of HIV infection in adults and adolescents

CLINICAL STAGE 1
Asymptomatic
Persistent generalized lymphadenopathy
CLINICAL STAGE 2
Moderate unexplained [a] weight loss (under 10% of presumed or measured body weight)
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infections
CLINICAL STAGE 3
Unexplained [a] severe weight loss (over 10% of presumed or measured body weight)
Unexplained [a] chronic diarrhoea for longer than one month
Unexplained [a] persistent fever (intermittent or constant for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis
Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained [a] anaemia (below 8 g/dl), neutropenia (below 0.5×10^9/l) and/or chronic thrombocytopenia (below 50×10^9/l)
CLINICAL STAGE 4[b]
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacteria infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis

Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
Recurrent septicaemia (including non-typhoidal *Salmonella*)
Lymphoma (cerebral or B cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

a Unexplained refers to where the condition is not explained by other conditions.

b Some additional specific conditions can also be included in regional classifications, such as the reactivation of American trypanosomiasis (meningoencephalitis and/or myocarditis) in the WHO Region of the Americas and penicilliosis in Asia.

Source: *WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children*. Geneva, WHO, 2006.

Sub-module

6.3

The use of ARV drugs for the HIV-infected IDU

OVERVIEW

Objectives:

By the end of the session participants will be able:

- To demonstrate knowledge and understanding of the overall mechanism of action of antiretroviral drugs (ARVs) and their role in preventing and controlling disease progression
- To describe the ARVs and regimens outlined in the revised 2006 WHO ART guidelines
- To demonstrate a detailed understanding of all the individual ARV drugs included in the 2006 guidelines
- To appreciate and understand the complexity of factors influencing the choice of ARV drugs for HIV-positive IDUs who require antiretroviral therapy (ART)

Time to complete session:

3 hours

Session content:

- Revise how ARVs work
- Review the goals of ART
- Examine the ARV drugs and regimens recommended by the revised 2006 WHO ARV guidelines

Training materials:

- PowerPoint presentation 6.3: The use of ARV drugs for the HIV-infected IDU
- Sub-module 6.3: The use of ARV drugs for the HIV-infected IDU
- Blank flipchart paper and pens
- Exercises 6.3.1–6.3.3

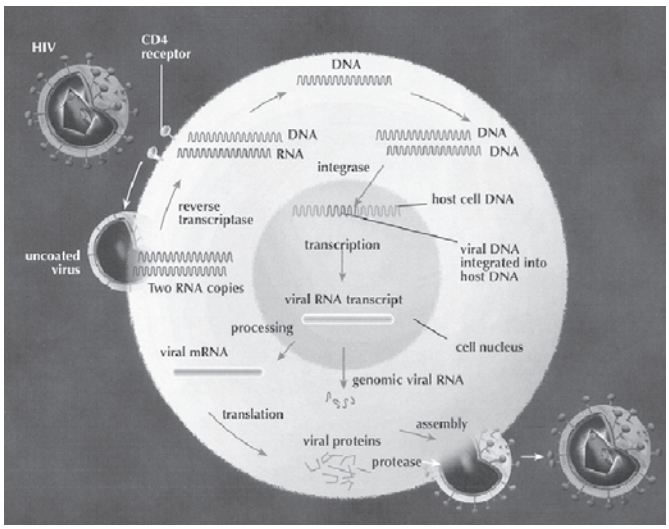
INTRODUCTION TO ARVs

Goals of ART

The goals of ART are to obtain maximal and durable suppression of HIV replication to maintain and restore immune function. This has the effect of delaying disease progression, prolonging survival and improving the quality of life. In addition the optimal goal of quality ART therapy is to prevent the emergence of drug-resistant strains and to reduce HIV transmission.

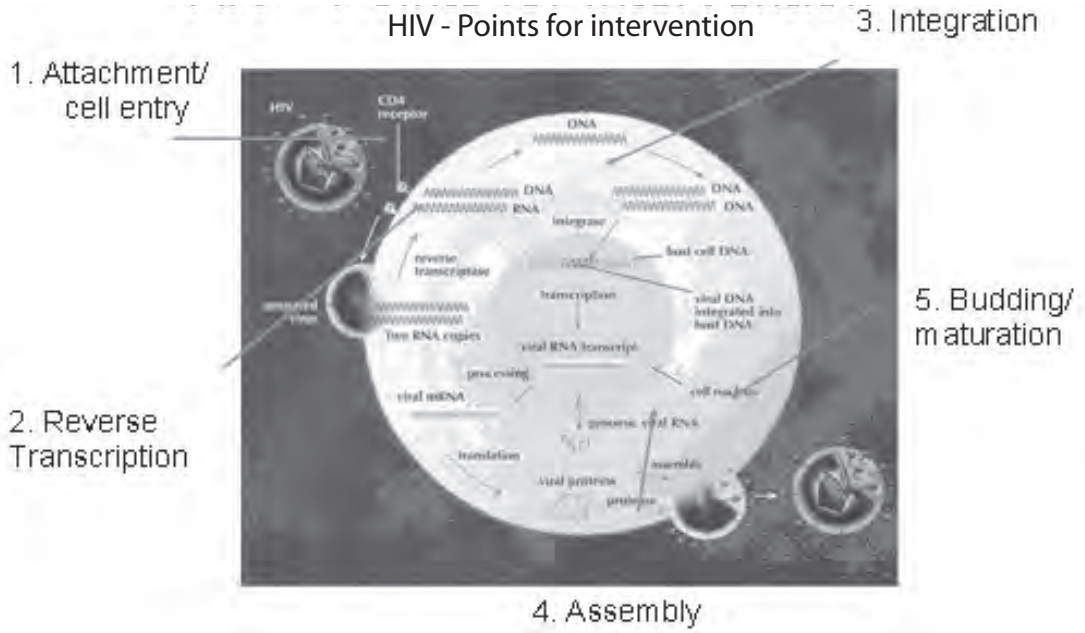
ART works by interfering with the replication cycle of the HIV and in doing so it reduces the amount of circulating virus in the plasma. This in turn decreases the infection (and death) rate of CD4 cells resulting in improved immune function.

Figure 7: Life-cycle of HIV



Source: Carey D. *Short course in HIV medicine*. Surrey Hills, New South Wales, Australia, Australasian Society for HIV Medicine (ASHM), 2005.

Figure 8: How ARVs interfere with the life-cycle of HIV

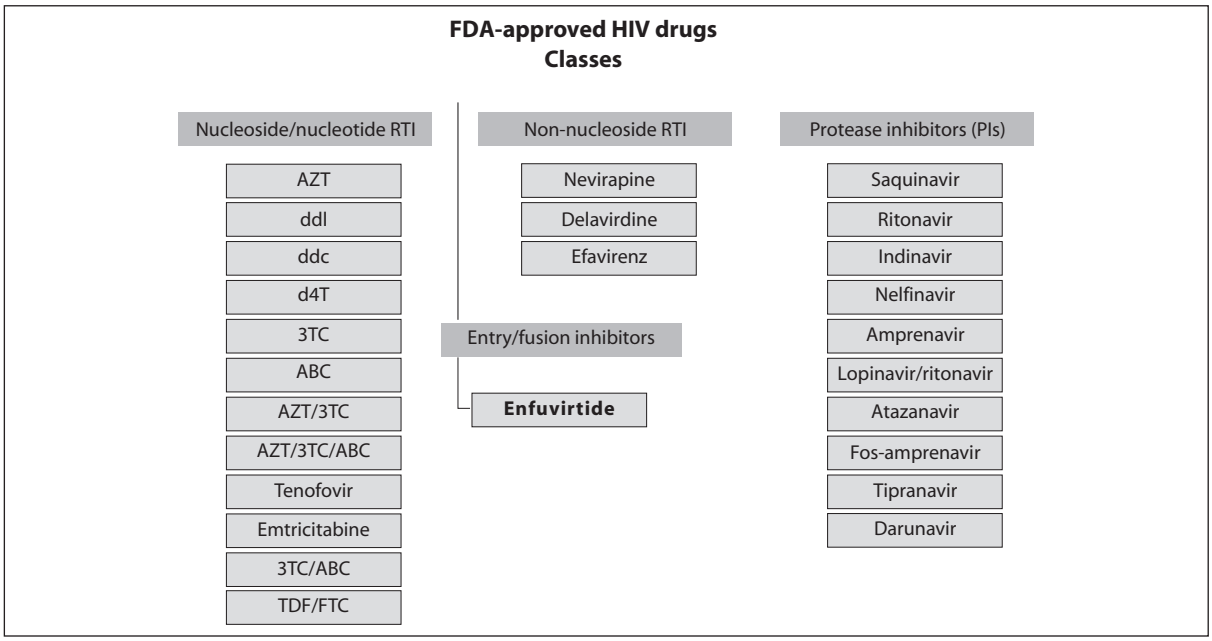


Source: Carey D. *Short course in HIV medicine*. Surrey Hills, New South Wales, Australia, Australasian Society for HIV Medicine (ASHM), 2005.

ARV DRUGS

There are a large number of ARVs that have been approved for use in HIV infection. These include the following US Food and Drug Administration (FDA)-approved drugs:

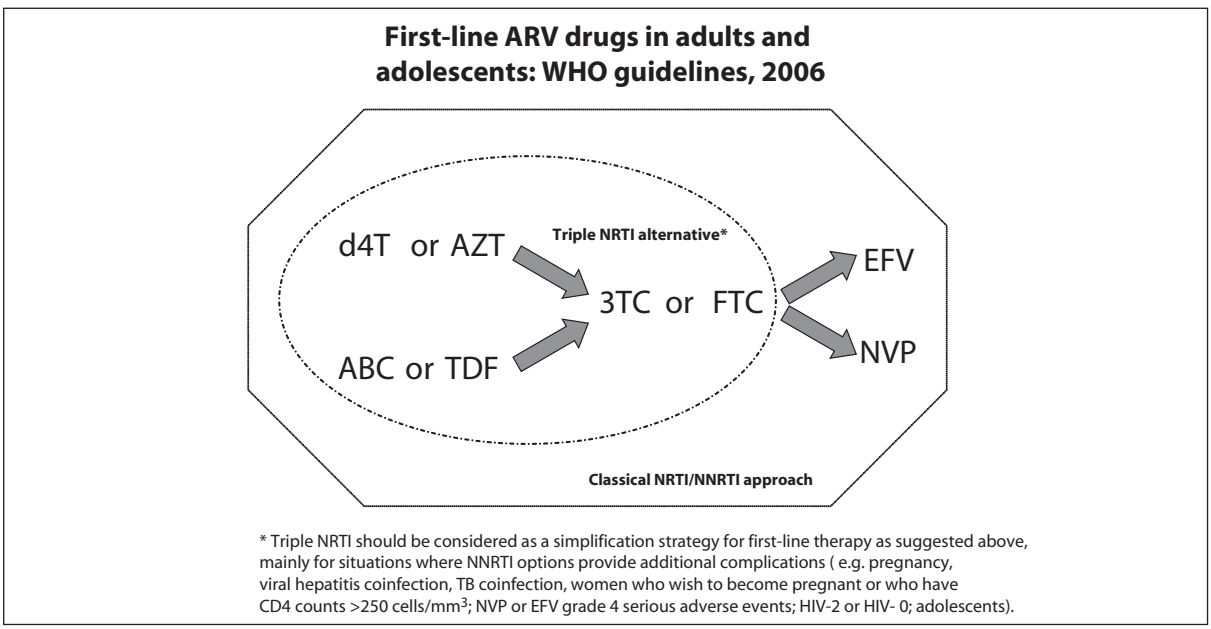
Figure 9. FDA-approval HIV drugs



REVISIONS TO THE WHO ART GUIDELINES

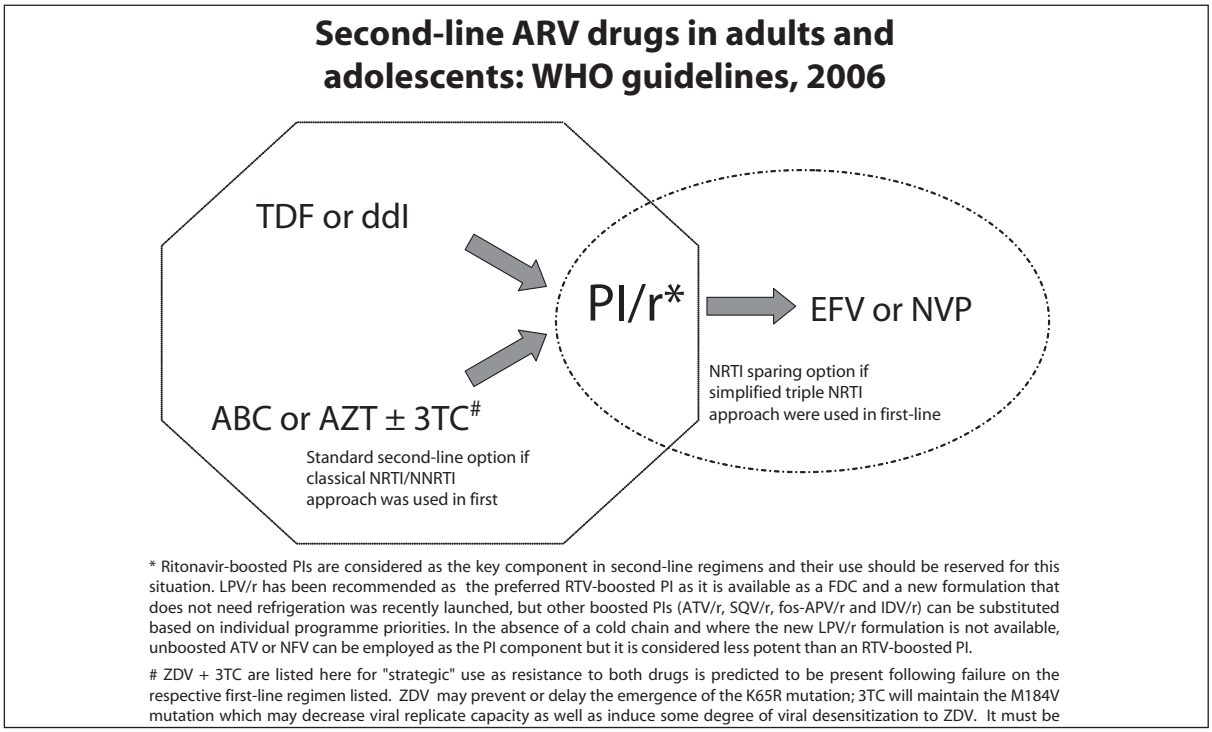
The WHO guidelines for ART therapy were originally developed in 2003 and underwent some minor revisions in 2004 and 2005. In 2006 there were some significant revisions to the WHO guidelines including the addition of abacavir (ABC), tenofovir (TDF) and emtricitabine (FTC) to recommended first-line regimens.

Figure 10. Revised first-line ARV drugs



Source: WHO. *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach*. Geneva, WHO, 2006.

Figure 11. Revised second-line ARV drugs



Source: WHO. *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach*. Geneva, WHO, 2006.

A large number of boosted protease inhibitors (PIs) have been added to the WHO-recommended second-line regimens. These include boosted atazanavir (ATZ), fos-amprenavir (fos-APV), saquinavir (SQV) and indinavir (IDV).

This means that many new ARV drugs are now available that clinicians need to learn about in addition to the specific use of ARVs for IDUs. These include:

- Stavudine (d4T): 30 mg (<60 kg) 40 mg (> 60 kg) twice a day
- Zidovudine (AZT): 300 mg twice a day
- *Lamivudine (3TC) : 150 mg twice a day (can be taken as 300 mg once a day)
- *Emtricitabine (FTC): 200 mg once a day
- *Abacavir (ABC): 300 mg twice a day (can be taken as 600 mg once a day)
- *Tenofovir (TDF): 300 mg once daily
- *Didanosine (ddI) enteric-coated: 400 mg (>60 kg), 250 mg (<60 kg) once daily
- *ddI 125 mg twice a day or 250 mg once a day (<60 kg); 200 mg twice daily or 400 mg once a day (>60 kg)
- Nevirapine (NVP): 200 mg twice daily
- *Efavirenz (EFV): 600 mg once daily
- Lopinavir (LPV) 400 mg/ritonavir (RTV) 100 mg (fixed-dose combination) (twice daily)
- *Saquinavir (SQV)1000 mg/RTV 100 mg (twice daily)
- *Fos-amprenavir (fos-APV): 700 mg/RTV 100 mg (twice daily)
- *Atazanavir (ATZ): 300 mg/RTV 100 mg (once a day)
- Indinavir (IDV): 800 mg/RTV 100 mg (twice daily)

* once-daily dosing possible

CHARACTERISTICS OF INDIVIDUAL ARV DRUGS

1. Lamivudine (3TC)

3TC is a well-tolerated cytidine analogue. Resistance develops rapidly; a single point mutation alone (M184V) is sufficient. However, this mutation increases the susceptibility to AZT, d4T, TDF. It delays accumulation of thymidine analogue mutations (TAMS) (multidrug NRTI resistance mutations) and can even reverse their effects. 3TC is also a potent inhibitor of HBV replication and is thus effective against hepatitis B infection.

Trade name: Epivir; component of Combivir, Epzicom, Trizivir, Kivexa. It exists also under other brand names or in other fixed-dose combinations (FDCs), or as generic 3TC.

Formulation:

Epivir tablets: 150 mg or 300 mg 3TC; oral solution 10 mg/ml

Combivir tablets: 150 mg 3TC + 300 mg AZT

Trizivir tablets: 150 mg 3TC + 300 mg AZT + 300 mg ABC

Epzicom/Kivexa: 300 mg 3TC and 600 mg ABC

Class: Nucleoside reverse transcriptase inhibitor (NRTI)

Oral dose Epivir: 300 mg qd or 150 mg bid

Food restriction: None

Side-effects: They are rare when using the individual drug. Fatigue, nausea, vomiting, diarrhoea, headache, insomnia, hair loss, myalgia and arthralgia may occur, but are usually due to other drugs in the combination (*see* AZT and ABC). Peripheral polyneuropathy, pancreatitis and lactic acidosis are rare.

Drug interactions/warnings: No significant drug interactions. However due to anti-HBV activity, discontinuing 3TC in patients with chronic B hepatitis may cause hepatitis flare.

Interactions with methadone and buprenorphine: Nil significant.

2. Abacavir (ABC)

ABC is a guanosine analogue with good CNS penetration. ABC is now licensed for once-daily dosing, both as an individual drug and as a component of FDCs. The main problem with ABC is hypersensitivity reaction. The drug is otherwise well-tolerated, possibly causing less mitochondrial toxicity than other drugs. Cross-resistance occurs with numerous other NRTIs. Resistance develops rapidly with triple NRTI regimens containing 3TC and TDF.

Trade names: Ziagen; component of Kivexa/Epzicom and Trizivir.

Formulation:

Ziagen tablets: 300 mg ABC; oral solution 20 mg/ml in 240 ml bottles

Epzicom/Kivexa tablets: 600 mg ABC + 300 mg 3TC

Trizivir tablets: 300 mg ABC + 150 mg 3TC + 300 mg AZT

Drug class: NRTI

Oral dose: 300 mg bid or 600 mg once a day (with or without food)

Food restriction: None

Side-effects: ABC causes a hypersensitivity syndrome in about 2–8% of patients. This usually occurs within the first six weeks after initiation of treatment. Pruritus and rash are common, but may also be absent. The hypersensitivity syndrome may present as just fever and slowly developing malaise. A genetic predisposition for the hypersensitivity syndrome (HLA-B*5701 allele) is likely. Other side-effects include gastrointestinal complaints (nausea, vomiting, diarrhoea, abdominal pain) and fatigue. Elevated liver enzymes, insomnia and dizziness are rare. Lactic acidosis and hepatic steatosis are rare and ABC can be used if this occurs with other NRTIs.

Comments/warning: ABC is contraindicated in cases with previously diagnosed ABC hypersensitivity and after interruption of therapy. Patients should be well advised about the hypersensitivity syndrome, but not frightened. If the symptoms are mild (*see below*), ABC should not be stopped too quickly, as an intercurrent infection may simulate the hypersensitivity syndrome. Therapy may be continued for one or two days under close observation. Rechallenge after suspected hypersensitivity syndrome is contraindicated, as a repeated allergic reaction can be worse or even fatal.

Patients should be told to consult a doctor **immediately** if at least two of the following symptoms occur:

- Fever
- Shortness of breath, sore throat or cough
- Rash (erythema and/or pruritus)
- Nausea, vomiting, diarrhoea or abdominal pain
- Extreme fatigue, diffuse pain or general malaise

ABC should not be used in a triple NRTI combination with 3TC and TDF due to rapid development of resistance.

Drug interactions: Alcohol (even small quantities) increases the area under the curve (AUC) of ABC by 41% and increases the half-life by 26%.

Interactions with methadone and buprenorphine: One study has shown an increase of 22% in oral methadone clearance but did not require a change in methadone doses because there were no withdrawal symptoms. However, this needs monitoring as some patients on methadone and ABC may require a dose alteration in OST.

3. Atazanavir (ATZ)

ATZ is a PI that has a favourable lipid profile although whether this will have implications for lipodystrophy remains to be seen. ATZ has a unique major resistance mutation that does not cause cross-resistance with other PIs. Another advantage is the possibility of once-daily dosing. Boosting ATZ with RTV is recommended (100 mg RTV + 300 mg ATZ), particularly when given in combination with TDF and EFV. The most important side-effects of ATZ are elevated bilirubin levels, which is medically inconsequential but may cause jaundice and scleral icterus.

Trade name: Reyataz

Formulation: 100, 150 and 200 mg capsules

Drug class: Protease inhibitor

Oral dose: 300 mg ATZ qd combined with 100 mg RTV once a day

Food restriction: Take with food (requires gastric acidity)

Side-effects: Hepatotoxicity, hyperbilirubinaemia (up to 50% of treated patients), elevated transaminases. Jaundice and scleral icterus are not unusual. Diarrhoea in approximately 30%. In addition: nausea, vomiting, headache, insomnia, abdominal pain, rash and asthenia can occur. In contrast to other PIs, dyslipidaemia is relatively rare. The effect on lipodystrophy remains unknown.

Comments/warning: Capsules should be swallowed whole without chewing.

Interactions: The following drugs are contraindicated: cisapride, pimozide, midazolam, triazolam, simvastatin, lovastatin, ergotamines, calcium antagonists and proton pump inhibitors.

Life-threatening interactions may occur with concomitant administration of amiodarone, lidocaine, tricyclic antidepressants and quinidine.

ATZ should not be given with rifampicin (reduces plasma levels of ATZ by 90%), St John's wort, and antacids, and used with caution in case of sildenafil, vardenafil. When combined with EFV, the ATZ dose should be increased to 400 mg (and still boosted with RTV 100 mg). When given concomitantly with TDF, ATZ should always be boosted with RTV 100 mg. Do not combine with IDV. ATZ should not be taken simultaneously with ddI tablets. Combining these drugs is only possible if ddI is taken at least two hours after ATZ/RTV and food. The reason is that the buffer in ddI chewable tablets prevents absorption of ATZ. Reduce: rifabutin dose by 75% (instead of 300 mg daily, give only 150 mg every other day or three times per week). Do not combine boosted ATZ with clarithromycin. Use with caution if impaired liver function. ATZ is contraindicated in patients with moderate to severe impairment of liver function. Contraception: an alternative to the pill is recommended.

Interactions with methadone and buprenorphine: ATZ is an inhibitor of CYP 3A4; however, clinically significant reactions with methadone and buprenorphine have not been reported.

4. Azidothymidine/zidovudine (AZT)

AZT has good CNS penetration, relatively low mitochondrial toxicity and good long-term tolerability.

Trade name: Retrovir; component of Combivir and Trizivir.

Formulation:

Retrovir capsules: 100 mg or 250 mg; tablets: 300 mg; 200 ml bottles for infusion

(10 mg/ml), 10 mg/ml syrup

Combivir tablets: 300 mg AZT + 150 mg 3TC

Trizivir tablets: 300 mg AZT + 150 mg 3TC + 300 mg ABC

Drug class: NRTI

Oral dose: 250 or 300 mg bid. In Combivir and Trizivir 300 mg bid

Food restriction: None

Side-effects: Nausea, vomiting, abdominal discomfort, altered taste, headache, myalgia and dizziness. Macrocytic anaemia (MCV almost always elevated and its steady increase over time can be a proof of regularly taking the drug), rarely neutropenia. Elevations in lactate dehydrogenase (LDH), creatine phosphokinase (CPK) and transaminases may occur. Fingernail discoloration (dark blue) after at least 2–6 weeks. Leg and gluteal myopathy is rare. Episodes of lactic acidosis are rare.

Interactions/warning: Do not combine with d4T! There is increased myelotoxicity if used with other myelosuppressive drugs, especially ganciclovir, but also co-trimoxazole, dapsone, pyrimethamine, interferon, sulphadiazine, amphotericin B, ribavirin and various other chemotherapeutic agents. Ribavirin antagonizes the antiviral activity of AZT in vitro. Concurrent use of AZT and ribavirin should therefore be avoided. Initially, monthly monitoring of blood count, transaminases, CPK and bilirubin is recommended. Gastrointestinal complaints can be treated symptomatically and usually subside after a few weeks. Anaemia can develop even after months.

Interactions with methadone and buprenorphine: Methadone increases levels of AZT by 30–40% thus monitoring should be done for signs of AZT toxicity such as anaemia, nausea and headaches. AZT has no effect on methadone levels. One study reported no significant interaction with buprenorphine.

5. Stavudine (d4T)

d4T is a thymidine analogue similar to AZT. Subjective tolerability is good. However, there is a growing body of unfavourable data on mitochondrial toxicity (lipoatrophy, lactic acidosis, peripheral neuropathy), particularly when given in combination with ddI.

Trade name: Zerit

Formulation: Capsules: 15 mg, 20 mg, 30 mg, 40 mg. Solution 1 mg/ml

Drug class: NRTI

Oral dose: 40 mg bid for body weight >60 kg; 30 mg bid for body weight <60 kg

Food restriction: None

Side-effects: Peripheral neuropathy, especially in combination with ddI (up to 24%). d4T has been linked to lipoatrophy more than other NRTIs. However, the following are less frequent than with AZT: diarrhoea, nausea, vomiting and headache. Very rare, but potentially fatal: lactic acidosis, which occurs mostly in combination with ddI (especially in pregnancy). Other side-effects: hepatic steatosis, pancreatitis.

Drug interactions/warning: d4T should not be combined with AZT. Contraindicated with existing peripheral neuropathy. If possible, do not use concurrently with other neurotoxic drugs zalcitabine [ddC], ethambutol, cisplatin, INH, vincristine, etc.). If symptoms of peripheral neuropathy occur, treatment with d4T should be discontinued.

Drug interactions with methadone/buprenorphine: Methadone reduces the AUC of d4T by 27%, which does not appear to be clinically significant and does not require dose adjustment. d4T has no effect on methadone levels and there are no reported interactions with buprenorphine.

6. Didanosine (ddI)

ddI is an NRTI that was introduced in the early 1990s. The main side-effects of ddI are gastrointestinal complaints. Pancreatitis is a specific, though rare, side-effect, which is thought to be dose-dependent. It may occur in up to 10% of patients, and can be fatal in individual cases. ddI has a long intracellular half-life and convenient once-daily dosing is possible; however, the drug must be taken on an empty stomach. Combination with d4T is also problematic as there are cumulative toxicities.

Trade name: Videx.

Formulation: Buffered chewable tablets 100 mg, 200 mg and 25 mg, which can also be dissolved in water.

Enteric-coated capsules: 125 mg, 200 mg, 250 mg, 400 mg

Powder: 4 g per bottle

Other locally produced formulations available in some countries.

Drug class: NRTI

Oral dose: 400 mg qd (body weight >60 kg) or 250 mg qd (body weight <60 kg)

Food restriction: ddI (both buffered and enteric-coated) must be taken on an empty stomach, at least 2 hours after or at the latest 1 hour before meals.

Side-effects: Diarrhoea, nausea, headache, rash. Pancreatitis is rare but can occur even after longer periods on treatment. Peripheral polyneuropathy. Lactic acidosis is unusual but can happen in combination with d4T.

Interactions/warning: Acute and chronic pancreatitis are contraindications. Use with caution in patients with alcoholism. The following drugs should be used with caution: ethambutol, cisplatin, disulfiram, ethionamide, INH, vincristine, etc. (peripheral neuropathy). Treatment with IDV, ATZ, dapsone, ketoconazole, itraconazole or tetracyclines should be given 2 hours before or after ddI. Initially, monthly monitoring of amylase, blood counts, transaminases and bilirubin is recommended. Patients should be informed about the risk of pancreatitis. ddI should be discontinued if there is clinical suspicion of pancreatitis, with no rechallenge. Do not use with TDF due to reduced efficacy.

Interaction with methadone and buprenorphine: When methadone is used concurrently with buffered ddI the AUC of buffered ddI was reduced by 63%. Thus, it is recommended to use enteric-coated ddI as this formulation has no clinically significant interaction when given concurrently with methadone. ddI has no effect on methadone levels and there is no evidence of interaction with buprenorphine although data are limited.

7. Efavirenz (EFV)

EFV is a frequently used NNRTI. It has multiple CNS side-effects (disturbances of sleep architecture, morning dizziness, somnolence, nightmares). Further disadvantages include drug interactions and cross-resistance with nevirapine.

Trade name: Sustiva, Stocrin

Formulation: Capsules: 50 mg, 100 mg, 200 mg, 600 mg

Drug class: NNRTI

Oral dose: 600 mg daily (1 capsule of 600 mg qd or 3 capsules of 200 mg qd), preferably before going to bed.

Food restriction: Best taken on empty stomach at night time (especially in the first month to minimize CNS side-effects) as meal increases AUC by 20% and peak level by 40%. Can take with a low-fat meal.

Side-effects: 50% of patients will have some form of neurological side-effects in the first month of treatment: nightmares, confusion, dizziness, somnolence, abnormal thinking, impaired concentration, insomnia and depersonalization. These CNS symptoms usually resolve after a few days/weeks. A rash (15%) may also occur in the first weeks, but severe cases of blistering, desquamation and ulceration are rare. Elevation of liver function tests and biliary enzymes, especially gamma-glutamyltransferase (GGT) can occur in addition to hypercholesterolaemia and hypertriglyceridaemia.

Interactions/warnings: Contraindicated in pregnancy. Contraindicated if concurrent treatment with ergotamines, astemizole, cisapride, midazolam, terfenadine and triazolam. Should not be combined with contraceptive pills. Should not be given in combination with SQV or amprenavir (APV) without RTV boosting (insufficient plasma levels of SQV and APV).

Dose adjustments needed in combination with:

- LPV: increase LPV dose to 4 capsules bid.
- ATZ: keep RTV boost and increase ATZ to 400 mg (ATZ/RTV: 400/100); take with meals.
- IDV: increase IDV dose to 1000 mg tid.
- Rifabutin: increase rifabutin dose to 450–600 mg/day.

Due to its long half-life, EFV should be discontinued at least 7–14 days before other backbone drugs, in order to prevent the development of resistance.

Interactions with methadone and buprenorphine: EFV induces the metabolism of methadone (by inducing CYP450) and can reduce methadone levels by up to 50% resulting in methadone withdrawal. ARV prescribers must consult with drug substitution team as methadone dose is likely to need titration upwards by 20–60% (one study reported that 68% of patients initiating EFV while on methadone required on average a 50% increase in their methadone dose). Because CYP450 induction associated with EFV may take up to 14 days to occur and because of the long half-life of methadone, symptoms of withdrawal may be delayed by 2–3 weeks. EFV also decreases buprenorphine levels but this was not associated with any clinically significant withdrawal symptoms. Buprenorphine does not alter EFV levels.

8. Emtricitabine (FTC)

Emtricitabine is a well-tolerated cytidine analogue, comparable to 3TC both biochemically and in its resistance profile. It has a significantly longer half-life and can be taken once a day. FTC is active against hepatitis B.

Trade name: Emtriva. Also in Truvada in combination with tenofovir

Formulation: Hard capsules with 200 mg; solution: 170 ml with 10 mg/ml

Drug class: NRTI

Dose: 200 mg qd (oral solution: recommended dose 240 mg = 24 ml)

Food restrictions: None

Side-effects: Probably rare. FTC is well-tolerated. Occasionally headache, nausea, diarrhoea, rash. Hyperpigmentation on palms and soles of feet.

Drug interactions/warning: No clinically significant interactions known.

Interactions with methadone and buprenorphine: No clinically significant interactions with either methadone or buprenorphine.

9. Fos-amprenavir (Fos-APV)

Fos-APV is a calcium phosphate ester of APV. It has improved solubility and is better absorbed than APV. This significantly reduces the number of pills compared with APV. Overall tolerability is fairly good, and Fos-APV has an interesting resistance profile and a variety of possibilities for dosing (*see below*).

Trade name: USA: Lexiva, Europe: Telzir

Formulation: 700 mg capsules

Drug class: Protease inhibitor

Dose: The recommended daily doses for **treatment-naive** patients vary:

- 1400 mg bid (without RTV) = 2 pills bid
- 1400 mg qd + 200 mg RTV qd = 2 + 2 pills once a day
- 700 mg bid + 100 mg RTV bid = 1 + 1 pills bid

The once-daily version is not recommended for PI-experienced patients. **PI-experienced** patients should therefore only receive the following dose: 700 mg bid + 100 mg RTV bid (1 + 1pills bid).

Food restrictions: None

Side-effects: Diarrhoea, nausea, vomiting, headache, rash (up to 20%). Rarely Stevens–Johnson syndrome (<1%).

Interactions/warning: Contraindicated: cisapride, pimozide, midazolam, triazolam, ergotamines. Flecainide and propafenone are also contraindicated when fos-APV is boosted with RTV. There may be life-threatening interactions on concurrent administration of amiodarone, lidocaine (systemic), tricyclic antidepressants and quinidine.

Do not use together with rifampicin (this reduces APV plasma levels by 90%), delavirdine or St John's wort. Use cautiously with simvastatin, lovastatin, sildenafil, vardenafil. Carbamazepine, phenobarbital, phenytoin and dexamethasone can lower plasma levels of APV.

EFV seems to lower APV plasma levels significantly (probably to an extent that is clinically relevant). However, this is not the case if fos-APV is boosted with RTV. But: if Fos-APV + RTV are administered once-daily, the RTV dose of RTV should be increased by 100 mg: EFV + 1400 mg fos-APV qd + 300 mg RTV qd. Twice-daily dosing does not require a dose adjustment of RTV. If fos-APV is used with rifabutin a dose reduction of rifabutin by at least 50% is needed. If fos-APV is boosted with RTV, a 75% reduction of the rifabutin dose is required (instead of 300 mg daily, only 150 mg every other day, or 150 mg three times per week). If fos-APV is boosted with RTV, ketoconazole and itraconazole doses above 200 mg daily are not recommended. Use with

caution in patients with sulfonamide allergy. Caution with reduced liver function (possibly dose reduction). There are no data on the combination with RTV for such cases. Contraception: an alternative to the pill is recommended. Caution: in combination with LPV plasma levels of both drugs are reduced!

Drug interactions with methadone and buprenorphine (based on studies of APV). Methadone levels are reduced 15–35% in patients also receiving fos-APV although withdrawal effects may not be associated with this reduction. Need to monitor patients on methadone and fos-APV carefully for withdrawal and may need to increase methadone dose.

10. Indinavir (IDV)

IDV was one of the first PIs to be licensed in 1996. Problems with side-effects limit its use today. There is cross-resistance with other PIs. IDV requires thrice-daily dosing on an empty stomach in its unboosted form, which is unacceptable for many patients. Therefore, IDV is now used almost exclusively with RTV boosting.

Trade name: Crixivan

Formulation: Capsules of 100 mg, 200 mg, 333 mg and 400 mg

Drug class: Protease inhibitor

Dose: In combination with RTV:

- 800 mg bid (two 400 mg capsules bid) plus 100 mg RTV bid (one 100 mg capsule bid)
- 400 mg bid (one 400 mg capsule bid) plus 400 mg RTV bid (four 100 mg capsules bid)

Dose without RTV: 800 mg tid (two 400 mg capsules tid) (not recommended by WHO)

Food restriction: None if boosted with RTV but if unboosted need to take IDV one hour before meals or two hours after meals. At least 1.5 L of fluid should be consumed daily to prevent nephrolithiasis.

Side-effects: Nephrolithiasis (in up to 25%). Symptoms (haematuria, flank pain) must be explained to the patient. The occurrence of nephrolithiasis and skin problems correlates with plasma levels. Less frequently: nephrotoxicity with elevated serum creatinine. Diarrhoea, nausea, vomiting. A sicca syndrome occurs relatively frequently (dry skin, mouth, eyes); ingrown toenails and paronychia; rarely alopecia. Asymptomatic hyperbilirubinaemia. Lipodystrophy ('crixibelly'), dyslipidaemia, disorders of glucose metabolism.

Drug interactions/warning: Concurrent use of rifampicin, astemizole, terfenadine, cisapride, triazolam, ergotamines, simvastatin, lovastatin, or St John's wort is contraindicated. The following dose adjustments are necessary:

- Rifabutin: 1000 mg IDV + 150 mg rifabutin
- Ketoconazole and itraconazole: 600 mg IDV tid
- Sildenafil: maximum 25 mg sildenafil/48 h

Interactions with methadone and buprenorphine: There appears to be no change in either the IDV or methadone concentrations. There are limited data on the interaction between IDV and buprenorphine.

11. Lopinavir/ritonavir (LPV/r)

Trade name: Kaletra

Formulation:

Capsules with 133.3 mg LPV + 33.3 mg RTV (production under discontinuation)

Tablets (new formulation) with 200 mg LPV + 50 mg RTV

Drug class: Protease inhibitor

Oral dose: 3 capsules bid or 2 tablets bid. When given in combination with EFV or NVP, the dose should be increased to 4 capsules or 3 tablets bid.

Food restrictions: Take with food

Side-effects: Mainly diarrhoea, bloating, nausea, dyslipidaemia and lipodystrophy. Also: headaches and elevated transaminases.

Interactions/warning: Drug interactions are numerous. All drugs metabolized by the CYP3A or CYP2D6 enzyme systems are contraindicated: flecainide, propafenone, astemizole, terfenadine, ergotamines, cisapride, pimozide, midazolam, triazolam. Rifampicin and St John's wort reduce the efficacy of LPV. Caution with: lovastatin, simvastatin (myopathy, rhabdomyolysis), carbamazepine, phenobarbital, phenytoin or sildenafil (hypotension), amiodarone, warfarin, lidocaine, tricyclic antidepressants, quinidine, cyclosporin, tacrolimus. Caution in patients with reduced liver function tests, especially in cases with hepatitis B or C coinfection or significantly elevated transaminases. If LPV is combined with ddI, the latter must be taken one hour before or two hours after LPV. Caution with contraceptive pills (contraception not safe). When used with rifabutin, the rifabutin dose should be reduced by 75% (i.e. to 150 mg qd every two days).

Interactions with methadone and buprenorphine: There are conflicting data on the interaction between Kaletra and methadone. One study showed that the AUC of methadone was reduced by 26–36% in patients taking both Kaletra and methadone concurrently but no patient reported any symptoms of opioid withdrawal or required an increase in methadone dose. However, another study reported that the AUC of methadone was reduced significantly in patients taking both Kaletra and methadone concurrently and that opioid withdrawal symptoms were significantly increased. Thus, patients taking both Kaletra and methadone should be monitored carefully and the methadone dose be increased as necessary. There are little data on the interaction between Kaletra and buprenorphine.

12. Nelfinavir (NFV)

Nelfinavir is a relatively well-tolerated PI, but it is slightly less potent than boosted PIs and levels of NFV do not increase with RTV boosting. An NFV-based PI regimen is less potent than NNRTI regimens. Main problems include high pill burden and frequent diarrhoea.

Trade name: Viracept

Formulation: 250 mg tablets; 625 mg tablets

Drug class: Protease inhibitor

Oral dose: 1250 mg bid

Food restriction: Take with high-fat meals.

Side-effects: Diarrhoea is common and nausea can also occur. Lipodystrophy, dyslipidaemia, reduced glucose tolerance.

Comments/warning: Contraindicated for co-medication with rifampin, oral contraceptive pills, astemizole, terfenadine, cisapride, triazolam, ergotamines, simvastatin, lovastatin and St. John's wort. In combination with rifabutin: reduce rifabutin to 150 mg qd and increase NFV dose to 1000 mg tid. Diarrhoea can usually be controlled with loperamide (2 mg with each fluid bowel movement, up to a maximum of 16 mg/day). Boosting with RTV is not advisable, as levels are not significantly changed.

I**nteractions with methadone and buprenorphine:** Results from studies on the effects of concurrent administration of NFV and methadone are conflicting. One study reported that significant decreases in methadone were observed, but without clinically significant opiate withdrawal. Other studies have reported withdrawal symptoms and dose increase. However, the manufacturer states that NFV reduces the AUC, C_{max} and C_{min} of methadone and that the dosage of methadone may need to be increased when co-administered with NFV. As with all of these interactions, clinical observation and tailoring of the methadone dose to the patient's symptoms of opioid craving and withdrawal is the guiding principle. There are little data on drug interactions between NFV and buprenorphine.

13. Nevirapine (NVP)

NVP is a frequently prescribed NNRTI, which is also used successfully for the prevention of mother-to-child transmission (PMTCT). As with all NNRTIs, a single point mutation is sufficient to develop high-level resistance. In order to prevent allergic reactions, lead-in dosing is always required. NVP has good long-term tolerability with a favourable lipid profile. The main problem, besides the development of resistance, is hepatotoxicity which occurs during the first months of treatment (*see below*).

Trade name: Viramune

Formulation: 200 mg tablets and 10 mg/ml suspension

Drug class: NNRTI

Oral dose: 200 mg tablet bid. Always start with lead-in dosing (200 mg once a day for 2 weeks), which reduces the frequency of rash. For resumption of treatment after treatment interruption, lead-in dosing is generally not necessary if the drug was well-tolerated. Due to its long half-life, NVP should be discontinued at least 7–14 days before other backbone drugs, in order to prevent the development of resistance.

Food restrictions: None

Side-effects: Hepatotoxicity and rash. Less frequently fever, nausea, drowsiness, headache and myalgia. These side-effects may occur with or without hepatotoxicity and/or rash. ALT elevation on NVP is almost the rule. To detect **hepatotoxicity** (occurs in 15%; defined as an increase in transaminases to at least three times the upper limit of normal), LFT should be monitored bi-weekly for the first two months. Thereafter, monthly tests are necessary, as more than half of the hepatotoxic episodes occur after the first quarter of treatment. In such cases, treatment must be interrupted until LFT returns to initial levels. Treatment is restarted with 200 mg qd. The dose may be increased to 200 mg bid only after a prolonged period of observation. If liver enzymes increase again, NVP should be permanently discontinued.

A **rash**, often pruritic and usually occurring within the first six weeks of treatment, can be treated with antihistamines if the mucous membranes are not involved and if transaminases

are normal. Topical formulations are effective against pruritus. NVP must be discontinued if a severe rash occurs; in these cases, steroids may be used (e.g. prednisone 1 mg/kg for 3–5 days). NVP should also be discontinued if other systemic symptoms occur (fever, conjunctivitis, myalgia, arthralgia, malaise). If the rash occurs during the first two weeks of treatment, the dose should not be increased until the rash has resolved completely. Prophylactic treatment with steroids or antihistamines is not advised.

Drug interactions/warning: Cautious use in hepatic dysfunction. Contraindicated if co-medication with rifampicin, ketoconazole, St John's wort and the pill. Azole derivatives: fluconazole should be used for antimycotic treatment. Dose adjustment in combination with:

- LPV: possibly increase Kaletra dose to 4 capsules bid.
- IDV: increase IDV dose to 1000 mg tid.
- Methadone: if withdrawal symptoms occur, dose may need to be increased.

NVP has a favourable long-term profile. In particular, lipid levels are usually positively influenced. GGT is almost always increased during long-term treatment. Values of up to 150 U/l can be tolerated. NVP should not be given for post-exposure prophylaxis.

Interaction with methadone and buprenorphine: When NVP is used concurrently with methadone, the methadone AUC decreases by approximately 46% due to CYP450 induction. Narcotic withdrawal has been reported when NVP was added to stable methadone treatment. Because CYP450 enzyme induction associated with NVP use may take up to 14 days to occur and because of the long half-life of methadone, symptoms of withdrawal may be delayed for up to 2–3 weeks. To offset this interaction, patients often require an increase in their methadone maintenance dose. One study reported that 75% of patients started on NVP while receiving concurrent methadone required an average increase of 16% (15–25%) in their methadone maintenance dose. Clinicians initiating an ART regimen consisting of NVP should contact methadone maintenance clinicians to ensure that the onset of withdrawal symptoms is promptly addressed by increasing the patient's methadone dose. Clinicians prescribing methadone maintenance therapy should develop plans for close monitoring of patients when adding nevirapine to their ARV regimens. There are limited data on the interactions of NVP and buprenorphine.

14. Ritonavir (RTV)

Due to its gastrointestinal side-effects, the therapeutic dose of RTV is hardly acceptable and rarely prescribed. However, RTV has become an important drug for boosting other PIs. In these combinations, when lower doses are used, the side-effects of RTV are tolerable. Numerous drug interactions must be considered.

Trade name: Norvir

Formulation:

100 mg soft gel capsules

80 mg/ml oral solution.

Drug class: Protease inhibitor

Oral dose: The dose of RTV used for boosting of other PIs is as follows:

Saquinavir:

- 100 mg RTV bid + 1000 mg SQV bid or
- 400 mg RTV bid + 400 mg SQV bid

Indinavir:

- 100 mg RTV bid + 800 mg IDV bid or
- 400 mg RTV bid + 400 mg IDV bid

Atazanavir:

- 100 mg RTV qd + 300 mg ATZ qd

Fos-amprenavir:

- 200 mg RTV qd + 1400 mg fos-APV qd (once-daily dosing is not suitable for treatment-experienced patients) or
- 100 mg RTV bid + 700 mg fos-APV bid.

Food restrictions: On its own RTV does not need food restrictions but as it is generally used to boost other PI drugs, food restrictions are related to the PI that is boosted by RTV.

Side-effects: Very frequent when RTV is used as single PI (600 mg bid) but relatively uncommon with dose used for boosting. Side-effects include: nausea, vomiting, diarrhoea, headache, perioral paraesthesia and electric sensations on arms and legs. Elevated transaminases and GGT, often significant dyslipidaemia, reduced glucose tolerance and, rarely, diabetes mellitus. Lipodystrophy.

Drug interactions/warning: Even the low boosting doses used in combination with other PIs have multiple drug interactions. The following are contraindicated when RTV is used: rifampicin, amiodarone, astemizole, bepridil, terfenadine, encainide, flecainide, cisapride, triazolam, ergotamine, simvastatin, lovastatin, quinidine and St John's wort. Sildenafil should be avoided. The following co-medications should be used with caution: methadone, immunosuppressants (cyclosporin, tacrolimus), macrolide antibiotics (erythromycin, clarithromycin), steroids, calcium antagonists, tricyclic antidepressants, other antidepressants (fluoxetine, paroxetine,sertraline), neuroleptics (haloperidol, risperidone, thioridazine), antimycotic drugs (ketoconazole, itraconazole), carbamazepine, tolbutamide, rifabutin, theophylline and warfarin.

Drug interactions with methadone and buprenorphine: Data on concurrent use of RTV and methadone are conflicting; in addition, as RTV is mostly used to boost other PIs it is important to examine interactions with these PIs and methadone in addition to RTV and methadone. One source relates that RTV inhibits CYP3A4 and modestly increases methadone concentration with no adjustments to methadone being required. Another source documents that when methadone and RTV are used concurrently the dose of methadone can be decreased by 36%. Thus, patients taking both Kaletra and methadone should be monitored carefully and an increase in the methadone dose may be necessary. There are little data on interactions between RTV and buprenorphine.

15. Saquinavir (SQV)

SQV was the first PI to be licensed for HIV therapy in 1995. It is well-tolerated except for gastrointestinal problems, and with no serious short-term problems. It is almost exclusively used together with a RTV boost. Invirase 500 (film-coated tablets) is now the preferred formulation of SQV.

Trade name: Invirase, Fortovase

Formulation:

500 mg film-coated tablets (Invirase 500) = preferred formulation of SQV

200 mg soft gel capsules (Fortovase)

Drug class: Protease inhibitor

Oral dose: Combination with RTV is generally preferred: Invirase or Fortovase: 1000 mg bid plus 100 mg RTV bid

Food restrictions: Take within 2 hours of a meal

Side-effects: Mainly gastrointestinal: diarrhoea, nausea, abdominal bloating and discomfort. Rarely, elevation of transaminases or GGT, headache. As with other PIs, lipodystrophy, dyslipidaemia and reduced glucose tolerance may occur with long-term treatment.

Drug interactions/warning: Contraindicated for co-medication with rifampicin, astemizole, terfenadine, cisapride, triazolam, ergotamine, simvastatin, lovastatin and St John's wort.

Interactions with methadone and buprenorphine. A study that evaluated the effects of SQV + RTV (400 mg/400 mg) on the pharmacokinetics of methadone showed reduction of methadone concentration; however, no study participant experienced withdrawal symptoms and no changes in methadone dosage were required. Another study evaluating the effects of daily SQV/RTV (1600 mg/100 mg) on unbound methadone identified that methadone concentration was unchanged. Researchers also reported reductions in SQV drug exposure; however, the majority of patients (83%) maintained minimum concentrations of SQV above the half maximal effective concentration (EC_{50}) for this drug. Therefore, there seems to be no clinically significant interaction for most patients receiving concurrent SQV and methadone. There are little data on the interaction of SQV/RTV and buprenorphine.

16. Tenofovir (TDF)

TDF has a good tolerability profile and probably only low mitochondrial toxicity. TDF also has efficacy against hepatitis B virus. It should not be used in triple NRTI regimens unless there is a special indication. Cautious use in patients with renal disease.

Trade name: Viread, Truvada (combined with FTC)

Formulation: 300 mg tablets

Drug class: Nucleotide reverse transcriptase inhibitor

Oral dose: 300 mg qd

Food restriction: No substantial effect but fatty meals increase absorption by 40%

Side-effects: Generally well-tolerated. Rarely: elevation of liver enzymes. Rare cases of renal failure have been reported, partly in the form of Fanconi syndrome, a defect of proximal tubular transport. Patients with existing renal disease should therefore either not receive TDF or otherwise always be given a lower dose. It is not currently known whether long-term treatment with TDF can lead to bone density changes. Animal studies showed changes in bone density at doses 30 times higher than the therapeutic dose.

Drug interactions/warning: Concurrent treatment with TDF and other drugs that are eliminated via active tubular secretion can lead to increased serum concentrations of both drugs: cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir. ATZ and LPV increase TDF levels but with no resulting toxicity. Larger controlled studies on the use of TDF in pregnancy are yet to be done. In monkey studies, TDF was effective in the prophylaxis of simian immunodeficiency virus (SIV) transmission, but also resulted in growth disorders.

Interactions with methadone and buprenorphine: Limited data but it appears that there is no significant interaction between TDF and methadone or buprenorphine.

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EXERCISE 6.3.1

Matrix of ARV drugs

Name	Class	How the drug works	Dosing recommendation	Food effect	Minor side-effects	Major toxicities	Interaction with methadone and buprenorphine	Interaction with ARVs and other drugs
AZT								
FTC								
EFV								
Fos-APV								

EXERCISE 6.3.2

Matrix of ARV drugs

Name	Class	How the drug works	Dosing recommendation	Food effect	Minor side-effects	Major toxicities	Interaction with methadone and buprenorphine	Interaction with ARVs and other drugs
d4T								
ABC								
SQV								
LPV								

EXERCISE 6.3.3

Matrix of ARV drugs

Name	Class	How the drug works	Dosing recommendation	Food effect	Minor side-effects	Major toxicities	Interaction with methadone and buprenorphine	Interaction with ARVs and other drugs
3TC								
TDF								
NVP								
IDV								

EXERCISE 6.3.4

Matrix of ARV drugs

Name	Class	How the drug works	Dosing recommendation	Food effect	Minor side-effects	Major toxicities	Interaction with methadone and buprenorphine	Interaction with ARVs and other drugs
ATZ								
ddI								
NFV								
RTV								

Sub-module

6.4

Selecting a first-line regimen and starting ART

OVERVIEW

Objectives:

By the end of the session participants will be able:

- To understand the issues that need to be addressed before an HIV-positive IDU can start ART
- To appreciate and understand the complexity of factors influencing the choice of ART regimens for HIV-positive IDUs
- To demonstrate a detailed understanding of all the ART regimens included those in the revised WHO 2006 Guidelines
- To analyse the most important aspects of the clinical and social history of an HIV-positive IDU and choose a suitable regimen for this client.

Time to complete session:

2 hours 30 minutes

Session content:

- Principles of treatment and care for HIV/AIDS in IDUs
- Selecting a first-line regimen: general principles
- Clinical criteria for starting ART
- Baseline clinical assessment
- Issues impacting the choice of ART regimen in IDUs

Training materials:

- PowerPoint presentation 6.4: Selecting a first-line regimen and starting ART
- Sub-module 6.4: Selecting a first-line regimen and starting ART
- Exercises 6.4.1 and 6.4.2

PRINCIPLES OF TREATMENT AND CARE FOR HIV/AIDS IN IDUs

As discussed in Sub-module 6.2, ART is as effective for IDUs as for other PLWHA. Given appropriate support, former and active IDUs can adhere to ART and should have equal access to it. Current or past drug use is not a criterion for deciding on whether or not to give ART. Despite this, special attention is required while giving ART in the presence of substance dependence and co-morbidities. Provision of good quality OST is an essential HIV care component and is highly effective in addressing opioid dependence and supporting ART adherence. IDUs who are not enrolled in an OST programme are three times less likely to be receiving ART than IDUs enrolled in such a programme (Celentano et al. 1998); however, the absence of OST should not be a barrier to starting ART in patients who need it. Additional adherence support strategies may be required for IDUs who cannot access OST. The basic WHO first-line ART regimens are suitable for most IDUs.

SELECTING A FIRST-LINE REGIMEN: GENERAL PRINCIPLES

The primary goals of ART are:

1. Reduction of HIV-related morbidity and mortality
2. Improvement in the quality of life
3. Preservation and/or restoration of immune function
4. Maximal and durable suppression of blood viral load

Decisions to initiate therapy should be based on clinical and immunological criteria, and the willingness and ability of the patient to accept therapy and undergo an ARV readiness/adherence education and counselling process.

In order to achieve the goals, the outpatient clinic needs to support:

1. A comprehensive care and treatment programme with a fully operational continuum of care programme
2. Maximum adherence to the ART regimen (>95%)
3. Rational choice of ART regimens and preservation of future treatment options

For any individual starting ART it is essential to consider:

- Efficacy: potency and durability of the ART regimen
- Convenience: pill burden, food restriction, heat-stability and ease of carrying drugs
- Safety:
  - Short-term
  - Long-term: cardiovascular system, lipodystrophy, body shape changes, diabetes
- Drug interactions
- Special conditions such as pregnancy
- Cost and availability

When selecting a first-line regimen for IDU clients, you also need to pay special attention to:

- Frequent co-morbidities: tuberculosis, hepatitis B and C, pregnancy
- Frequent cotreatments:
  - TB treatment (rifampicin-based regimens)
  - Interferon/ribavirin (IFN/RBV) treatment in hepatitis
  - OST
- Regimens that optimize adherence (e.g. once daily, suitable for directly observed treatment [DOT], low pill burden, minimal side-effects)

CLINICAL CRITERIA FOR STARTING ART

The timing of starting ART is important. It is best to start ART before a client is too sick to respond well; however, this needs to be balanced against rushing into starting ART too early and limiting options for the future. Starting lifelong ART is rarely an emergency measure. In general, opportunistic infections (OIs) are responsible for most of the morbidity and mortality; therefore, they should be identified and treated before considering ART. It is also very important that a client receiving OST is stable before commencing ART.

Table 1: When to start antiretroviral therapy

WHO clinical staging	CD4 count available	CD4 count not available
1	**Treat** if <200 cells/mm^3 (**Consider treatment** if below 350 cells/mm^3, particularly if closer to 200–250 cells/mm^3)	**No treatment**
2	**Treat** if <200 cells/mm^3 (Consider treatment if below 350 cells/mm^3, particularly if closer to 200–250 cells/mm^3)	**Treat** if total lymphocyte count (TLC) <1200 cells/mm^3
3	**Treat** but consider CD4 counts for better management and decision-making in some situations (e.g. TB)	**Treat** irrespective of TLC
4	**Treat** irrespective of CD4 count	**Treat** irrespective of TLC

Source: WHO guidelines, 2006.

Reviewing of the client before commencing ART should only be done when all other aspects of care have been initiated, when patients have started co-trimoxazole prophylaxis, and they are linked to all services. The clinical benefits of taking ART are usually not seen before 6–8 weeks after commencing therapy. Laboratory improvement takes much longer.

Starting ART before the patient really understands the overriding importance of strict, long-term adherence to treatment, will result in a poor outcome for that individual. Poor compliance or defaulting from follow-up will lead to the rapid development of viral resistance, which will limit the benefit of treatment and future treatment options.

The decision to start therapy should only be made after careful assessment of the clinical state, review of immune function AND considering the patient's acceptance of or readiness for treatment and the need for adherence.

BASELINE CLINICAL ASSESSMENT

1. Staging of HIV disease including the CD4 count where available (or TLC)
2. Major medical conditions and coinfections (TB, HBV, HCV, stability of OST, major psychiatric illness)
3. Pregnancy
4. Previous ART
5. Current medications, including OST and traditional therapies
6. Assess for current opportunistic infections (OIs)
7. Baseline laboratory tests – including TB screening
8. Baseline weight and functional status

Baseline tests prior to starting ART:

- HIV test (if no prior confirmation is available)
- CBC (including TLC)
- HBV, HCV serologies (if available)
- Rapid plasma reagin (RPR) test (for syphilis) if available
- Liver function tests (LFT), renal function tests
- Pregnancy test
- CD4 count or TLC (if CD4 is not available)
- Chest X-ray (CXR) and sputum x 3 (if a clinical suspicion of TB exists)

Clinicians should make sure that a client is stable on OST (i.e. number of days not attended, recent changes in dosing) and ascertain concurrent substance use. Clinicians also need to make sure that they have informed other relevant health workers involved in the management of a client, particularly those involved in OST about the initiation of ART. Clinicians in both fields will need to carefully monitor IDUs on ART and OST for symptoms of withdrawal or overdose.

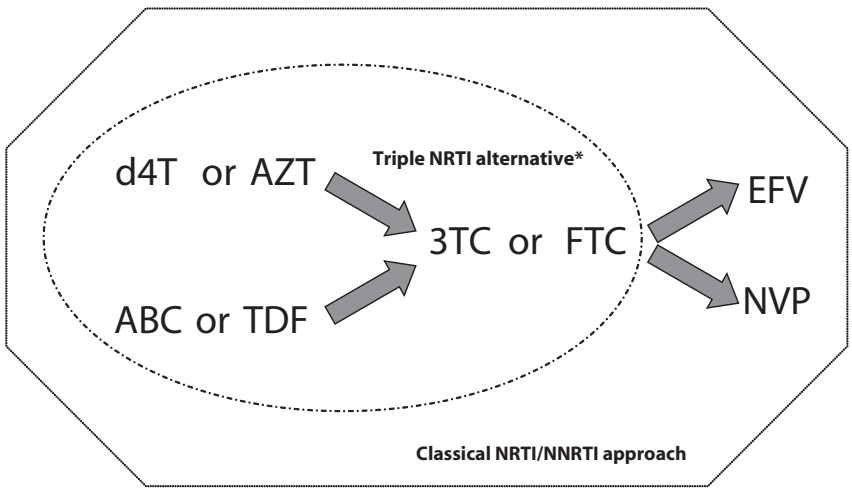
Preparation of the client and treatment supporters

It is important that clients and treatment supporters are well informed and committed to ART. They need to demonstrate an understanding of:

- HIV/AIDS
- ART and the need for lifelong treatment
- The importance of adherence
- Side-effects of ARVs
- The need for follow up post-treatment

Patients will be more likely to continue medications if they know what to expect, avoid and manage side-effects, and are able to contact someone if side-effects occur. In addition, clinicians need to ensure that a client is well educated about the potential interactions between OST and ART. Clinicians must discuss potential drug interactions with patients receiving methadone or buprenorphine including the possibility of withdrawal symptoms and the need to potentially increase the dose of methadone.

Figure 12: First-line regimens recommended by WHO



* Triple NRTI should be considered as a simplification strategy for first-line therapy as suggested above, mainly for situations where NNRTI options provide additional complications (e.g. pregnancy, viral hepatitis coinfection, TB coinfection, women who wish to become pregnant or who have CD4 counts >250 cells/mm^3; NVP or EFV grade 4 serious adverse events; HIV-2 or HIV- 0; adolescents).

Source: WHO, guidelines, 2006

ISSUES IMPACTING THE CHOICE OF ART REGIMEN IN IDUs

Co-morbidity factors:

- If chronic HBV is present, 3TC, FTC and TDF are active against both infections. At least one of them should be employed in the combination.
- NVP may not be used if there is coexisting significant liver disease (HCV, HBV, alcohol). Simple serological positivity is not a sufficient criterion to avoid the use of NVP.
- EFV may not be used in individuals with serious psychiatric disorders.
- In alcohol users, the potential for pancreatitis and peripheral neuropathy is increased with d4T.
- Pregnant women or those who wish to become pregnant should avoid EFV.
- Co-treatment factors:
  - If the treatment of TB includes rifampicin, EFV should be chosen rather than NVP as it is less likely to cause hepatotoxicity.
  - If the treatment of TB includes isoniazid, avoid d4T as the risk of peripheral neuropathy is much higher if both drugs are used.
  - Interactions with methadone/ARV.
  - Interactions with buprenorphine/ARV.
  - EFV and pegylated intrferon (PEG-IFN) are associated with the risk of severe depression.

Table 2: Choosing the nucleoside reverse transcriptase inhibitor (NRTI) backbone

• **d4T**
– Can be used for most patients – well-tolerated
– Twice-daily dosing
– Long-term mitochondrial toxicity (lactic acidosis and lipoatrophy)
– Should not be used if neuropathy is present or patient on other neurotoxic drugs
– Increased risk of pancreatitis/neuropathy if heavy alcohol intake
– No interaction with methadone/buprenorphine
• **AZT**
– Preferred for use in pregnant women
– Twice-daily dosing
– Preferred for use in patients with a history of neuropathy
– Can cause anaemia and pancytopenia
– Should be avoided in cases of severe anaemia (Hb <8 g/dl)
– More "minor" side-effects than other NRTIs
– Methadone – increased AZT toxicity
• **ABC**
– Well tolerated
– Hypersensitivity reaction
– Less mitochondrial toxicity than d4T, AZT
– Limited interaction with methadone/buprenorphine
• **TDF**
– Once-daily dosing
– Well tolerated
– Cannot use if underlying renal disease
– Limited mitochondrial toxicity
– No interaction with methadone/buprenorphine

Table 3: Choosing a non-nucleoside reverse transcriptase inhibitor (NNRTI): NVP versus EFV?

• **NVP**
– Avoid if liver enzymes are >2.5 upper limit of normal (ULN)
– Avoid if patient taking rifampicin
– Possibly avoid if (before starting ART) CD4 count >250 cells/mm^3 (women) and CD4 count >400 cells/mm^3 (men)
– No food restrictions
– Can use in pregnant women
– Interaction with methadone
• **EFV**
– Can be used in patients with a history of hepatitis
– Once-daily dosing
– Food restriction – should be taken on an empty stomach
– Avoid in women of childbearing age and never use in pregnancy
– Can be used with rifampicin
– "Minor" CNS side-effects common
– Caution if patient has a history of psychiatric illness
– Interaction with methadone

When to use triple NRTIs

A triple NRTI-containing regimen should be considered as a simplification strategy for other first-line regimens where NNRTIs provide additional complications since the rate of failure with triple NRTI regimens is high; so this strategy should be used only if absolutely necessary (for example, pregnancy, viral hepatitis coinfection, TB coinfection, women who wish to become pregnant or who have CD4 counts >250 cells/mm^3, NVP or EFV grade 4 serious adverse event (SAE).

Notes on commencing NVP

For the first two weeks, once-daily NVP (one 200 mg tablet) should be given to reduce side-effects (liver damage and skin rash). Once the patient has tolerated once-daily NVP (for the first 14 days), the dose should be increased to 200 mg twice a day.

Deferral of ART treatment

Sometimes ART needs to be deferred. This can be related to pregnancy, the presence of acute OIs which need treatment before ARVs are started, instability on OST, lifestyle instability, or potential adherence problems.

TB or possible TB

In the HIV-infected patient, TB may have few symptoms and advanced TB and HIV can be clinically indistinguishable – weakness, fever, weight loss, and cough may be absent. All clients must be

screened for TB before ART is started. The clinician should always consider whether there is active TB and exclude this as far as possible. Sometimes the diagnosis cannot be proven and the TB services must be involved. See national HIV guidelines on lymph node disease and wasting syndrome.

If TB is being treated, remember it is the TB that will kill in the short term rather than the HIV. ARVs should be deferred and may not be needed yet. If they are needed, they are best deferred until after the intensive (rifampicin-containing) phase of treatment because of a heavy pill burden, drug side-effects and drug interactions.

Potential poor adherence

Whether this is due to poor support, difficulty of access, a poor level of understanding, chaotic and unstable lifestyle or psychiatric disorder, ART should not be commenced until these problems have been addressed. Reasons for known poor adherence to other interventions such as TB treatment or co-trimoxazole treatment or past clinic attendance should be investigated.

CD4 count $>$ 200 cells/mm^3 or total lymphocyte count $>$ 1200 cells

Those patients whose CD4 count is above 200 cells/mm^3 and who do not fulfil the clinical criteria for ART, should be reviewed regularly and the CD4 count and TLC repeated every 3–6 months. It should be explained that starting ART too soon is not advised, given that ARVs have side-effects and virological failure on the initial regimen is likely at some point. Starting ARVs before they are really needed is not only unnecessary, but also not good for long-term outcomes.

First trimester of pregnancy

Risks and benefits need careful explanation – NOT an absolute contraindication to starting therapy, in the very sick – EFV should not be used because of possible damage to the fetus (seen in animal studies).

Renal, bone marrow or hepatic dysfunction:

- Creatinine >300 micromol/L (>3 mg/dl)
- Haemoglobin <7 g/dl
- SGPT (ALT) >5 times ULN (> 175/200 IU/l)

If ART is deferred, the toxicity/abnormalities should be investigated and treated, and ART can be reconsidered.

Ongoing support

If a client is not eligible/suitable for ART, they should be offered all other supportive care, including co-trimoxazole prophylaxis, drug substitution counselling, OST (if appropriate), early treatment of OIs, psychosocial support and monitoring.

All patients, regardless of their eligibility for ART, should be encouraged to make use of available ongoing counselling services and supported in all aspects of "positive living".

Principles for starting ART in IDUs

- Treat OIs first.
- Ensure stability of OST.

- Co-morbidities and co-treatment interactions should be taken into consideration while selecting ARVs.
- Involve the client and other relevant health workers in decision-making about ART – educate ALL about the potential for side-effects and interaction with OST.
- Use specific strategies (use of fixed-dose combinations [FDC] blister packs, once-daily drugs, directly observed treatment [DOT]/supervised treatment) to support adherence.
- Ensure careful ongoing monitoring and support – side-effects, interactions with OST and adherence support.

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EXERCISE 6.4.1

Relative advantages and disadvantages of different first-line regimens

Instructions: Use what you have learned about individual ARV drugs in the last session to examine the profiles of two potential first-line ART regimens and list the advantages and disadvantages in relation to:

1. Adherence factors
2. Co-morbidities – HBV, HCV, TB, pregnancy, psychiatric illness, alcoholism
3. Co-treatment interactions – HBV, HCV, TB, methadone, buprenorphine

Relative advantages and disadvantages of different first-line regimens

	Efficacy of regimen	Adherence	Interaction with OST	HBV	HCV	TB	Alcohol	Pregnancy	Psychiatric illness
Group 1									
d4T, 3TC, EFV									
TDF, 3TC, NVP									
Group 2									
AZT, 3TC, EFV									
d4T, 3TC, NVP									
Group 3									
TDF, 3TC, EFV									
AZT, 3TC, ABC									
Group 4									
AZT, 3TC, NVP									
AZT, 3TC, TDF									

EXERCISE 6.4.2

Case studies: Selecting a first-line regimen

Instructions: Examine and discuss each case study and then document the following:

- *Outline your first choice of ART regimen for this client.*
- *Why did you choose this regimen?*
- *What would be a suitable alternative to this regimen?*
- *What other issues do you need to consider in the management of this client?*
- *What are the major issues you would need to counsel and educate each patient on for this regimen?*

Case study 1: Dave

A 38-year-old male ex-IDU has lost approximately 10 kg of weight over the past six months, and has been hospitalized four times recently for recurrent bacterial pneumonia. He is a heavy drinker but has good family support, and you think his adherence will be good. Twelve years ago he was hospitalized for six months for a psychotic episode. He complains of numbness in his toes. He also has oral candidiasis. His TLC is 900 cells/mm^3. His ALT is 105 IU/L.

Case study 2: Navi

A 22-year-old woman presents with a recent diagnosis of HIV. She is four months pregnant. She has oral thrush but no other symptoms. She and her partner are both currently injecting heroin approximately five times a day. Her physical examination is normal except for several infected injecting sites. The CD4 count is 150 cells/mm^3. Her Hb is 8.8 g/dl and other baseline laboratory tests are unremarkable.

Case study 3: Huong

A 25-year-old man requests ART. He had a CD4 count done at another health centre and it was 180 cells/mm^3. He is hepatitis B and hepatitis C positive. He has been stable on 80 mg methadone daily for the past eight months. He has missed picking up his daily methadone dose only on four days out of those eight months. He still injects heroin occasionally and regularly takes benzodiazepines. His AST is 350 IU/L.

Case study 4: Tuyet

An 18-year-old woman presents with a CD4 count of 120 cells/mm^3. She was admitted to hospital three months ago with TB meningitis and was started on buprenorphine at that time. She has been stable on 24 mg buprenorphine three times per week and has not used heroin since being discharged from hospital. She has finished the intensive phase of her TB treatment and is now on isoniazid and ethambutol for another six months. She has hepatitis B (HBsAg positive) and the AST is 55 IU/L. Hepatitis C is negative. Her Hb is 7.9 g/dl.

Sub-module

6.5

Monitoring IDUs on ART and managing side-effects and toxicities within the first year

OVERVIEW

Objectives:

By the end of the session participants will be able:

- To outline "what to expect" for someone on ART in the first six months of therapy
- To understand the routine monitoring processes that should be carried out for all HIV-positive IDUs on ART, including the difference between routine monitoring and monitoring that is required when a toxicity arises
- To understand the impact of OST on routine monitoring and the drug interactions, side-effects and toxicities commonly associated with taking ART and OST together
- To demonstrate the ability to deal with minor side-effects common in individuals starting first-line ART
- To demonstrate an understanding of the management of major side-effects in an individual taking first-line ARV drugs during the first year of treatment
- To understand when and how to switch ARV drugs in the first-line regimen in the event of toxicity.

Time to complete session:

2 hours

Session content:

- What to expect in the first six months of ART
- Immune reconstitution inflammatory syndrome (IRIS)
- Routine monitoring of first-line ART
- Management of adverse events on a first-line regimen
- Management of serious toxicities within the first year of ART
- Drug substitutions due to toxicity
- Safely stopping ART to avoid the development of resistance

Training materials:

- PowerPoint presentation 6.5: Monitoring IDUs on ART and managing side-effects and toxicities within the first year
- Sub-module 6.5: Monitoring IDUs on ART and managing side-effects and toxicities within the first year
- Blank flipchart paper and pens
- Exercises 6.5.1 and 6.5.2

WHAT TO EXPECT IN THE FIRST SIX MONTHS OF ART

The first six months on ART are critical as it is the time where clinical and immunological improvement should start to occur. It is also a period when clinical management of an individual on ART may be complicated by drug toxicities and IRIS. Complications in the first few weeks following initiation of ART are seen most commonly when therapy is started in patients with severe immunodeficiency (CD4 count <100 cells/mm^3). The apparent failure of treatment in a patient with advanced HIV disease to improve initially does not necessarily reflect a poor response to ART. It takes time for HIV replication to be controlled by ART and for the patient's immune system to strengthen. It also takes time for reversal of the catabolism associated with HIV infection, particularly in patients with significant HIV-associated wasting.

The development of a new or recurrent OI in the first six months after ART initiation does not indicate treatment failure and is not an indication to stop or switch ART.

CD4 count recovery

In most patients, CD4 cell counts rise with the initiation of therapy and immune recovery. This response may not be so dramatic if the baseline CD4 count is very low. However, some patients with CD4 counts below 10 cells/mm^3 can achieve an effective CD4 recovery over time, although some may never reach a CD4 count of >200 cells/mm^3.

In those who achieve a good CD4 response, a subsequent progressive decline in CD4 counts in the absence of intercurrent illness indicates immunological failure. The baseline CD4 count and the trend of the CD4 response assessed by regular six-monthly CD4 counts are needed to best characterize and define immunological failure.

Early ARV toxicity

First-line drug toxicities fall into two categories: (1) early toxicities which usually present in the first few weeks to months of therapy; and (2) long-term toxicities. Common early and potentially severe toxicities are hypersensitivity to NVP, which normally occurs within the first few weeks of therapy, and AZT-related anaemia and neutropenia, which typically present in the first few months of therapy. Careful clinical and laboratory monitoring is required in the first few months of ART as many of the acute toxicities, if not identified early, can evolve into life-threatening and fatal events.

Mortality on ART

While the aim of ART is to decrease mortality and morbidity, mortality is highest in the first six months of ART than during the subsequent period on therapy. Some studies have recorded a mortality rate of between 2% and 10% on ART and most studies report that 60–70% of deaths occur in the first three months of treatment. It appears that there is a greater risk of death in patients with disseminated TB (and other severe OIs) and a pre-ART CD4 cell count <50 cells/mm^3.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

IRIS is a spectrum of clinical signs and symptoms resulting from the restored ability to mount an inflammatory response associated with immune recovery. It can present as a paradoxical worsening of an individual's clinical condition several weeks into therapy with the signs and symptoms of a previously subclinical and unrecognized OI or as an autoimmune disease. Typically, IRIS occurs within 2–12 weeks of the initiation of ART, although it may present later. The incidence of IRIS is estimated to be 10% among all patients initiating ART and up to 25% among patients initiating ART with a CD4 cell count <50 cells/mm^3.

Risk factors predicting the likelihood of IRIS include: initiating ART close to the time of diagnosis of an OI; being ARV-naive at the time of diagnosis of an OI; initiating ART when the CD4 count is <50 cells/mm^3; and having a more rapid initial decrease in the HIV-1 RNA level in response to ART than in patients with higher CD4 counts.

IRIS has been reported in association with a large number of HIV-related infections and inflammatory conditions. The most frequently occurring IRIS events are associated with mycobacterial disease (TB or *Mycobacterium avium* complex [MAC] infection) and cryptococcal disease. Together, mycobacterial and cryptococcal disease account for approximately 60% of all cases of IRIS in developed country settings.

IRIS may be mild and resolve without treatment (e.g. it may involve a mild rash and fever or a transient flare of hepatic enzymes in a patient with HIV/hepatitis B coinfection, or it may be severe and life-threatening, as in patients with cryptococcal meningitis or TB). The management of IRIS includes treatment of the causative pathogen in order to decrease the antigenic load, continuation of ART and the use of corticosteroids. Prednisolone (or prednisone) at 0.5 mg/kg/ day for 5–10 days is suggested in moderate to severe cases of IRIS. Wherever possible, when IRIS is diagnosed, ART should be continued and the OI or inflammatory condition should be treated. If this is not possible and a person is very ill (rare event), ART should be temporarily interrupted, the OI or inflammatory condition should be treated, and then the same ART regimen should be restarted.

It is important to distinguish IRIS from treatment failure, which is the reason to not diagnose treatment failure in the first 6 months of ART.

An improved immune response can lead to:

1. Regression of OI (protective) but may also result in
2. IRIS (immunopathological)

Early (first months): unmasking and/or recognition of an ongoing infection due to improved immune response (usually occurs soon after ART)

Late: reconstituting immune system leads to reaction to previously treated infection or non-replicating antigens (may occur later after starting ART)

Presentations of TB IRIS:

- Fever
- Lymphadenopathy
- Splenic abscess
- Arthritis or osteomyelitis
- Gastrointestinal disease
- Pulmonary infiltrates
- Skin lesions
- Parotitis
- Severe manifestations
  - Spleen rupture
  - Compressive lymphadenopathy causing dyspnoea or ureteric obstruction

IRIS: common pathogens

Early (first 3 months) viable pathogens

- MAC lymphadenitis
- TB paradoxical reactions

- Cryptococcal meningitis
- Cytomegalovirus (CMV) retinitis
- Varicella zoster virus (VZV)/herpes simplex virus (HSV) disease
- Inflammatory progressive multifocal leukoencephalopathy (PML)
- Kaposi sarcoma
- HCV/HBV hepatotoxicity
- Others

Late (3–24 months), mainly non-viable pathogens

- Immune recovery uveitis
- Cryptococcal disease
  - Aseptic meningitis
  - Lymphadenitis
  - Brain/spinal cord lesions
- MAC lymphadenitis
- *Histoplasma* lymphadenitis

Management of IRIS

- Rule out new OIs.
- Rule out drug toxicity.
- Rule out drug failure.
- If IRIS is suspected, is it a:
  - Manifestation of new or ongoing infection (early presentation)?
  - Reconstituting immune reaction to non-replicating antigens (late presentation)?
- Avoid interruption of ART.
- Treat with antimicrobials if new infection is suspected, continue previous therapy.
- Anti-inflammatory medications:
  - Non-steroidal anti-inflammatory drugs.
  - Corticosteroids: no definitive protocol though clinicians often use prednisone 1 mg/kg/day with tapering over several weeks

ROUTINE MONITORING OF FIRST-LINE ART

ART needs to be carefully monitored for possible side-effects and toxicities, for adherence to treatment, and for measuring the success or failure of treatment.

The time-frames for routine monitoring depend on what model of dispensing is used for ARVs and OST, but the following monitoring is required:

- Minor side-effects (clinical evaluation)
- Toxicities (laboratory and clinical evaluation)
- Adherence (self-report, pill count, visual aids)
- Stability of OST (clinical evaluation)
- Is the ARV regimen working? (laboratory and clinical evaluation)

Additional monitoring should be done when there are side-effects and symptoms of toxicity, or issues with adherence or stability of OST.

1. Monitoring for side-effects

Side-effects of ART are monitored by regular clinical evaluation (history and examination) and by routine laboratory monitoring plus additional laboratory testing when symptoms and signs of toxicity occur.

Major side-effects need to be distinguished from minor ones. Minor side-effects such as nausea, fatigue, rash, insomnia can be very difficult for the client but they usually subside after 2–4 weeks of ART. They can be managed by careful counselling and clinical management (e.g. paracetamol for headache, anti-emetics for nausea and vomiting, antihistamines for insomnia). It is important to manage these minor side-effects because they can affect adherence, particularly if they persist and are not dealt with.

Major side-effects are those where ARVs cause significant clinical or laboratory abnormality and need careful clinical management. They often require a change in the drug combination. Major side-effects are diagnosed by a combined evaluation of clinical findings (history and examination) and laboratory results.

Regular clinical monitoring should be done for skin rash, jaundice, fever, fatigue, CNS disturbance, peripheral neuropathy and any other unexpected clinical problems. Regular or routine laboratory monitoring includes:

- On NVP – check ALT 4 weeks after starting NVP– then every 3 months
- On EFV – check LFT every 6 months
- On AZT – check complete blood count (CBC) at 4 weeks after starting AZT and then every 3 months

Additional laboratory testing should be done immediately if the following symptoms/signs occur:

- CBC – extreme fatigue or symptoms of anaemia
- LFT and hepatitis B/C serology – signs of hepatitis and liver failure
- LFT and CBC – severe rash with mucosal involvement

If an abnormality is detected, more frequent monitoring is required.

Table 4: Monitoring for side-effects of ART

d4T		
Peripheral neuropathy (usually occurs after 6 months on d4T but occasionally occurs earlier)	History of sensory and motor change (burning, tingling, pain, motor loss) in the hands and feet. On examination – may find neurological signs in the periphery.	
Lactic acidosis and hepatitic steatosis (can occur any time after two months on d4T but most commonly after eight months)	May be asymptomatic or patient may complain of fatigue, shortness of breath, nausea, vomiting, diarrhoea, dizziness, myalgia	Do LFT, lactate (if possible), bicarbonate, anion gap, hepatic ultrasound any time if clinical suspicion
Lipoatrophy (usually occurs after 12–24 months on d4T)	Change in body shape with loss of fat from arms, legs and face	
Metabolic disorders (insulin resistance and high cholesterol + triglycerides)	May be clinical signs of hyperlipidaemia and insulin resistance – usually diagnosed by laboratory monitoring	Fasting lipids and blood sugar level/oral glucose tolerance test (OGTT)
AZT		
Anaemia (usually occurs within the first month of taking AZT)	May be asymptomatic but usually patient complains of fatigue	Routine CBC (Hb) at 4 weeks or do CBC any time if clinical suspicion

Table 4: Monitoring for side-effects of ART (contd)

Neutropenia (usually occurs at around six months of AZT)	May be asymptomatic but usually patient complains of fatigue and is unwell	Routine CBC (WBC) at 6 months or do CBC any time if clinical suspicion
Lactic acidosis and hepatitic steatosis (usually occurs after 12 months on AZT but can occur as early as 4 months)	May be asymptomatic or patient may complain of fatigue, shortness of breath, nausea, vomiting, diarrhoea, dizziness, myalgia	Do LFT, lactate (if possible), bicarbonate, anion gap, hepatic ultrasound any time there is clinical suspicion
Lipoatrophy (usually occurs after 12–24 months on AZT)	Change in body shape with loss of fat from arms, legs and face.	
Metabolic disorders (insulin resistance and high cholesterol + triglycerides)	May be clinical signs of hyperlipidaemia and insulin resistance – usually diagnosed by laboratory monitoring	Fasting lipids and blood sugar level/OGTT
NVP		
Severe rash (Stevens–Johnson syndrome): usually occurs within first month of NVP but can happen any time	On examination – severe blistering rash with mucosal involvement, fever, fatigue	LFT may be abnormal
Severe hepatotoxicity (2 types): • Early: usually occurs within first 4 weeks and is hypersensitivity reaction • Late: is related to hepatotoxicity and is more common in those with abnormal liver function	Patient unwell with jaundice, nausea, vomiting	Routine LFT at week 4 then every 3 months. Take blood for LFT any time if clinical suspicion
Hyperlipidaemia	May be clinical signs of hyperlipidaemia but usually diagnosed by laboratory monitoring	Fasting lipids – increased total cholesterol but usually increased high-density lipoprotein (HDL) or low-density lipoprotein (LDL)
EFV		
Severe rash (Stevens–Johnson syndrome, rare)	On examination – severe blistering rash with mucosal involvement, fever and fatigue	LFT may be abnormal
Hepatotoxicity (rare on EFV but take blood if symptomatic)	Patient unwell with jaundice, nausea, vomiting	Once-yearly LFT
Depression, paranoia, suicidal thoughts (any time – usually within first year)	Diagnosed by mental health history and examination	
Hyperlipidaemia	May be clinical signs of hyperlipidaemia but usually diagnosed by laboratory monitoring	Increased total cholesterol – LDL >HDL

Source: Burdon R et al. *ARV therapy clinical handbook*. Viet Nam, Family Health International, 2006.

2. Monitoring the success of ARV therapy

The CD4 cell count is the best laboratory marker of the strength of a patient's immune system and should increase as ART suppresses replication of HIV and less CD4 cells become infected. However, it takes several months for the CD4 count to increase after starting ART (particularly for those with a low baseline CD4 count) although clinical improvement can start after only a few weeks. For those clinics without access to CD4 count measurement, the success of ART can be measured by weight gain, increased energy, better functional status, fewer symptoms and less OIs.

Where possible, a CD4 cell count should be repeated six months after starting ART. If an individual is not improving on ART with good adherence and in the absence of on OI, especially TB, the ARV regimen may need to be changed because it is probably not working (failure).

Note: The TLC is not useful for monitoring ART.

Table 5: First-line ARV monitoring protocol

Assessment	Pre-ART	ARV Wk 1	ARV Wk 2	ARV Wk 3	ARV Wk 4 (1 mo)	ARV Wk 6	ARV Wk 8 (2 mo)	ARV Wk 12 (3 mo)	ARV Wk 16 (4 mo)	ARV Wk 20 (5 mo)	ARV Wk 24 (6 mo)	7 mo	8 mo	9 mo	10 mo	11 mo	12 mo
Dispense ARVs (a)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALT/AST for patient on NVP (once per year if on EFV)	X				X			X			X						X
CBC	X				X			X			X			X			X
Physical exam	X				X		X	X			X			X			X
Hep B/Hep C*	X																X
CD4 count	X										X						X
Adherence assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OST assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ARV dispensing: (1st month) weekly x 4 , (2nd month) 2-weekly x 2, (3rd month) assess to determine if continuing 2-weekly or increasing to monthly dispensing

* Only need to repeat Hep B and C each year if it has previously been negative.

3. Monitoring adherence

Once initiated on ART, the client should routinely return to the clinic for ARV refills, health check-ups and adherence counselling. Ideally, in the first month of treatment the client will see the adherence counsellor every week, in the second month every fortnight and from then on monthly. If someone needs more intensive adherence support they may continue to be seen weekly. The HBC teams and PLWHA support groups have an extremely important role in supporting adherence and following up people who may have missed appointments or not picked up their ARV drugs.

After the first few months on ART, clients should have taken ownership of their ART regimen, and developed fixed habits to help them remember well how to take medications on time, and are supported and motivated to stay healthy.

However, it is important to remember that multiple factors influence adherence over time, and as people's lives change, barriers to adherence also change and reaching good adherence can become more complex. For example, it is easy to remember to take ARVs when you are sick and living at home with parents and not working, but as you become healthy and strong and perhaps start working again this can change. Although adherence counselling needs to change over time, the adherence counselling approach remains the same.

Step 1: Assess adherence with the client using the standard MOH adherence monitoring form/ checklist.

This involves asking clients when and how they are taking their medications and whether they are having any difficulty taking them. The adherence counsellor should document the number of times that medication has been missed (to determine adherence) and ask clients the reasons why they may have missed their ARV drugs. They should also ask about any changes in lifestyle (e.g. a new job, new living arrangement, etc.).

If the client is adherent, the adherence counsellor should praise the client (and their treatment supporter) and give positive reinforcement (and their treatment supporter) for their hard work. If the client has had difficulties with adherence, the counsellor should move to steps 2 and 3.

Step 2: Assess reasons for non-adherence and identify solutions to problems.

If the client is not adherent, it is important that the adherence counsellor work with the client (and their treatment supporter) to identify new adherence barriers and determine solutions to barriers.

Step 3: Revise treatment adherence plan.

If new barriers and solutions to adherence have been determined, it is important that the counsellor and client revise the treatment adherence plan based on new solutions. The counsellor should schedule a follow-up visit to see how well the new adherence plan is working and provide additional support (within one week) and then provide more regular ongoing adherence support until the adherence plan is working well.

It is important that at every visit adherence counsellors:

- Reinforce and check clients' understanding about their ART regimen.
- Discuss side-effects and what to do if they occur.
- Reinforce information and check clients' understanding about missed doses (*see below*).
- Always ask if they have any questions.

Advice on missed doses:

First: Take your pills right away when you remember that you forgot to take them.

Next: Estimate how much time there is before you are due to take your pills again.

- If your next pill-taking time is 4 hours or more away, you can take your pills at this time, just as you had planned.
- If your next pill-taking time is less than 4 hours away, DO NOT take your next dose of pills at the time you had planned. You should wait until 4 hours after the time you just took your pills and then take your next dose of pills.
- If you forget more than 2 doses of pills in one week, talk with your doctor or nurse to find out what to do.

4. Monitoring OST

It is very important that OST be monitored frequently – especially in the first month of ART when NNRTIs can potentially reduce methadone levels and cause a client to have withdrawal symptoms. This is a very critical time for adherence and future treatment success – the dose of methadone needs to be increased in up to 60% of clients on NNRTIs.

MANAGEMENT OF ADVERSE EVENTS ON A FIRST-LINE REGIMEN

Disabling and even life-threatening side-effects do occur with patients on ART therapy. These side-effects include severe rash, hepatotoxicity, peripheral neuropathy, bone marrow suppression, severe psychiatric disturbance and rarely, lactic acidosis. When they do occur, decisions regarding the appropriate action to be taken can be difficult and complex, and the subsequent pages aim to provide practical guidance on the more commonly encountered adverse reactions.

Regardless of their severity, side-effects may affect adherence to therapy. Discussing the potential side-effects of the ART regimen with the patient before the ART is started and during the early stages of treatment is very important. The patient should be familiar with the signs and symptoms of toxicities that are serious and require immediate contact with the health-care team. This is particularly important for toxicities that can be life-threatening, including NVP-associated Stevens–Johnson syndrome, hepatitis and lactic acidosis.

To avoid confusion with drug side-effects and problems with deciding which drug is responsible: do not start ART therapy at the same as other drugs (especially co-trimoxazole and TB drugs).

Grading and managing the severity of side-effects (Tables 6 and 7)

Table 6. Estimating the grade of severity of the toxicity

Grade 1	**Mild.** *Transient or mild discomfort: no limitation in activity; no medical intervention/therapy required*
Grade 2	**Moderate.** *Limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required*
Grade 3	**Severe.** *Marked limitation in activity, some assistance usually required; medical intervention/ therapy required, hospitalization possible*
Grade 4	**Severe, life-threatening.** *Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care*

Source: WHO guidelines, 2006.

Table 7. Guiding principles in the management of ARV drug toxicity

1. Determine the seriousness of the toxicity.
2. Evaluate concurrent medications and establish whether the toxicity is attributable to ART or to a non-ART medication taken at the same time.
3. Consider other disease processes (e.g. viral hepatitis in an individual on ART who develops jaundice) because not all problems that arise during treatment are caused by ART.
4. Manage the adverse event according to the severity.
   - **Grade 4 (severe life-threatening reactions):** Immediately discontinue all ART, manage the medical event (i.e. symptomatic and supportive therapy) and reintroduce ART using a modified regimen (i.e. substituting another ARV for the offending drug) when the patient is stabilized.
   - **Grade 3 (severe reactions):** Substitute the offending drug without stopping ART.[a]
   - **Grade 2 (moderate reactions):** Consider continuation of ART for as long as feasible. If the patient does not improve on symptomatic therapy, consider single-drug substitution.[a]
   - **Grade1 (mild reactions)** are bothersome but do not require a change in therapy.
5. For mild and moderate reactions, stress the maintenance of adherence despite toxicity.
6. If there is a need to discontinue ART because of life-threatening toxicity, all ART should be stopped until the patient is stabilized.

[a] One exception to point 4 in the table is the substitution of EFV for NVP, which is recommended following a Grade 1 or 2 NVP-related rash and/or hepatotoxicity.

Source: WHO guidelines, 2006.

Minor side-effects: within the first four weeks of starting therapy

Nausea, vomiting, diarrhoea, abdominal discomfort and bloating, headache, fever, muscle aches and pains, and fatigue are common complaints in the first few weeks of ART. It is important to assess the client clinically with a full history and examination. Order laboratory tests as indicated (e.g. CBC if someone is complaining of fatigue). Use symptomatic treatment such as paracetamol for headache and anti-emetics for nausea. Remember that methadone can increase the levels of AZT and thus usually minor side-effects may be more severe. Give plenty of support and reassurance; let them know that these symptoms are common and will usually go away with time. The client is likely to need closer monitoring, so schedule more frequent follow-up visits at the outpatient clinic or ask the home-based care (HBC) team to check on the client. If the client seems well, continue all medication with support from clinic staff, the HBC team, PLWHA supporters and treatment supporters. Fear is lessened with appropriate adherence preparation and information. Provide phone numbers and ask the client to call the outpatient care if there is a worsening in condition.

Reassure patients that ART does **DOES NOT** have to be stopped for these minor side-effects.

Serious side-effects: within the first four weeks of starting therapy

- Skin rash: usually related to NVP (*see* algorithm 1)
- Hepatotoxicity: usually related to NVP (*see* algorithm 2)
- Marrow suppression: usually related to AZT, particularly in combination with co-trimoxazole (*see* algorithm 3)

Serious side-effects that occur between two and six months of ART

- Hepatotoxicity: usually related to NVP but a flare of HBV/HBC can occur as part of IRIS (*see* algorithm 2)
- Peripheral neuropathy: d4T can cause a serious and debilitating peripheral neuropathy, particularly in combination with other neurotoxic drugs, most commonly isoniazid (*see* algorithm 4)
- Lactic acidosis: can occur after 4 months of being on an NRTI but this is quite rare – it usually happens after 6–9 months of being on ARVs (*see* algorithm 5)

MANAGEMENT OF SERIOUS TOXICITIES WITHIN THE FIRST YEAR OF ART

Rash due to NVP

Rash due to NVP occurs in 17–25% of patients; such rash is usually observed in the first 2–6 weeks of treatment. The incidence is reduced by the two-week lead-in dosing with once-daily NVP (200 mg once daily 2 weeks). It is usually erythematous and maculopapular, and may or may not be itchy. It is often located on the trunk, face and extremities.

Management of NVP rash (see algorithm 1)

1. Assess severity of rash and whether there is mucosal involvement ± systemic features.
2. Assess for hepatotoxicity which can occur with rash.
3. If mild, manage with mild steroid cream and anti-inflammatory drugs.
4. Monitor the patient.

Early NVP hepatotoxicity

Early NVP hepatotoxicity usually occurs in the first 6–16 weeks (most frequently during the first 6 weeks) of treatment and seems to be a hypersensitivity reaction. It may be accompanied by drug rash, eosinophilia and systemic symptoms, and can progress to liver necrosis and death. This reaction occurs primarily in those with a high CD4 count when starting the drug (women with CD4 count >250 cells/mm^3 and men with CD4 counts >400 cells/mm^3). It can be minimized by frequent monitoring in the first 12 weeks of therapy, careful counselling to patients, and discontinuing NVP if a patient has clinical symptoms and the LFT is elevated 5–10 x ULN (*see* algorithm 2).

Late NVP hepatotoxicity

Late hepatotoxicity occurs in 15% of patients and is more common in those with chronic HBV and /or HCV. This form of hepatotoxicity is similar to that seen with other ARV drugs and is more benign. It can be asymptomatic and only detected by laboratory testing (elevation in transaminase levels). Thus, LFT should be monitored frequently in the first three months of NVP treatment. Guidelines vary but usually discontinuation is recommended if ALT>5–10 x ULN or the patient is symptomatic.

AZT-related anaemia and pancytopenia

Bone marrow suppression due to AZT is related to the pre-existent bone marrow reserve, AZT dose and duration of treatment. Anaemia usually occurs within 4–6 weeks and neutropenia occurs

after 12–24 weeks. It can be avoided by not initiating AZT in those with low Hb and by careful monitoring – check CBC at 4 weeks and then every 4 weeks (more frequently if symptomatic). It can also be avoided by not using AZT when other myelosuppressive drugs are being used. It can be managed by stopping AZT and switching to another suitable NRTI (± transfusion, erythropoietin, G-CSF) (*see* algorithm 3).

d4T-related peripheral neuropathy

The frequency of peripheral neuropathy is 5–15% (up to 24% in some cohorts) and it appears to be related to mitochondrial toxicity. It is much more likely when d4T is combined with ddI, which is why this combination should be avoided. The usual onset is 2–6 months. It resolves if d4T is stopped promptly, but the recovery is slow. It is important not to use d4T if there is baseline peripheral neuropathy or in combination with neurotoxic drugs (e.g. isoniazid).

Lactic acidosis

Lactic acidosis ± hepatic steatosis is related to mitochondrial toxicity caused by NRTI drugs d4T>AZT>3TC>ABC>TDF. Lactic acidosis is relatively rare (1–14/1000) and can occur any time between 1 and 20 months of treatment. Patients present with symptoms of nausea, vomiting, abdominal pain, fatigue, myalgia, malaise, dyspnoea, weight loss. Laboratory tests show a high serum lactate plus abnormal LFT, and hepatic steatosis on liver ultrosound. If the lactic acidosis is very severe stop all NRTIs. If it is mild, switch to a different NRTI with less mitochondrial toxicity (e.g. ABC, TDF) (*see* algorithm 5).

Hypersensitivity to ABC

Hypersensitivity to ABC occurs in 3–5% of patients. It presents with fever, malaise, myalgias, rash, gastrointestinal symptoms, dyspnoea, pulmonary infiltrates. The onset is usually in the first 2–6 weeks of therapy, although late cases have been reported. ABC hypersensitivity appears to be associated with HLA B57.1 (Class I) – which is rare in Asian races. If ABC hypersensitivity syndrome is suspected never rechallenge as this is associated with cardiovascular collapse and death.

Moderate or severe toxicity may require substitution with a drug in the same ARV class but with a different side-effect or toxicity profile. Severe life-threatening toxicity requires discontinuation of all ART until the patient is stable and the toxicity has resolved.

DRUG SUBSTITUTIONS DUE TO TOXICITY

The general principle for substituting an ARV drug due to drug toxicity is that it should involve a drug belonging to the same ARV class but without the same side-effects (e.g. substitution of AZT or TDF for d4T in cases of neuropathy, TDF or d4T for AZT when anaemia occurs, or NVP for EFV in case of CNS toxicity or in pregnancy). Given the limited number of ARV drug options available in resource-limited settings, drug substitutions should generally be limited to situations where toxicity is moderate to severe (grade 3) or life-threatening (grade 4). The only exception to this is the substitution of EFV for NVP following a non-severe (grade 1 or 2) NVP-related rash and/or hepatotoxicity.

When a severe or life-threatening toxicity occurs, it is appropriate to temporarily discontinue the entire ART regimen until the toxicity has resolved. A revised regimen can then be introduced.

For some life-threatening toxicities, it may not be possible to identify an optimal substitute drug within the drug class concerned. For example, in the case of NVP-associated Stevens–Johnson syndrome, substitution with another NNRTI drug is not recommended because of the potential for class-specific toxicity. This situation would require a change to either a triple NRTI regimen (e.g. substituting a third NRTI – ABC or TDF, for NVP if AZT/3TC was the original dual NRTI component), or substituting a PI for NVP, thereby introducing a drug class reserved for second-line regimens. If a PI is used, it must be noted that no potent and durable regimens have been identified for recommendations following initial PI failure. For life-threatening or more complex clinical situations, consultation with and/or referral to a district or regional hospital centre is recommended.

Switching drugs requires that the clinical and laboratory monitoring protocol needs to be reviewed and additional adherence counselling support may be required to review the dosing schedule, food restrictions and requirements, and potential side-effects.

Table 8: ARV substitution options in case of toxicity

ARV DRUG	Common associated toxicity	Suggested substitute
d4T	Lactic acidosis Lipoatrophy/metabolic syndrome	TDF or ABC
	Peripheral neuropathy	AZT or TDF or ABC
AZT	Severe anaemia or neutropenia Severe gastrointestinal intolerance	d4T or TDF or ABC
	Lactic acidosis	TDF or ABC
NVP	Hepatotoxicity	EFV or TDF or a PI
	Hypersensitivity reaction	TDF or ABC (or a PI)
	Severe or life-threatening rash (Stevens–Johnson syndrome)	
EFV	Persistent and severe central nervous system toxicity	NVP or TDF or ABC
	Potential teratogenicity (first trimester of pregnancy or woman not on adequate contraception)	NVP or ABC

Source: WHO guidelines, 2006.

SAFELY STOPPING ART TO AVOID THE DEVELOPMENT OF RESISTANCE

NNRTIs have a longer half-life than NRTIs, leading to a concern that stopping all drugs simultaneously may lead to exposure to drugs from the NNRTI class only and the possibility of resistance developing to the NNRTIs. NVP and EFV can take up to 14 days to be fully excreted, and if all three drugs in an ART regimen are stopped together there is the risk that the NNRTIs will persist as a single agent and allow EFV and NVP resistance to develop. When restarted, the NVP/EFV regimen will be less effective and treatment failure will occur at some time.

To safely stop an NVP- or EFV-containing regimen, stop the NVP or EFV first and then 2 weeks later, stop the other two drugs. Resistance is unlikely to arise to the other two ARV drugs, because the client is only taking two drugs for a short period of time and for a lot of that time NVP and EFV are still in the body.

This is also a useful strategy to adopt if a client is stopping the ART regimen for any personal reason, or if forced to stop ART for any reason (e.g. client cannot afford the drugs). This will limit resistance, thus allowing use of the same regimen again when the patient decides to restart ART.

However, if the patient has a life-threatening toxicity, all ARV drugs should be stopped simultaneously until the patient is stabilized.

An example:

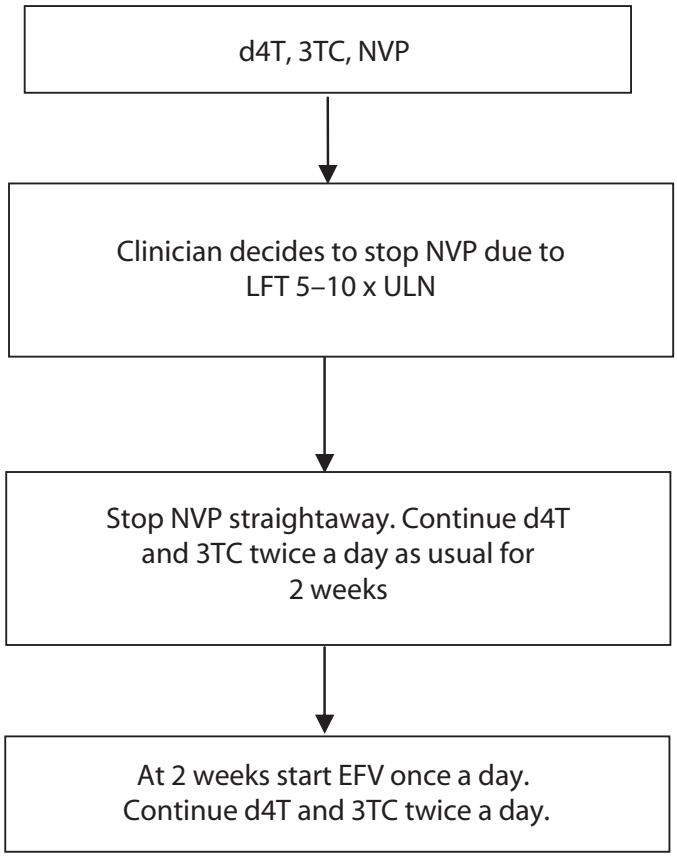
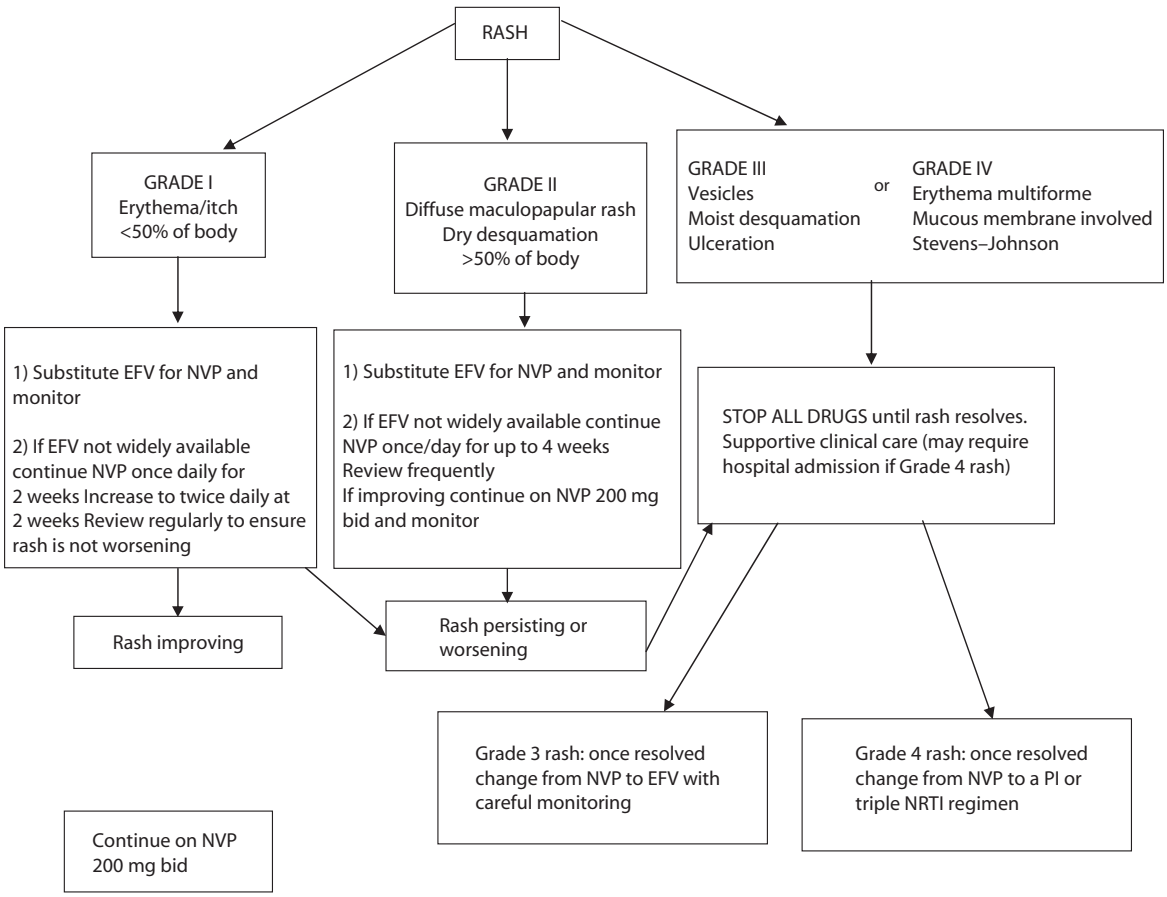


Figure 13: Algorithm 1: Rash due to NVP

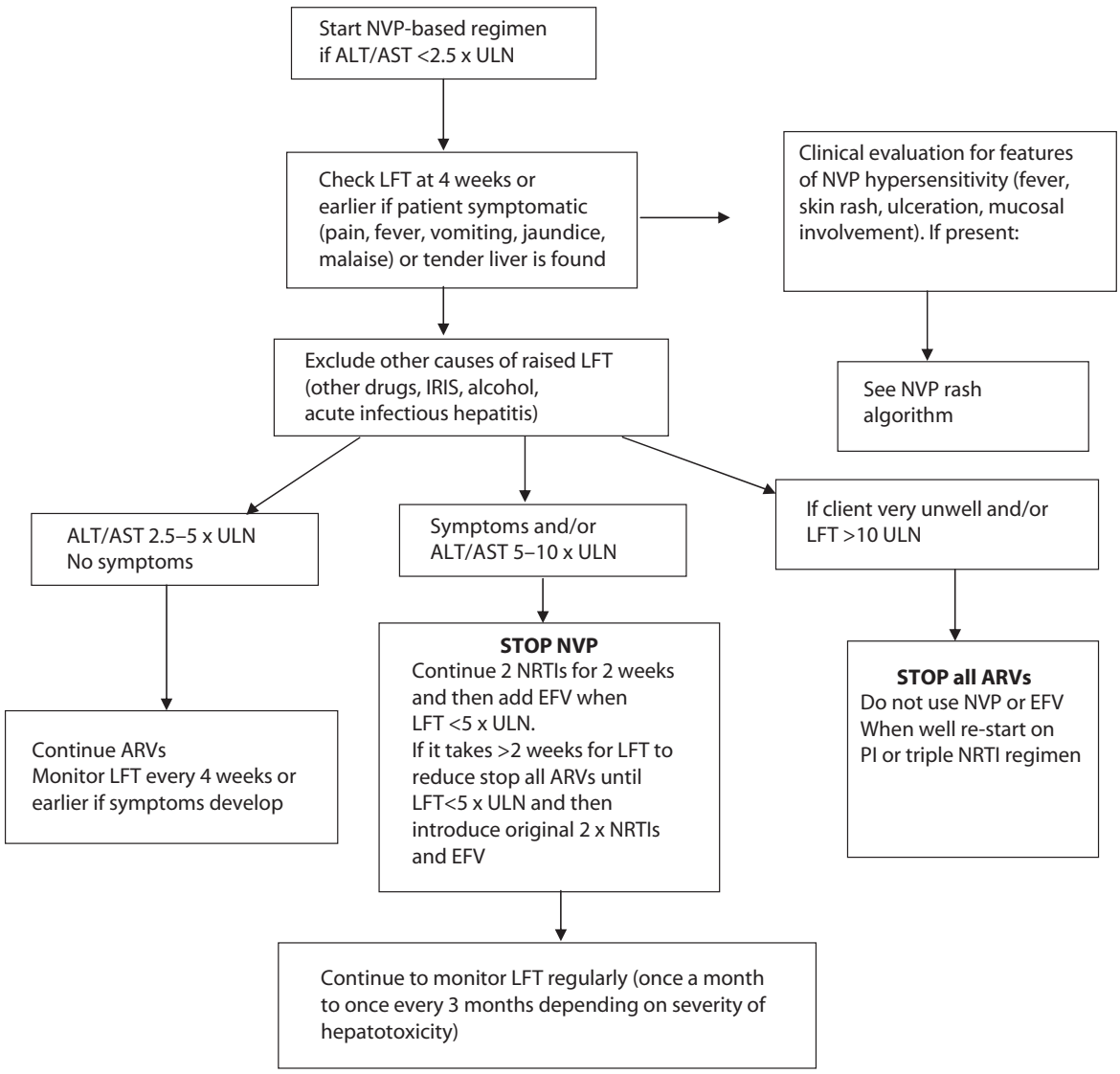
- NVP rash is most likely in the first 2–6 weeks of treatment.
- DO NOT START ART at the same time as co-trimoxazole, TB drugs or other OI treatment to avoid confusion with side-effects.
- NVP rash is less likely when you scale up the dose of NVP slowly; in fact, you should use NVP 200 mg once a day for two weeks before increasing the dose to 200 mg twice daily.



Source: Burdon R et al. *ARV therapy clinical handbook*. Viet Nam, Family Health International, 2006.

Figure 14: Algorithm 2: hepatotoxicity with NVP

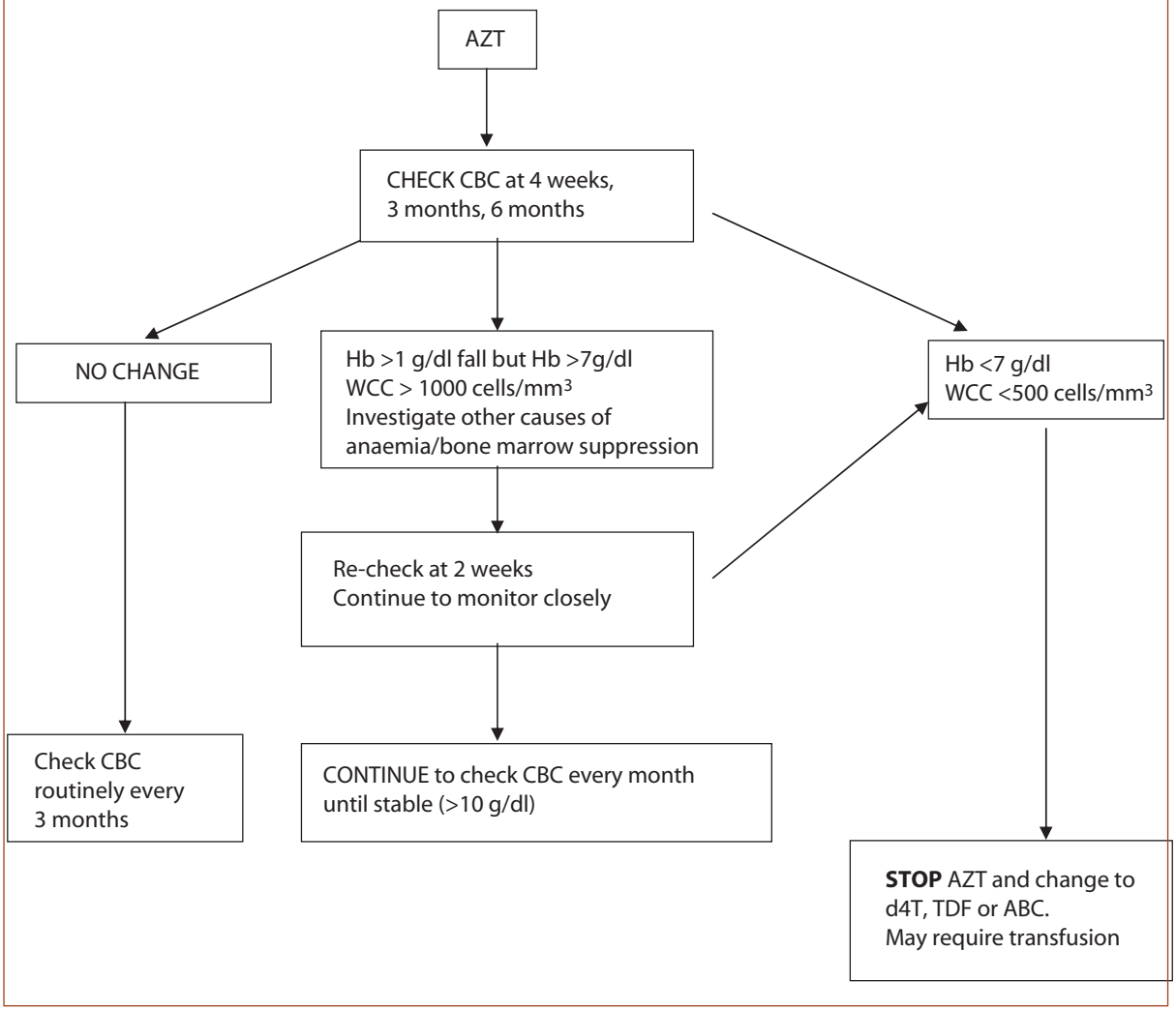
- **DO NOT start NVP** at the same time as other drugs that may cause liver damage (rifampicin, isoniazid and pyrazinamide).
- Always have **BASELINE** liver enzymes **and HBV/HCV** serology if possible.
- **DO NOT start NVP** if enzymes >2.5 x ULN.



Source: Burdon R et al. *ARV therapy clinical handbook*. Viet Nam, Family Health International, 2006.

Figure 15: Algorithm 3: AZT and bone marrow toxicity

- **Always** check baseline CBC.
- **DO NOT start AZT** if Hb <8 g/dl or WCC <1000 cells/mm^3.
- **DO NOT start AZT** if patient on other marrow suppressing drugs – high dose CTX or ganciclovir.
- **DO NOT start AZT** if an acute OI is being treated.

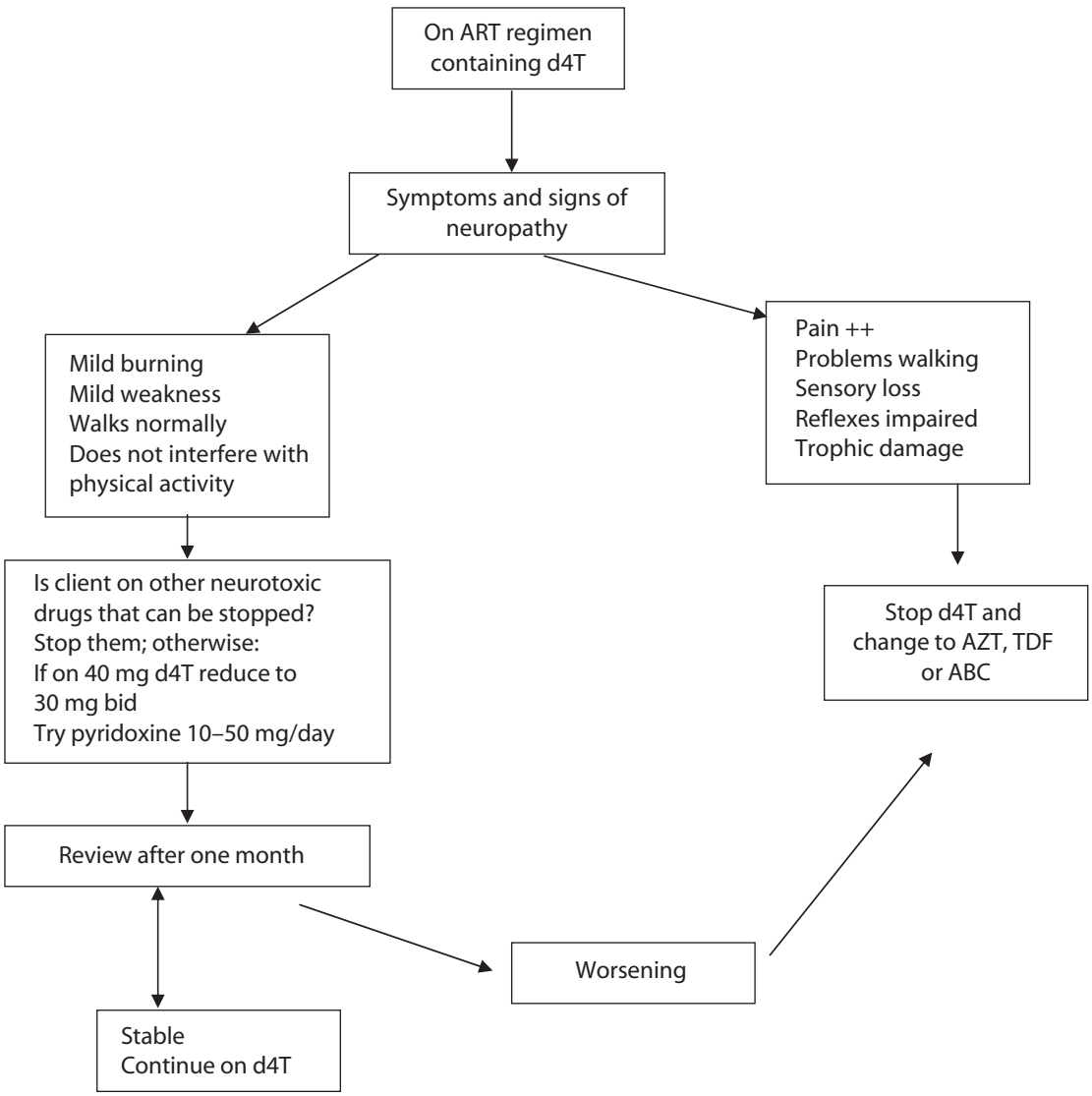


Source: Burdon R et al. *ARV therapy clinical handbook*. Viet Nam, Family Health International, 2006.

Figure 16: Algorithm 4: d4T and peripheral neuropathy

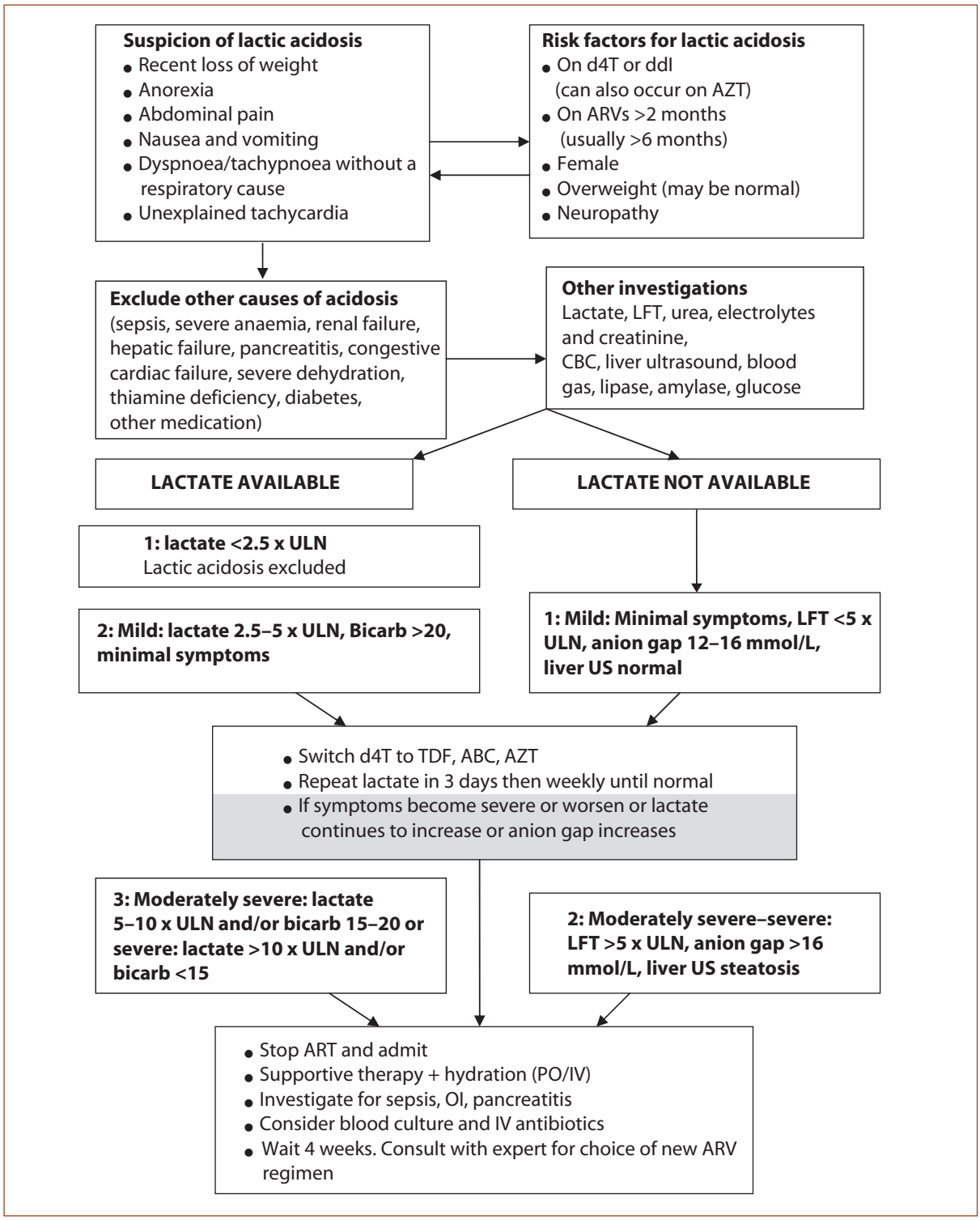
d4T related peripheral neuropathy can occur any time after 6 months of being on treatment.

- **AVOID using d4T** if using other neurotoxic drugs especially isoniazid.
- **ALWAYS** ask about symptoms of neuropathy at monitoring visits.
- **ALWAYS** check reflexes and look for sensory and trophic changes in the feet.



Source: Burdon R et al. *ARV therapy clinical handbook*. Viet Nam, Family Health International, 2006.

Figure 17: Algorithm 5: NRTIs and lactic acidosis



Source: Burdon R et al. ARV therapy clinical handbook. Viet Nam, Family Health International, 2006.

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EXERCISE 6.5.1

Case studies: Managing major first-line toxicities in the first year of treatment

Instructions: Examine and discuss each case study and then document the following:

- *Which ARV drug do you think is responsible for this presentation?*
- *What is your differential diagnosis for this presentation?*
- *How would you exclude other causes for this presentation?*
- *What advice will you give clients to help them minimize the impact of these symptoms?*

Case study 1: Dave

A 38-year-old male ex-IDU has lost approximately 10 kg of weight over the past six months and has been hospitalized four times recently for recurrent bacterial pneumonia. He is a heavy drinker but has good family support and you think his adherence will be good. Twelve years ago he was hospitalized for six months for a psychotic episode. He complains of numbness in his toes. He also has oral candidiasis. His TLC is 900 cells. His ALT is 105 IU/l.

You prescribed AZT, 3TC, NVP.

Dave comes in for his two-week check-up. He complains of feeling extremely tired and achy and has a headache that will just not subside. He has spent much of the past few days in bed. He is frustrated with feeling like this and wants to stop his drugs.

- *Which ARV drug do you think is responsible for this presentation?*
- *What is your differential diagnosis for this presentation?*
- *How would you exclude other causes for this presentation?*
- *What changes would you make to the ART regimen?*
- *What advice will you give the client to help him adjust to this new regimen?*

Case study 2: Navi

A 22-year-old woman presents with a recent diagnosis of HIV. She is four months pregnant. She has thrush but no other symptoms. She and her partner are both currently injecting heroin approximately five times a day. Her physical examination is normal except for several infected injecting sites. The CD4 count is 150 cells/mm^3. Her Hb is 8.8 g/dl and other baseline laboratory tests are unremarkable.

You prescribed AZT, 3TC, NVP.

One week after she started this regimen she comes into the clinic saying that she does not think she can keep taking the drugs as she is so nauseous. She has vomited twice daily during the week. She is otherwise well but is worried that she is not eating and about the effect this will have on the baby.

- *Which ARV drug do you think is responsible for this presentation?*
- *What is your differential diagnosis for this presentation?*
- *How would you exclude other causes for this presentation?*
- *What changes would you make to the ART regimen?*
- *What advice will you give the client to help her adjust to this new regimen?*

Case study 3: Huong

A 25-year-old man requests ART. He had a CD4 count done at another health centre and it was 180 cells/mm^3. He is hepatitis B and hepatitis C positive. He has been stable on 80 mg methadone daily for the past eight months. He has missed picking up his daily methadone dose only on four days out of those eight months. He still injects heroin occasionally and regularly takes benzodiazepines. His AST is 350 IU/L.

You prescribed d4T, 3TC, EFV.

Huong comes in with his brother after two weeks of taking the above regimen. His brother is worried because Huong has not been sleeping very well and when he does sleep he wakes up screaming with vivid nightmares. Huong is a bit slow during the day and does not seem to be able to concentrate for very long. He has been "hanging out" for the past day or two and has had to inject heroin on three occasions.

- *Which ARV drug do you think is responsible for this presentation?*
- *What is your differential diagnosis for this presentation?*
- *How would you exclude other causes for this presentation?*
- *What changes would you make to the ART regimen?*
- *What advice will you give the client to help him adjust to this new regimen?*

Case study 4: Tuyet

An 18-year-old woman presents with a CD4 count of 120 cells/mm^3. She was admitted to hospital three months ago with TB meningitis and was started on buprenorphine at that time. She has been stable on 24 mg buprenorphine three times per week and has not used heroin since being discharged from hospital. She has finished the intensive phase of her TB treatment and is now on isoniazid and ethambutol for another six months. She has hepatitis B (HBsAg positive) and the AST is 55 IU/l. She is hepatitis C negative. Her Hb is 7.9 g/dL.

You prescribed d4T, 3TC, NVP.

Two weeks after she started this regimen she comes in with a rash. The rash is a red, itchy, macular rash that covers her chest, arms and back but is over less than 50% of her body. She seems quite well in herself.

- *Which ARV drug do you think is responsible for this presentation?*
- *What is your differential diagnosis for this presentation?*
- *How would you exclude other causes for this presentation?*
- *What changes would you make to the ART regimen?*
- *What advice will you give the client to help her adjust to this new regimen?*

EXERCISE 6.5.2

Case studies: Managing major first-line toxicities in the first year of treatment

Instructions: Examine and discuss each case study and then document the following:

- *Which ARV drug do you think is responsible for this presentation?*
- *What is your differential diagnosis for this presentation?*
- *How would you exclude other causes for this presentation?*
- *What changes would you make to the ART regimen?*
- *What advice will you give the clients to help them adjust to this new regimen?*

Case study 1: Dave

A 38-year-old male ex-IDU has lost approximately 10 kg of weight over the past six months and has been hospitalized four times recently for recurrent bacterial pneumonia. He is a heavy drinker but has good family support and you think his adherence will be good. Twelve years ago he was hospitalized for six months for a psychotic episode. He complains of numbness in his toes. He also has oral candidiasis. His TLC is 900 cells. His ALT is 105 IU/l.

You prescribed AZT, 3TC, NVP.

Dave comes in for his two-week check-up. He complains of feeling extremely tired and achy and has a headache that will just not subside. He has spent much of the past few days in bed. He is frustrated with feeling like this and wants to stop his drugs.

Dave has been doing well on his ART after the initial problems. He was in last week for his routine three-month clinical assessment and you find that now his LFT has become a little more abnormal. His ALT is now 250 IU/L and his AST is 261 IU/L. He is completely asymptomatic.

- *Which ARV drug do you think is responsible for this presentation?*
- *What is your differential diagnosis for this presentation?*
- *How would you exclude other causes for this presentation?*
- *What changes would you make to the ART regimen?*
- *What advice will you give the client to help him adjust to this new regimen?*

Case study 2: Navi

A 22-year-old woman presents with a recent diagnosis of HIV. She is four months pregnant. She has thrush but no other symptoms. She and her partner are both currently injecting heroin approximately five times a day. Her physical examination is normal except for several infected injecting sites. The CD4 count is 150 cells/mm^3. Her Hb is 8.8 g/dl and other baseline laboratory tests are unremarkable.

You prescribed AZT, 3TC, NVP.

One week after she started this regimen she comes into the clinic saying that she does not think she can keep taking the drugs as she is so nauseous. She has vomited twice daily during the week. She is otherwise well but is worried that she is not eating and about the effect this will have on the baby.

Navi comes in eight weeks after she started her first-line regimen. The nausea improved with your advice on taking AZT with food and taking some metoclopramide (Maxolon) but she now feels so tired she can hardly get out of bed. She tells you that she started back on the methadone programme approximately three weeks ago. On examination she looks a little pale and tired and is a little short of breath at rest. You check her Hb and it is only 6.1 g/dl.

- *Which ARV drug do you think is responsible for this presentation?*
- *What is your differential diagnosis for this presentation?*
- *How would you exclude other causes for this presentation?*
- *What changes would you make to the ART regimen?*
- *What advice will you give the client to help her adjust to this new regimen?*

Case study 3: Huong

A 25-year-old man requests ART. He had a CD4 count done at another health centre and it was 180 cells/mm^3. He is hepatitis B and hepatitis C positive. He has been stable on 80 mg methadone daily for the past eight months. He has missed picking up his daily methadone dose only on four days out of those eight months. He still injects heroin occasionally and regularly takes benzodiazepines. His AST is 350 IU/l.

You prescribed d4T, 3TC, EFV.

Huong comes in with his brother after two weeks of taking the above regimen. His brother is worried because Huong has not been sleeping very well and when he does sleep he wakes up screaming with vivid nightmares. Huong is a bit slow during the day and does not seem to be able to concentrate for very long. He has been "hanging out" for the past day or two and has had to inject heroin on three occasions.

Huong's issues with CNS side-effects settled down and his methadone dose was increased to 110 mg per day. He has been stable for some time. Five months after he started ART, he is

brought to the clinic semi-conscious. His respiratory rate was markedly increased and his LFT results are raised by 15–20 x ULN.

- *Which ARV drug do you think is responsible for this presentation?*
- *What is your differential diagnosis for this presentation?*
- *How would you exclude other causes for this presentation?*
- *What changes would you make to the ART regimen?*
- *What advice will you give the client to help him adjust to this new regimen?*

Case study 4: Tuyet

An 18-year-old woman presents with a CD4 count of 120 cells/mm^3. She was admitted to hospital three months ago with TB meningitis and was started on buprenorphine at that time. She has been stable on 24 mg buprenorphine three times per week and has not used heroin since being discharged from hospital. She has finished the intensive phase of her TB treatment and is now on isoniazid and ethambutol for another six months. She has hepatitis B (HBsAg positive) and the AST is 55 IU/l. She is hepatitis C negative. Her Hb is 7.9 g/dl.

You prescribed d4T, 3TC, NVP.

Two weeks after she started this regimen she comes in with a rash. The rash is a red, itchy, macular rash that covers her chest, arms and back but is over less than 50% of her body. She seems quite well in herself.

Tuyet comes in for her six-month clinical assessment and you notice that she has to be helped up the stairs by her mother. She complains of burning and tingling, which is worse in her feet than her hands. She is unable to ride a motorbike any longer. On neurological examination she has marked by reduced sensory perception in her feet and hands and has lost her ankle reflexes.

- *Which ARV drug do you think is responsible for this presentation?*
- *What is your differential diagnosis for this presentation?*
- *How would you exclude other causes for this presentation?*
- *What changes would you make to the ART regimen?*
- *What advice will you give the client to help her adjust to this new regimen?*

Sub-module

6.6

Treatment failure, second-line therapy and long-term toxicities

OVERVIEW

Objectives:

By the end of the session participants will be able:

- To demonstrate an understanding of resistance and its role in treatment failure, including the role of adherence and missed doses in creating drug resistance
- To evaluate when it is necessary to put a client on second-line therapy
- To demonstrate an understanding of the side-effects and major toxicities of second-line ARVs and how to manage these when they arise
- To understand the routine monitoring processes that should be carried out for all HIV-positive IDUs on second-line ART, including the difference between routine monitoring, monitoring of OST and monitoring if a toxicity arises
- To demonstrate an understanding of the long-term toxicities of both the first- and second-line ARVs including how these impact on lifestyle and adherence.

Time to complete session:

3 hours and 45 minutes

Session content:

- Treatment failure and resistance
- Initiating second-line therapy
- Managing toxicities on second-line therapy

Training materials:

- PowerPoint presentation 6.6: Treatment failure, second-line therapy and long-term toxicities
- Sub-module 6.6: Treatment failure, second-line therapy and long-term toxicities
- Flipchart paper and pens
- Exercises 6.6.1 and 6.6.2

TREATMENT FAILURE AND RESISTANCE

When an ART regimen does not adequately suppress replication of HIV it is known as treatment failure. HIV is "resistant" to some or all the medications in the ART regimen being used and there is laboratory or clinical evidence of decline in the health of the client due to worsening immune competency.

What is resistance?

In the majority of patients who have never received ART, the wild-type, or non-mutated virus predominates. During therapy the wild-type virus disappears or is suppressed. This creates the environment in which the mutant virus can become the dominant species. If the mutant virus is able to replicate in the presence of ARVs (i.e. there is ARV drug in the body but it is not enough to stop viral replication), strains of virus will emerge that have evolved resistance to that ARV drug. Such a situation occurs when an individual is taking ARV drugs but viral replication is not fuly suppressed (i.e. related to poor adherence). However, poor adherence is not the only reason that a person with HIV may not respond well to a particular ARV regimen. Patients may have been infected with virus that is already resistant to the first-line regimen that they have been started on. In addition to this, HIV can mutate over a period of time and drug resistance can occur even with perfect adherence (although very rarely).

Causes of treatment failure

- Patient factors (related to adherence)
  - Patients forget (travel, work, daily routine changes)
  - Patients start to feel better
  - Patients needs to hide that they take drugs (fear of disclosure)
  - Regimen complexity – may have many tablets
  - Side-effects
  - Substance use
  - Fear of medications
  - Denial of need for treatment
- Prescribing factors
  - Incorrect combinations or doses
  - Incorrect drugs if ARVs have been used in the past and resistance a possibility
  - Drug interactions if other medications (e.g. TB medications) are not taken into account when choosing a regimen
- Viral factors (out of control of the patient and health worker)

Diagnosing treatment failure

The decision on when to switch from first-line to second-line therapy is critical. If the decision is made too early, the months or years of potential further survival benefit from any remaining first-line effectiveness is lost; if it is made too late, the effectiveness of second-line therapy may be compromised and the patient is put at an additional and appreciable risk of death.

The time of switching is dictated by the diagnosis of treatment failure, and this can be measured in three ways: (1) clinically, by disease progression and WHO staging; (2) immunologically, using trends in CD4 counts over time; and (3) virologically, by measuring HIV viral loads (plasma HIV-1 RNA levels).

It is difficult in resource-limited settings to make an accurate diagnosis of treatment failure because the possibilities for laboratory investigation are limited. If clinical correlates alone are used it is likely that many patients will switch with advanced disease, at appreciable risk of death from OIs, and will have high viral loads with extensive drug resistance. The value of immunological monitoring in defining ART failure largely depends on having a baseline CD4 count before commencing ART and on having longitudinal CD4 measurements while on ART. One-off (spot) CD4 counts while on ART are difficult to interpret when making decisions about treatment success or failure. Viral load measurements are not widely available in resource-limited settings and will remain restricted because of their cost. In this situation treatment failure can only be assessed on the basis of clinical or immunological grounds.

Table 9: Clinical, immunological and virological definitions of treatment failure for patients on a first-line ART regimen (WHO ART guidelines, 2006)

Clinical failure[a]	New or recurrent WHO stage 4 conditions [b,c]
CD4 cell failure[d]	• Fall of CD4 count to pre-therapy baseline (or below); or • 50% fall from the on-treatment peak value (if known); or • Persistent CD4 levels below 100 cells/mm^3 [d]
Virological failure	Plasma viral load above 10 000 copies/ml [e]

a A clinical event must be differentiated from IRIS.

b Certain WHO clinical stage 3 conditions (e.g. pulmonary TB, severe bacterial infections) may be an indication of treatment failure and thus require consideration for second-line therapy.

Some WHO clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, oesophageal candidiasis, recurrent bacterial pneumonia) may not be indicators of treatment failure and thus do not require consideration of second-line therapy.

c Without concomitant infection to cause transient CD4 cell decrease.

d Some experts consider that patients with persistent CD4 cell counts below 50 cells/mm^3 after 12 months on ART may be more appropriate.

e The optimal viral load value at which ART should be switched has not been defined. However, values of more than 10 000 copies/ml have been associated with subsequent clinical progression and appreciable CD4 cell count decline.

Clinical disease progression as an indicator of treatment failure

Treatment failure should not be diagnosed by clinical criteria until:

1. There has been a reasonable trial of first-line therapy for at least six to twelve months.
2. Adherence has been assessed and optimized.
3. Intercurrent OIs have been treated and resolved.
4. IRIS has been excluded.

Clinical treatment failure cannot be diagnosed in the first six months of ART because the majority of adverse clinical events in the first six months of therapy represent IRIS related to pre-existing conditions or adverse drug reactions.

Table 10: Clinical staging events to guide decision-making on diagnosing treatment failure and switching to a second-line regimen

New or recurrent event on ART [a]	Recommendations	Additional management options
Asymptomatic (T1)	Do not switch regimen	• Maintain scheduled follow-up visits, including CD4 monitoring (if available) • Continue to offer adherence support
Stage 2 event (T2)	Do not switch regimen [b]	• Treat and manage staging event • Assess and offer adherence support • Check if on treatment for at least six months • Assess continuation or reintroduction of OI prophylaxis • Schedule earlier visit for clinical review and consider CD4 (if available) [c]
Stage 3 event (T3)	Consider switching regimen [b d]	• Treat and manage staging event and monitor response • Assess and offer adherence support • Check if on treatment for at least six months • Check CD4 cell count (if available) [c d] • Assess continuation or reintroduction of OI prophylaxis • Institute more frequent follow up
Stage 4 event (T4)	Switch regimen [b e]	• Treat and manage staging event and monitor response • Check if on treatment for at least six months • Assess continuation or reintroduction of OI prophylaxis • Check CD4 cell count (if available) [c] • Assess and offer adherence support

a Refers to clinical stages while on ART for at least six months (termed T1, T2, T3, T4).

b Differentiating of OIs from IRIS is necessary.

c Treat and manage the staging event before measuring CD4 cell count.

d Certain WHO clinical stage 3 conditions (e.g. pulmonary TB, severe bacterial infections) may be indicators of treatment failure and thus require consideration of second-line therapy; response to appropriate therapy should be used to evaluate the need for switching of therapy.

e Some WHO clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, oesophageal candidiasis, recurrent bacterial pneumonia) may not be indicators of treatment failure and thus do not require consideration of second-line therapy; response to appropriate antimicrobial therapy should be used to evaluate the need to switch therapy.

Source: WHO Guidelines, 2006.

The development of a new or recurrent WHO stage 3 or 4 condition on treatment (but after the first six months of ART) is considered evidence of HIV disease progression and treatment failure. However TB can occur at any CD4 level and does not necessarily indicate ART failure. The response to TB therapy should be used to evaluate the need to switch ART. With pulmonary TB and some extrapulmonary TB diagnoses (e.g. simple lymph node TB or patients with uncomplicated pleural disease), if there is a good response to TB therapy, the decision to switch ART can be postponed. This also applies if severe and/or recurrent bacterial infections (as stage 3 or 4 events) or oesophageal candidiasis respond well to therapy. If it is unclear whether clinical failure should be diagnosed, a one-off CD4 count may assist the diagnosis (do not switch if CD4 >200 cells/mm^3).

Diagnosing treatment failure by immunological criteria (CD4 count)

Progressive severe immunodeficiency demonstrated by a declining CD4 cell count over time indicates treatment failure. Persistent low CD4 counts on ART (100 cells/mm^3 after six months – although some advocate the use of a figure of 50 cells/mm^3) also represent treatment failure. Ideally, any measurement of CD4 count that may indicate the need to consider switching should be repeated and confirmed before any change is implemented.

Definitions of immunological failure are:

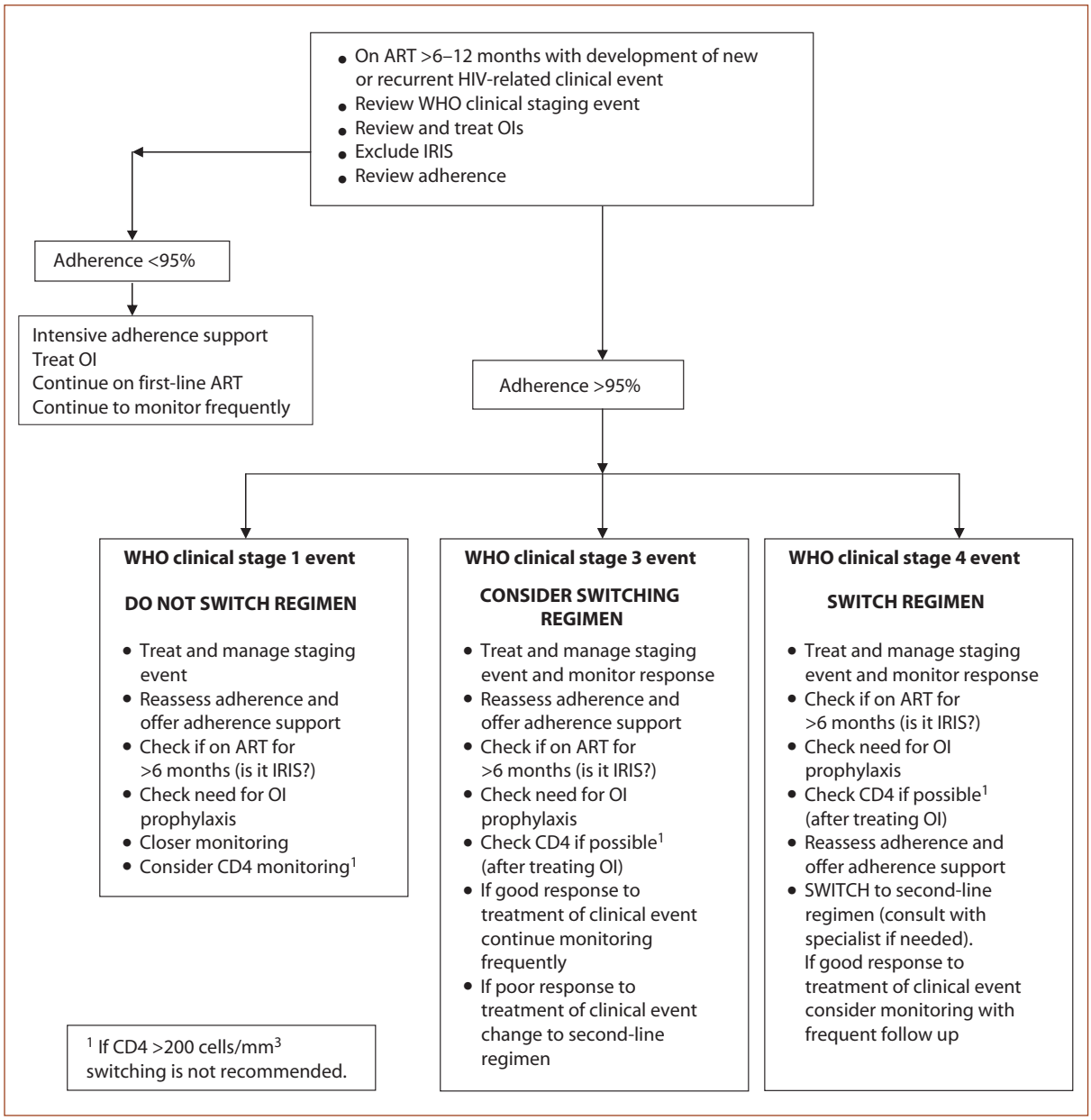
1. CD4 count below 100 cells/mm^3 (or 50 cells/mm^3) after six months of therapy
2. A return to, or a fall below, the pre-therapy CD4 baseline count after six months of therapy, or
3. A 50% decline from the on-treatment peak CD4 count (if known).

Infections can result in a transient CD4 count decrease and thus treatment failure should not be diagnosed by immunological criteria until intercurrent infections are diagnosed and treated, and time has been given for recovery. The CD4 count should then be repeated before a decision is made to switch therapy. It should also be noted that it can be difficult to track the true peak of a CD4 count when they are only done every six months, and therefore it may be problematic to diagnose immunological failure on the basis of a 50% decline from the on-treatment peak CD4 value.

The CD4 cell count can also be used to determine when not to switch therapy (e.g. in a patient with a new clinical stage 3 event for whom switching is being considered or in a patient who is asymptomatic). In general, switching should not be recommended if the CD4 cell count is above 200 cells/mm^3.

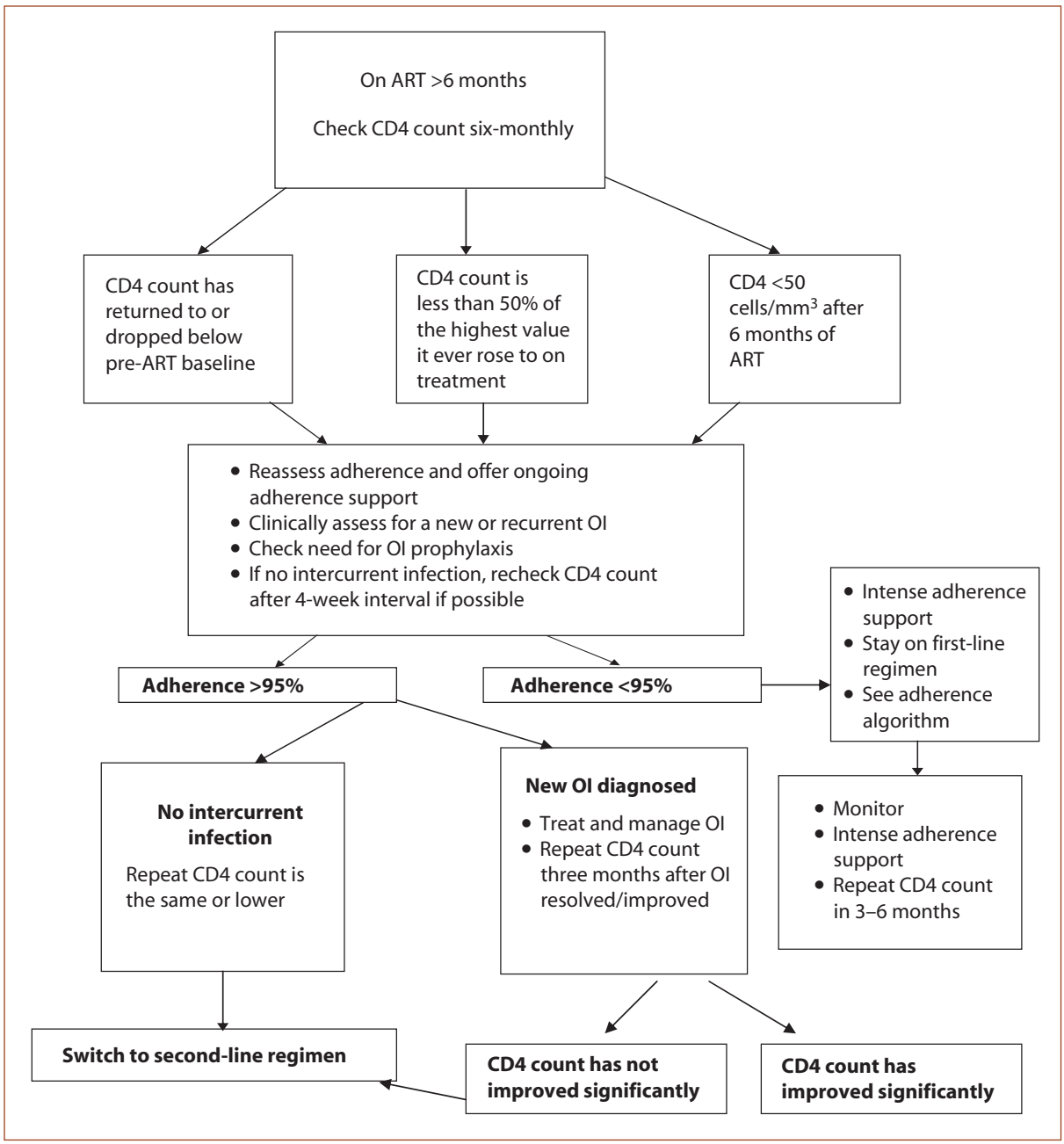
Where possible and in particular where there are difficulties in making a decision regarding switching to a second-line ART regimen, a second (repeat) CD4 cell count should be obtained to confirm immunological failure before the switch occurs.

Figure 18: Algorithm 6: Diagnosing treatment failure by clinical criteria



Source: Burdon R et al. *ARV therapy clinical handbook*. Viet Nam, Family Health International, 2006.

Figure 19: Algorithm 7: Diagnosing treatment failure by immunological criteria



Source: Burdon R et al. *ARV therapy clinical handbook*. Viet Nam, Family Health International, 2006.

INITIATING SECOND-LINE THERAPY

It is important to distinguish between the need to change ART due to treatment failure versus the need to change ART due to drug toxicity. Where therapy is being changed due to drug toxicity, it is appropriate to substitute one drug of the same class but with a different toxicity profile. In the case of **treatment failure**, it is recommended that the **entire regimen be changed**. The new second-line regimen needs to include drugs that have activity against the patient's virus strain and should ideally include three new drugs, one of them drawn from at least one new class, in order to increase the likelihood of treatment success and minimize the risk of cross-resistance. The PI class is reserved for second-line treatment in most resource-limited settings and should be supported by two new (unused) NRTIs where possible.

Other factors that influence decisions about second-line therapy include: the potency of the ARV drugs, potential resistance patterns from prior ART and potential for compliance/tolerance; assessment of adherence to medications; and preparation of the patient for the implications of the new regimen.

It is of critical importance to carefully re-assess patient adherence prior to changing ART.

A thorough review of adherence (and possible re-enrolment in the adherence education and counselling process) is required before initiating second-line therapy. Education and counselling about the different ways to take second-line drugs and the different side-effects are required. Clients need to understand that, due to the current limitations of the availability of second-line ARV drugs in most resource-limited settings, this regimen may be the last chance for successful ART.

A detailed history of current and past ARV medications as well as other HIV-related medications should be obtained in order to make appropriate choices about the new ART regimen and avoid drugs that may have cross-resistance.

General principles for second-line therapy

- Do not change a single drug or add a single drug to a failing regimen; it is important to use an entirely new regimen with three new drugs.
- Do not substitute EFV with NVP and vice versa due to high rates of cross-resistance in this class.
- Do not use ddI and TDF together.

The following regimens are possible for those who have failed a standardized first-line ARV regimen:

Table 11: Possible second-line regimens

First -line regimen		Second-line regimen	
		RTI component	PI component [a]
STANDARD STRATEGY	AZT or d4T + 3TC [b] + NVP or EFV	ddI + ABC or TDF + ABC or TDF + 3TC (± AZT) [c]	PI/r [d]
	TDF + 3TC [b] + NVP or EFV	ddI + ABC or ddI + 3TC (± AZT) [c]	
	ABC + 3TC [b] + NVP or EFV	ddI + 3TC (± AZT) [c] or TDF + 3TC (± AZT) [c]	
ALTERNATIVE STRATEGY	AZT or d4T + 3TC [b] + TDF or ABC	EFV or NVP ± ddI	

a NFV does not need refrigeration and can be used as a PI alternative in places without a cold chain.

b 3TC and FTC are considered interchangeable because they are structurally related and have similar pharmacological properties and resistance profiles.

c 3TC can be considered for retention in second-line regimens to potentially reduce viral fitness, confer residual antiviral activity and maintain pressure on the *M184V* mutation to improve viral sensitivity to AZT or TDF. AZT may prevent or delay the emergence of the *K65R* mutation.

d There are insufficient data to detect differences among currently available RTV-boosted PIs (ATV/r, FPV/r, IDV/r, LPV/r and SQV/r) and the choice should be based on individual programme priorities (*see* text). In the absence of a cold chain, NFV can be employed as the PI component but it is considered less potent than an RTV-boosted PI.

Source: WHO. *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach*. Geneva, WHO, 2006.

Special considerations for clients who are IDUs

Treatment situation	Second-line preferential	Second-line alternatives
IDU without other significant clinical co-morbidities or co-treatments but needs ART	ABC + ddI+ LPV/r (or other boosted PI)	NFV can be substituted for LPV/r or other boosted PI. EFV or NVP can be substituted for ABC or ddI if neither were used in the first-line regimen.
IDU with HIV/HBV with indication to treat HBV and ART	ABC + ddI+ LPV/r (or other boosted PI) and retention continuation of 3TC and/or TDF	AZT, 3TC, TDF plus LPV/r (or other boosted PI) EFV or NVP can be substituted for ABC or ddI if neither were used in the first-line regimen.
IDU with TB/HIV using TB regimens with rifampicin and needs ART	ABC + ddI+ LPV/r and additional dose RTV (or other boosted PI)	Maintain the PI and substitute rifampicin for rifabutin in TB regimen with adjustments in ARV dose if needed.

Source: Pontali E. Presentation made at KL meeting. HIV clinical protocols for IDU. Geneva, WHO, 2006.

Table 12: Food restrictions, side-effects and major toxicities of commonly used second-line ARV drugs

Didanosine (ddI)	**Meal/food restrictions** • MUST take on empty stomach (60 minutes before a meal and 2 hours after a meal) **Minor side-effects that can be troubling to the client** • Gastrointestinal intolerance is very common **Major toxicities** • Pancreatitis, peripheral neuropathy, lactic acidosis
Abacavir (ABC)	**Meal/food restrictions – None** **Minor side-effects that can be troubling to the client** • Well tolerated **Special considerations for the health worker** • Hypersensitivity reaction is rare. It can be fatal if a patient who has had a hypersensitivity reaction takes ABC again.
Tenofovir (TDF)	**Should be taken with food** **Minor side-effects that can be troubling to the client** • Well tolerated (occasionally causes gastrointestinal upset) **Major toxicity** • Renal dysfunction • Monitor renal function and electrolytes
Lopinavir/ritonavir (LPV/r)	**Meal/food restrictions** • Should be taken with food **Minor side-effects that can be troubling to the client** • Diarrhoea and gastrointestinal upset is very common (50–60% of patients). This can be managed with diet, loperamide, calcium supplements. **Major toxicities** • Elevated LFT common • Can cause metabolic changes such as increased cholesterol and triglycerides and insulin resistance • Fat redistribution can occur
Nelfinavir (NFV)	**Meal/food restrictions** • Should be taken with food (preferably one high in fat) **Minor side-effects that can be troubling to the client** • Diarrhoea and gastrointestinal upset is very common (10–30% of patients). This can be managed with diet, loperamide, calcium supplements. • Skin rash in about 20% of patients **Major toxicities** • Elevated LFT common – if 5–10 x ULN may need to stop NFV • Can cause metabolic changes such as increased cholesterol and triglycerides and insulin resistance • Fat redistribution can occur

Source: WHO guidelines, 2006 and Vitoria and Gilks, WHO, 2005.

Table 13: Side-effects and interactions of protease inhibitors

	Indinavir	Saquinavir	Nelfinavir	Lopinavir/r	Atazanavir	Fos-amprenavir
Minor side-effects	Gastrointestinal intolerance (10–15%) Dry skin, paronychia, alopecia	Gastrointestinal intolerance (10–20%) Headache	Gastrointestinal intolerance (10–30%) Skin rash (20%)	Gastrointestinal intolerance	Gastrointestinal intolerance	Gastrointestinal intolerance Skin rash (19%)
Major toxicity within first year	Nephrolithiasis and nephrotoxicity Abnormal LFT	Abnormal LFT	Abnormal LFT	Abnormal LFTs	Indirect bilirubin ↑ Jaundice or scleral icterus Abnormal LFT Prolonged PR interval	Abnormal LFT
Long-term toxicity	Lipodystrophy, hyperlipidaemia, insulin resistance	Lipodystrophy, less lipidaemia, insulin resistance	Lipodystrophy, hyperlipidaemia, insulin resistance	Lipodystrophy, hyperlipidaemia, insulin resistance	Lipodystrophy, insulin resistance, Minimal lipid changes	Lipodystrophy, hyperlipidaemia, insulin resistance
Interaction with methadone	IDV alone – no interaction but boosted IDV may need to increase methadone dose	SQV alone – minimal effect but boosted SQV may need to increase methadone dose	No interaction – but conflicting data (monitor)	Methadone levels decrease – may need to increase methadone dose	No interaction reported	Small reduction in methadone level (monitor). Methadone may decrease fos-APV levels

Source: Burdon R. FHI, Viet Nam (using information from Bartlett JG, Gallant JE. *Medical management of HIV infection*. Baltimore, John Hopkins University School of Medicine, 2007)

Steps in initiating and monitoring second-line therapy

- Review adherence support – may need to re-enrol in adherence process
- Reassess with full clinical review
- Reassess baseline laboratory tests
- Inform client and treatment supporter of all possible side-effects (especially diarrhoea on PIs)
- Make sure all health workers at the outpatient clinic are aware of the change in regimen and know how to manage the side-effects
- Review monitoring protocol

Baseline tests for second-line therapy include:

- A recent (within the past 1–3 months) CD4 count
- CBC
- LFT
- NFV and LPV/r – fasting lipids and blood sugar level or OGTT
- TDF – baseline renal function

(If second-line regimen includes AZT/3TC, EFV or NVP – *see* Module 6.5 for recommended baseline tests and requirements for ongoing monitoring.)

Regular or routine laboratory monitoring includes:

- Regular CBC
- Three-monthly LFT
- CD4 count test (where possible) every six months
- On NFV and LPV/r – annual fasting lipids and fasting blood sugar level
- On TDF – six-monthly renal function

(If second-line regimen includes AZT/3TC, EFV or NVP – *see* Module 6.5 for regular monitoring requirements.)

Additional laboratory tests should be done immediately any time that the following symptoms/signs occur:

- CBC – extreme fatigue or symptoms of anaemia
- LFT and hepatitis B/C serology – signs of hepatitis and liver failure
- LFT and CBC – severe rash with mucosal involvement
- Urea, electrolytes, creatinine – signs of renal failure
- Blood sugar level – signs of diabetes, insulin resistance or features of lipodystrophy
- Lipids – signs of clinical lipodystrophy or hyperlipidaemia or "fatty liver" on ultrasound
- Lactate – clinical signs and symptoms of lactic acidosis, hepatic steatosis on ultrasound

If abnormality is detected, more frequent monitoring is required.

Table 14: Monitoring for side-effects of ARVs

ARV	Diagnosed by clinical evaluation	Diagnosed by laboratory monitoring
ABC		
ABC hypersensitivity	Signs to watch for include: fever; skin rash (70%); severe nausea, vomiting, diarrhoea or abdominal pain; arthralgia, cough and shortness of breath. It usually happens in the first 6 weeks on ABC (commonly in first 2 weeks). STOP ABC and never give again.	Check CBC and LFT (but this is a clinical diagnosis).
Lactic acidosis and hepatitic steatosis	May be asymptomatic or patient may complain of fatigue, shortness of breath, nausea, vomiting, diarrhoea, dizziness, myalgia.	Do LFT, lactate, HCO_3, anion gap, liver US if possible – may be a clinical diagnosis.
ddI		
Pancreatitis	Acute abdominal pain with systemic features	Do amylase
Lactic acidosis and hepatic steatosis	See above.	Do LFT, lactate, HCO_3, anion gap, liver US if possible – may be a clinical diagnosis
Peripheral neuropathy	Occurs in patients usually after they have been on the drug for 2–6 months. Symptoms include pain, numbness and tingling of the hands or feet.	
Lipoatrophy	Change in body shape with loss of fat from arms, legs and face	
TDF		Renal failure – monitor urea, electrolytes and creatinine
LPV/r		
Fat redistribution (lipodystrophy)	Fat accumulation can occur within the abdominal cavity, upper back, breasts and subcutaneous tissue. Loss of peripheral fat (from buttocks, arms and legs) can also occur.	Monitor fasting cholesterol, triglycerides, blood sugar level
Increased triglycerides/ cholesterol		Diagnosed through routine monitoring of fasting cholesterol and triglycerides. Can cause an increase in cholesterol (particularly LDL) and triglycerides. Usually happens after 3–6 months
Insulin resistance and diabetes	Frank diabetes is rare.	Monitor fasting blood sugar level (OGTT is best).

Table 14: Monitoring for side-effects of ARVs (contd.)

ARV	Diagnosed by clinical evaluation	Diagnosed by laboratory monitoring
Abnormal liver function		Monitor LFT. Can cause rises in liver enzymes (3–5 x ULN) which are asymptomatic. If enzymes become x10 ULN LPV/r may need to be stopped.
NFV		
Fat redistribution (lipodystrophy)	Fat accumulation can occur within the abdominal cavity, upper back, breasts and subcutaneous tissue. Loss of peripheral fat (from buttocks, arms and legs) can also occur.	Monitor fasting cholesterol, triglycerides, blood sugar level
Increased triglycerides/ cholesterol		Diagnosed through routine monitoring of fasting cholesterol and triglycerides. Can cause an increase in cholesterol (particularly LDL) and triglycerides. Usually happens after 3–6 months
Insulin resistance and diabetes	Frank diabetes is rare.	Monitor fasting blood sugar level (OGTT is best).
Abnormal liver function		Monitor LFT. Can cause rise in liver enzymes (3–5 x ULN) which are asymptomatic. If enzymes become x10 ULN or patient symptomatic stop NFV.

Source: Burdon R et al. *ARV therapy clinical handbook*. Viet Nam, Family Health International, 2006.

MANAGING TOXICITIES ON SECOND-LINE THERAPY

Minor side-effects

The most common minor side-effects on second-line ARV regimens are gastric intolerance associated with ddI and diarrhoea and gastrointestinal upset on NFV and LPV/r. The use of anti-diarrhoeal agents, calcium supplements and bulk-producing agents can assist in controlling diarrhoea. It is important to maintain good hydration if diarrhoea is a problem.

Major toxicities and their management

Lipodystrophy is typically characterized by some combination of the following symptoms and disorders in persons on ART: (1) dyslipidaemia consisting of elevated total cholesterol, low HDL cholesterol and elevated triglycerides; (2) insulin resistance with hyperglycaemia, particularly in susceptible individuals; (3) visceral, breast and/or local fat accumulation; (4) generalized diminution of subcutaneous fat mass (lipoatrophy).

Lipoatrophy is characterized by the loss of subcutaneous fat in the face, arms, legs, abdomen and/or buttocks. It is primarily associated with NRTIs (d4T> ddI > AZT) but the use of PIs with these NRTIs seems to accelerate the subcutaneous fat loss. There are limited options for dealing with lipoatrophy when it occurs with PI-based regimens. If an individual is on a second-line regimen that contains one of the NRTIs more prone to causing lipoatrophy (e.g. d4T, ddI and AZT), consider switching to one of the NRTIs less likely to cause this (i.e. ABC or TDF).

Fat accumulation can occur within the abdominal cavity, the upper back, breasts and subcutaneous tissue and is usually associated with PIs. Fat accumulation in the abdomen or viscera is commonly accompanied by insulin resistance, glucose intolerance and dyslipidaemia – a syndrome referred to as the *metabolic syndrome* or *syndrome X*. If fat accumulation occurs, an individual should be screened with fasting lipids and blood sugar level/OGTT. Switching ARV drugs is of no benefit. Advice on diet and weight loss can be given but is of limited benefit.

Hyperlipidaemia: The initiation of PI-containing regimens generally leads to changes in lipids, including a rise in total cholesterol and both HDL and LDL cholesterol. Some NRTIs can also affect lipid levels. The management of hyperlipidaemia should include advice on diet and lifestyle change, and substituting ARV drugs to those with least lipid-raising properties (e.g. a triple NRTI regimen) where possible. If these measures do not work or are not possible, the use of specific lipid-lowering agents should be considered. When using lipid-lowering agents it is important to take into consideration drug interactions with ART therapy. Given these interactions it is recommended that initially low doses of pravastatin 20 mg daily or atorvastatin 10 mg once a day be used with careful monitoring of adverse events. Fibrates have a better effect on treating elevated triglyceride levels and are less likely to interact with PIs than the statins. Fibrates can be used simultaneously with pravastatin.

Insulin resistance: The relative impact of different ART combinations on insulin sensitivity and glucose handling has not been extensively studied in persons with HIV infection. Available data suggest a role for several PIs, most notably IDV, RTV, LPV/r. The clinical management of type 2 diabetes is the same as in the general population. Management should begin with counselling on diet and lifestyle modification. If frank diabetes manifests, insulin-sensitizing agents can be used.

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EXERCISE 6.6.1

Case studies: Managing major first-line ART toxicities in the first year of treatment

Instructions: Examine and discuss each case study and then document the following:

- *What diagnoses would you need to exclude before you diagnose treatment failure?*
- *What is your preferred second-line therapy?*
- *What are some alternatives to your preferred second-line therapy?*
- *What additional tests will you need to add to your routine monitoring repertoire?*
- *What major side-effects and toxicities will you tell the client about?*

Case study 1: Dave

A 38-year-old male ex-IDU has lost approximately 10 kg of weight over the past six months and has been hospitalized four times recently for recurrent bacterial pneumonia. He is a heavy drinker but has good family support and you think his adherence will be good. Twelve years ago he was hospitalized for six months for a psychotic episode. He complains of numbness in his toes. He also has oral candidiasis. His TLC is 900 cells. His ALT is 105 IU/L.

You prescribed AZT, 3TC, NVP.

Dave comes in for his two-week check-up. He complains of feeling extremely tired and achy and has a headache that will just not subside. He has spent much of the past few days in bed. He is frustrated with feeling like this and wants to stop his drugs.

Dave has been doing well on his ART after the initial problems. He was in last week for his routine three-month clinical assessment and you find that now his LFT has become a little more abnormal. His ALT is now 250 IU/L and his AST is 261 IU/L. He is completely asymptomatic.

You kept Dave on a regimen of AZT, 3TC and NVP. He did well on this regimen and his LFT remained at this level but you monitored them regularly – they did not worsen and Dave did not become symptomatic. You have now been seeing Dave for three-and-a-half years. Over the past five months he has lost 13 kg (he now weighs 51 kg) and has had diarrhoea (5–8 loose stools a day) for the past two-and-a-half months.

- *Is this treatment failure? What diagnoses would you need to exclude before you diagnose treatment failure?*
- *What is your preferred second-line therapy?*
- *What are some alternatives to your preferred second-line therapy?*

- *What additional tests will you need to add to your routine monitoring repertoire?*

- *What major side-effects and toxicities will you tell the client about?*

Case study 2: Navi

A 22-year-old woman presents with a recent diagnosis of HIV. She is four months pregnant. She has thrush but no other symptoms. She and her partner are both currently injecting heroin approximately five times a day. Her physical examination is normal except for several infected injecting sites. The CD4 count is 150 cells/mm^3. Her Hb is 8.8 g/dl and other baseline laboratory tests are unremarkable.

You prescribed AZT, 3TC, NVP.

One week after she started this regimen she comes into the clinic saying that she does not think she can keep taking the drugs as she is so nauseous. She has vomited twice daily during the week. She is otherwise well but is worried that she is not eating and about the effect this will have on the baby.

Navi comes in eight weeks after she started her first-line regimen. The nausea improved with your advice on taking AZT with food and taking some metoclopramide (Maxolon) but she now feels so tired she can hardly get out of bed. She tells you that she started back on the methadone programme approximately three weeks ago. On examination she looks a little pale and tired and is a little short of breath at rest. You check her Hb and it is only 6.1 g/dl.

Navi required a blood transfusion and you changed her ARV regimen to d4T, 3TC and NVP (and increased her methadone dose). She did well on this regimen and had a healthy baby who was recently confirmed HIV-negative. Navi has been on this regimen for 18 months. She came off the methadone programme again and she has not been attending clinic appointments regularly. She was recently admitted to hospital with PCP and when she was in hospital she started back on methadone. She is keen to try ART again as she felt so much better when she was on them last time.

- *Is this treatment failure? What diagnoses would you need to exclude before you diagnose treatment failure?*

- *What is your preferred second-line therapy?*

- *What are some alternatives to your preferred second-line therapy?*

- *What additional tests will you need to add to your routine monitoring repertoire?*

- *What major side-effects and toxicities will you tell the client about?*

Case study 3: Huong

A 25-year-old man requests ART. He had a CD4 count done at another health centre and it was 180 cells/mm^3. He is hepatitis B and hepatitis C positive. He has been stable on 80 mg methadone daily for the past eight months. He has missed picking up his daily methadone dose only on four days out of those eight months. He still injects heroin occasionally and regularly takes benzodiazepines. His AST is 350 IU/L.

You prescribed d4T, 3TC, EFV.

Huong comes in with his brother after two weeks of taking the above regimen. His brother is worried because Huong has not been sleeping very well and when he does sleep he wakes up screaming with vivid nightmares. Huong is a bit slow during the day and does not seem to be able to concentrate for very long. He has been "hanging out" for the last day or two and has had to inject heroin on three occasions.

Huong's issues with CNS side-effects settled down and his methadone dose was increased to 110 mg per day. He has been stable for some time. Five months after he started ART, he is brought to the clinic semi-conscious. His respiratory rate was markedly increased and LFT results are raised by 15–20 x ULN.

It turns out that Huong had lactic acidosis associated with d4T and you switched the d4T for TDF. He has done very well on this regimen (his CD4 count reached 450 cells/mm^3 one year ago) and has been on this regimen for five years. He is still on the methadone programme. His CD4 count has been slowly decreasing over the past year. Eighteen months ago it was 450 cells/mm^3 (the highest it had reached) and the one you did last week was 190 cells/mm^3.

- *Is this treatment failure? What diagnoses would you need to exclude before you diagnose treatment failure?*
- *What is your preferred second-line therapy?*
- *What are some alternatives to your preferred second-line therapy?*
- *What additional tests will you need to add to your routine monitoring repertoire?*
- *What major side-effects and toxicities will you tell the client about?*

Case study 4: Tuyet

An 18-year-old woman presents with a CD4 count of 120 cells/mm^3. She was admitted to hospital three months ago with TB meningitis and was started on buprenorphine at that time. She has been stable on 24 mg buprenorphine three times per week and has not used heroin since being discharged from hospital. She has finished the intensive phase of her TB treatment and is now on isoniazid and ethambutol for another six months. She has hepatitis B (HBsAg positive) and the AST is 55 IU/L. She is hepatitis C negative. Her Hb is 7.9 g/dl.

You prescribed d4T, 3TC, NVP.

Two weeks after she started this regimen she comes in with a rash. The rash is a red, itchy, macular rash that covers her chest, arms and back but is over less than 50% of her body. She seems quite well in herself.

Tuyet comes in for her six-month clinical assessment and you notice that she has to be helped up the stairs by her mother. She complains of burning and tingling, which is worse in her feet than her hands. She is unable to ride a motorbike any longer. On neurological examination she has marked by reduced sensory perception in her feet and hands and has lost her ankle reflexes.

You changed Tuyet to ABC, 3TC and NVP. She has now been on this regimen for four years and has done very well. Her lifestyle is stable. She is off the buprenorphine programme and has had a job for the last year. Over the past four months she has lost a lot of weight and tells you that it is very difficult to swallow any food – she even has trouble swallowing her tablets.

- *Is this treatment failure? What diagnoses would you need to exclude before you diagnose treatment failure?*
- *What is your preferred second-line therapy?*
- *What are some alternatives to your preferred second-line therapy?*
- *What additional tests will you need to add to your routine monitoring repertoire?*
- *What major side-effects and toxicities will you tell the client about?*

EXERCISE 6.6.2

Case study: Managing long-term toxicities

Instructions: Examine and discuss this case study and then document the following:

- *Which ARV drug do you think is responsible for this presentation?*
- *What is your differential diagnosis for this presentation?*
- *How would you exclude other causes for this presentation?*
- *What changes would you make to the ART regimen?*
- *What advice will you give the client to help him/her to adjust to this new regimen?*

Case study 1: Dave

A 38-year-old male ex-IDU has lost approximately 10 kg of weight over the past six months and has been hospitalized four times recently for recurrent bacterial pneumonia. He is a heavy drinker but has good family support and you think his adherence will be good. Twelve years ago he was hospitalized for six months for a psychotic episode. He complains of numbness in his toes. He also has oral candidiasis. His TLC is 900 cells. His ALT is 105 IU/l.

You prescribed AZT, 3TC, NVP.

Dave comes in for his two-week check-up. He complains of feeling extremely tired and achy and has a headache that will just not subside. He has spent much of the past few days in bed. He is frustrated with feeling like this and wants to stop his drugs.

Dave has been doing well on his ART after the initial problems. He was in last week for his routine three-month clinical assessment and you find that now his LFT has become a little more abnormal. His ALT is now 250 IU/l and his AST is 261 IU/l. He is completely asymptomatic.

You kept Dave on a regimen of AZT, 3TC and NVP. He did well on this regimen and his LFT remained at this level but you monitored them regularly – they did not worsen and Dave did not become symptomatic. You have now been seeing Dave for three-and-a-half years. Over the past five months he has lost 13 kg (he now weighs 51 kg) and has had diarrhoea (5–8 loose stools a day) for the past two-and-a-half months.

You diagnosed treatment failure and started him on ddI, ABC and LPV/r. He has now been on this regimen for three-and-a-half years. Although he complained a lot initially he has managed the diarrhoea on LPV/r well and he takes antidiarrhoeals occasionally. He has a moderate degree of abdominal fat deposition but this does not bother him. The last time you did blood tests on Dave his fasting blood sugar level was 12 – his LDL cholesterol was 10.5. Dave smokes 20 cigarettes a day, he still drinks alcohol heavily and his mother died of a heart attack at the age of 47 years.

- *Which ARV drug do you think is responsible for this presentation?*
- *What is your differential diagnosis for this presentation?*
- *How would you exclude other causes for this presentation?*
- *What changes would you make to the ART regimen?*
- *What advice will you give the client to help him to adjust to this new regimen?*

Annex 1

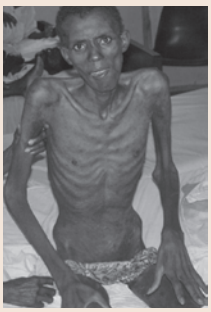
Presentation 6.1: IDU access to ART

IDU access to ART

Session objectives

- Describe the current access of IDUs to ART programmes
- Explore personal beliefs and preconceptions about IDU access to ART
- Identify barriers restricting access of IDUs to HIV care including ART
- Understand and describe the evidence refuting commonly held perceptions about IDUs and ART that prevent IDUs from accessing ART programmes
- Explore successful models for providing quality ART to IDUs

ART has turned HIV into a manageable chronic disease



Sources: Viet Nam CDC Harvard Medical School AIDS Partnership. *Clinical training*. Ho Chi Minh City, 2006.

ART offers:

- The opportunity to improve the prognosis and quality of life of IDUs living with HIV/AIDS
- An incentive to make contact with health-care facilities – facilitating prevention, care and treatment for all aspects of HIV and IDU care

Activity 1: Individual exercise

- Use Exercise 6.1
- Do you personally think that active IDUs can take ART successfully?
- What are the reasons you think active IDUs can (or cannot) successfully take ART?

However…IDUs are often excluded from ART

- Russia 2002: IDUs made up 90% of HIV cases yet no active IDUs were on ART
- Ukraine 2002: IDUs make up 69% of HIV cases but only 20% on triple combination ART
- In France, Canada and the USA: multiple studies have found that the majority of HIV-infected individuals who are not on ART are active IDUs

Or ART is inadequate

- Swiss study demonstrated that IDUs outside a drug treatment programme had a significantly higher risk for inadequate treatment.
- In Italy a study revealed that ART was started later in the course of HIV disease in IDUs compared with non-IDUs, and IDUs were less likely to be prescribed protease inhibitors.

In South-East Asia

- A 2004 study found that in Asia only 1–5% of IDUs access prevention and treatment services
- Lack of funding and infrastructure to provide ART and other services to IDUs
- Thailand 2004: Very few IDUs out of the 30 000 on ART

Activity 2: Brainstorm

Why do barriers to accessing ART exist for IDUs?

What do the WHO guidelines say?

- "Access to HIV treatment should not be artificially restricted due to political or social constraints. Specifically, there should not be categorical exclusion of IDUs from any level of care. All patients who meet eligibility criteria and want treatment should receive it, including IDUs, sex workers and other populations."

And the US Department of Health and Human Services

- "No individual patient should automatically be excluded from consideration for ART simply because he or she exhibits a behavior or other characteristic judged by some to lend itself to non-adherence."

The current misperceptions across many parts of the world

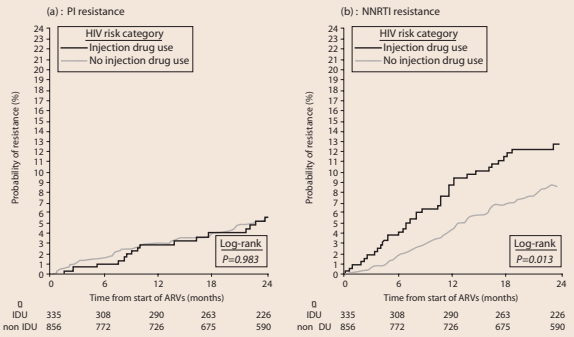
1. IDUs are poor candidates for ART due to poor adherence.
2. IDUs must be on OST to access ART.
3. IDUs do not do as well on ART as non-IDUs.
4. Medical complications such as HBV/HCV make HIV difficult to treat and less responsive to ART.

Adherence among IDUs

- 2001: Brazil study of 673 poor patients in San Paulo – overall adherence 69%
- 2000: French study: IDUs on buprenorphine and ART demonstrated 78% adherence
- 2002: study in Ireland where ART was offered at methadone clinic – 58% achieved VL<50 copies/ml at 48 weeks
- 2004: study in Baltimore, USA of 286 patients – 58% of those who received ART at methadone clinic achieved VL<50 copies/ml at 48 weeks compared with 39% of non-drug users self-administering ART

Rates of ART resistance by IDU status

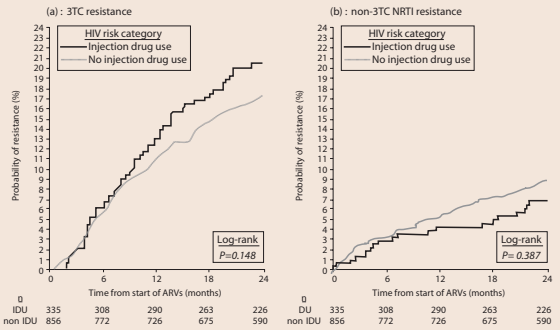
ART among injecting drug users



Source: Wood et al. *AIDS*, 2005.

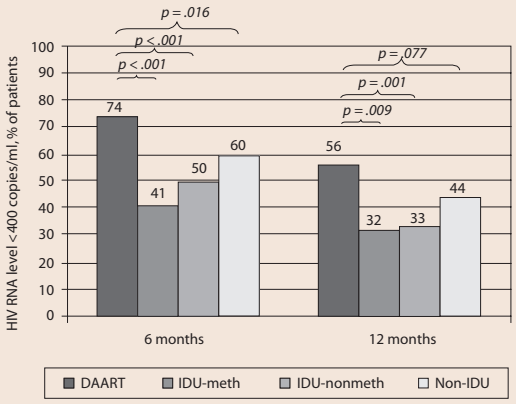
Rates of ART resistance by IDU status

ART among injecting drug users



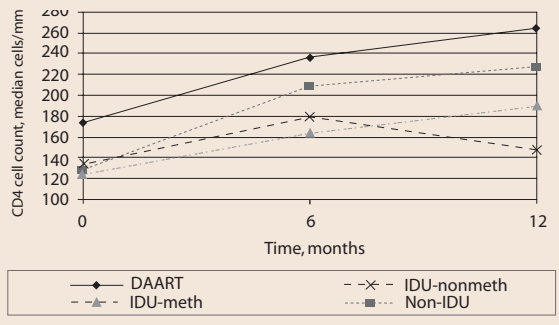
Source: Wood et al. *AIDS*, 2005.

Directly administered ART



Source: Lucas G et al. *Clinical Infectious Diseases,* 2006.

Directly administered ART



Sources: Lucas G et al. *Clinical Infectious Diseases*, 2006.

Potential limitations of DOT

- Many regimen are twice daily
- ART is lifelong
- Resource-intensive and difficult to sustain
- Negative impact on individual freedom
- Need for randomized controlled trials
- Cost-effectiveness needs to be evaluated

Must IDUs be on substitution therapy to be successful on ART?

- Continuing drug use is one of the major behavioural features that impact negatively on adherence.
- Some studies have shown that active injectors have lower rates of adherence than non-users or non-injectors.

However ...

- 2001: Baltimore, USA – study of 796 patients, active IDUs achieved adherence of 66% without any special support
- Former IDUs had higher levels of adherence (83%) than those who had never used drugs at all (76%)
- 2004: US study of mobile needle exchange – for those who received peer support plus ART, adherence rates of 85% after six months (even though 35% were homeless and 74% deeply depressed)

AND

- Some studies have shown that the regular and stable attendance at a clinic is more important than drug substitution therapy itself.
- Success of the ART programme in Brazil (mostly cocaine users) indicates that adherence is related to social and community support.

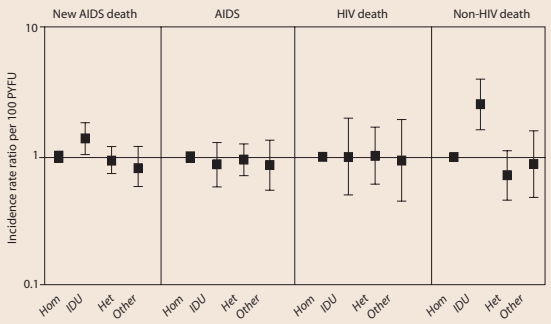
ART adherence and providers

- Surveys of physicians have shown that a physician's judgement of patient adherence is critical for prescription of ART.
- Physicians have been shown to be consistently poor at predicting those who can be "adherent".
- Satisfaction with one's physician has been associated with higher levels of adherence.
- Willingness to start ART has been associated with patient trust in physician.
- Among IDUs, being treated by a physician with experience in treating HIV was associated with increased ART uptake.

Do IDUs on ART do as well as non-IDUs?: HIV treatment efficacy data

- In 1999 a large cohort study of 6645 patients on ART from 51 centres across Europe found no difference between IDUs and non-drug users in either CD4 counts or virological responses
- 2004: Canadian study of 1522 IDUs and non-IDUs: those who adhered to ART experienced similar increases in CD4 count
- 2004: US study of clients of a mobile syringe exchange programme – peer support plus ART – at six months 77% reduction viral load <400 copies/ml and 25% increase in CD4 count

Risk of AIDS and death by HIV exposure category (EuroSIDA)



Source: Mocroft A et al.; for the EuroSIDA study group. *AIDS*, 2004.

Outcomes: HIV/hepatitis coinfection

- HBV and HCV have limited impact on HIV disease progression
- Moderate increase in overall mortality among viral hepatitis coinfected persons, due to excess liver disease mortality
- Incidence of liver disease mortality relatively low
- Risk of liver disease mortality in era of ART probably stable, with some reduction in risk through improved immune function balanced by hepatotoxicity

Basic care package for HIV-infected drug user

- ACCESS to the following services:
  - VCT
  - Clinical services: diagnostic, therapeutic (ART + OI)
  - "Adherence" programmes: DOT, linked to DST programmes
  - Counselling and support
  - Drug rehabilitation/harm reduction programmes

Source: Dr C Lee

Basic requirements

DU-friendly services:

- Non-judgemental staff
- DU experienced staff (trained on working with DUs)
- Accessible services: location, time, convenience, built into existing programmes
  - community clinics (training family physicians)
  - linked to methadone clinics / DOT
  - once-daily ART regimens
- Continuum of care: "Home–community –hospitals"

General requirements to scale up ART for IDUs

- Universal access to treatment legislation
- Primary health care
- OST scale up
- Research on ARV interactions with drugs used by IDUs
- National ART guidelines include ART for IDUs
- Training for health-care providers caring for HIV-positive IDUs
- Comprehensive care and treatment programmes for IDUs
- Treatment literacy tailored for IDUs

Annex 2

Presentation 6.2: General HIV care for IDUs

General HIV care for IDUs

Acknowledgement: Viet Nam CDC Harvard AIDS Partnership

Session objectives

- Outline the health problems of HIV-positive IDUs and the essential components of health-care service delivery for them
- Describe the common non-HIV related infections and medical conditions of HIV-positive IDUs including their management
- Describe common OIs and their management
- Outline the difference between primary and secondary OI prophylaxis
- Perform an initial evaluation of an HIV-positive IDU at the HIV clinic

Looking after IDUs with HIV

- IDUs with HIV present with clinical and psychosocial difficulties related both to HIV and injecting drug use
- Often poly-substance use
- May have difficulties in dealing with health professionals (and vice versa)
- Special care is needed to ensure they get the best service available and keep using the services
- IDUs are anxious about any contact with authorities and institutions

Activity 1: Small group work

- What are some of the common health problems among HIV-positive IDUs?
- What are some of the ingredients that make up a good model of care for HIV-positive IDU clients?

Common health problems among HIV-positive IDUs

- OIs characteristic of HIV
- Infection with other bloodborne viruses (HBV and HCV) leading to liver disease
- Drug-related hepatitis
- Increased risk of TB
- Other bacterial infections – soft tissue infections, pneumonia and endocarditis
- Traumatic injuries
- STIs
- Overdose
- Psychiatric co-morbidity
- Poly-substance use

Different comprehensive care models

1. One site that provides HIV primary care and substance dependence treatment
   HIV care at substance dependence treatment clinic or, alternatively, substance dependence treatment offered at a primary HIV care clinic
2. Close proximity between separate clinics for HIV care and substance dependence treatment
3. Primary care practitioners offering both HIV care and substance dependence treatment

A major challenge

A major challenge in delivering care to IDUs is their need for multiple services that concurrently address both biomedical and psychosocial issues.

Medical care for HIV-positive IDUs

- Requires a multidisciplinary team with experience in both HIV infection and injecting drug use
- Linked with harm reduction services for OST and drug counselling services
- Linked with social services and community and home-based support
- Provide ART and adherence support
- Encourage involvement of peer educators
- Provide education and promote active participation in health
- Accessible and affordable services
- User-friendly with non-judgemental staff

The first visit

- Establish a relationship
- Psychosocial assessment – including drug and alcohol use
- Clinical and laboratory assessment – including WHO staging
- Prioritize immediate needs
- Formulate a management plan

Psychosocial assessment
(refer to Module 3)

- Basic demographic information
- Employment/education
- Living situation and social support
- Financial resources
- Mental health assessment – anxiety, depression
- Substance use history and current use
- Client's knowledge, attitudes and beliefs about HIV and transmission
- Nutrition
- Transportation
- Parenting/child needs (including guardianship plans)

Clinical and laboratory assessment

- Confirm HIV status and risk assessment
  - Where tested, what risk factors, needs confirmatory testing?
  - Status of family members/sex or IDU partners, and are they on ART?
- Medical history
  - Past medical history, especially TB, hepatitis B and C
  - ART history
  - Medications and allergies
  - Contraception and pregnancy status
  - Current symptoms – particularly fever, SOB, diarrhoea, weight loss
- Examination
  - Weight and vital signs
  - WHO functional status
  - All systems particularly lymph nodes, anaemia, thrush, skin infections, respiratory infections
  - Possible indications of substance dependence
- Laboratory tests
  - CD4 count or TLC, viral load, LFTs, FBC, HBV and HCV, syphilis serology, TB screening, STI screening

Review: WHO staging

- Stage I: Asymptomatic
- Stage II: <10% weight loss, skin conditions, recurrent bacterial processes, herpes zoster
- Stage III: >10% weight loss (with fatigue, fever or diarrhoea, all >1 month), thrush, oral hairy leukoplakia (OHL), pulmonary TB
- Stage IV: AIDS or bedridden >50% of the time

Activity 2: WHO staging

Four case studies

- Use Exercises 6.2.1 and Annex 1

Laboratory staging: CD4 count

- Do not rely on the CD4 count as the sole predictor of immunodeficiency
- Consider hyposplenism/splenectomy as a cause of falsely elevated CD4 counts
- Factors that influence CD4 counts include use of steroids, intercurrent illness, seasonal and diurnal variation, analytical variation
- Correlation of laboratory markers with clinical state

Laboratory staging: TLC

- TLC can be used to roughly estimate the level of immunosuppression, when correlated with the presence of symptoms and WHO staging
- TLC <1200 cells and symptoms of AIDS correlates well with a CD4 <200 cells/mm^3
- TLC <1200 cells when there are no symptoms of AIDS is not a good predictor of CD4 count
- WHO stage III or IV and TLC >1200 cells should still be considered immunosuppressed

Activity 3: Role Play

- Turn to Exercise 6.2.2
- Break into four groups
- This activity takes approximately 30 minutes
  - 20 minutes role-play
  - 10 minutes small group discussion of role-play
- Each group needs to choose:
  - A facilitator
  - A doctor
  - A client

Summary: the first visit

- Establish a relationship
- Identify immediate psychosocial needs including the assessment of drug use and potential for OST
- Identify immediate medical needs (such as OIs, other infections)
- Perform WHO clinical staging
- Assess need for OI prophylaxis
- Perform laboratory testing and initial assessment for ART
- Start providing some education
- Refer to peer support, community support

Management of common health problems in IDUs

- Hepatitis A, B and C: screening, vaccination and prevention
- Tuberculosis
- STIs
- Soft tissue injury
- Overdose

Hepatitis

- Hepatitis/HIV coinfection is extremely important for clinical management
- Important to do baseline screening: HAV IgG, HBsAg and HCV Ab plus LFT
- Offer anti-HBV vaccination to those who may have negative serology
- Provide prevention messages

STI screening and management

- STI rates can be much higher in the IDU population – may be related to sex work or exchange of sex for money or drugs
- STIs are important for many reasons – particularly as they increase risk of HIV transmission
- Important to offer integrated STI diagnosis and management
- Offer etiological, syndromic management plus annual screening (chlamydia, gonorrhoea, syphilis)
- Do Pap smears

Soft tissue infections

- Abscesses are common among IDUs (prevalence of up to 32% in some settings)
- Most common organisms are skin and oral flora, including *Staphylococcus aureus*, Gram-negative bacteria and mixed anaerobic bacteria
- Contamination is often related to injection practices and not the drugs used
- Less commonly, drugs or injection equipment may be contaminated with *Clostridium tetani* or *C. botulinum*, and may cause cases or clusters of tetanus or wound botulism

Soft tissue infections can be reduced by:

- Cleaning skin thoroughly before each injection
- Using a sterile syringe (or at least a sterile needle) for every injection
- Rotating injection sites
- Keeping tetanus vaccinations up-to-date
- Avoiding intramuscular injection of cocaine

Risk factors for overdose

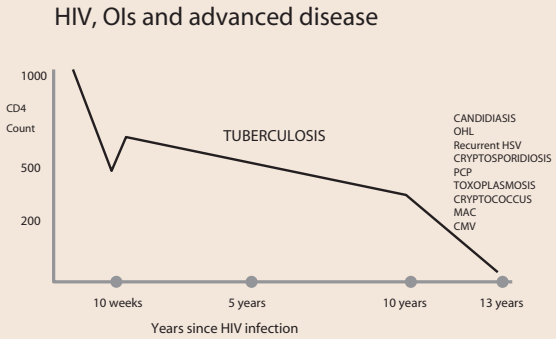
- Age: late 20s or early 30s
- Using heroin for 5–10 years
- Recent release from detoxification or correctional facility
- Using heroin outdoors
- Using heroin alone
- Mixing heroin with alcohol or benzodiazepines
- Concurrent serious medical conditions, particularly pulmonary and hepatic dysfunction

Patients can be taught

- The risks of mixing depressants with heroin
- The risk of reinitiating heroin use after a period of abstinence
- To recognize the signs of a possible heroin overdose in another user and immediately call for medical help (many people who overdose are not alone)

Diagnosis and management of OIs

HIV, OIs and advanced disease



Sources: Viet Nam CDC Harvard Medical School AIDS Partnership. *Clinical training*. Ho Chi Minh City, 2006.

Prevalence of OIs among persons with AIDS, Thailand (2 series)

Prevalence

• Tuberculosis	29–37%
• Cryptococcosis	19–38%
• Wasting syndrome	8–28%
• *Pneumocystis carinii* pneumonia	5-20%
• Bacterial pneumonia	4%
• Oesophageal candidiasis	3–6%
• *Penicillium marneffei* infection	3%
• Toxoplasmosis	2–3%
• Cryptosporidiosis	1–2%

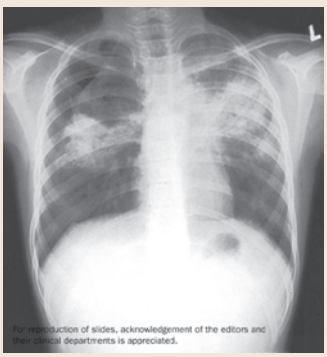
Sources: Chariyalertsak S et al. *Clinical Infectious Diseases,* 2001; Amornkul PN et al. *AIDS*, 1999.

OIs and tumours in HIV/AIDS inpatients in NICRTM n= 220

• Oral thrush	43%
• Wasting syndrome	33%
• Tuberculosis	28%
• Penicilliosis	11%
• Shingles	5%
• Septicaemia	5%
• Cerebral toxoplasmosis	3%
• MAC infection	3%
• PCP	2%
• Leishmaniasis	0,5%
• Aspergillosis	0,5%

Source: Le Dang Ha et al. *Clinical training*. Ho Chi Minh City, Viet Nam, 2006.

Tuberculosis



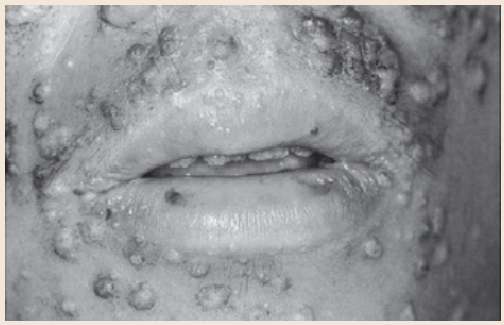
Source: Viet Nam CDC Harvard Medical School AIDS Partnership. *Clinical training*. Ho Chi Minh City, Viet Nam, 2006.

Difficulties in diagnosing TB in HIV-infected clients

- Clients with early HIV infection present with typical TB symptoms fever, cough, fatigue, weight loss, night sweats. CXR appearances are typical of TB and smear is usually positive.
- Late HIV infection patients may just have fever and weight loss (severe wasting plus diarrhoea and anaemia).
- In late stage HIV, CXR may not suggest TB – with no cavities and often not upper lobe disease. Smear will often be negative.
- Miliary disease is common and X-ray may even be normal.
- Extrapulmonary TB is much more common in PLWHA, particularly with advanced disease and low CD4 counts.

Penicilliosis

- Manifestation: typical skin lesions
- Additional symptoms:
  - + Fever (>38^{0}C)
  - + Hepatomegaly
  - + Splenomegaly
  - + Weight loss
- Diagnosis
  - Blood culture (+)
  - Microscopic examination of skin lesions



Source: Viet Nam CDC Harvard Medical School AIDS Partnership. *Clinical training*. Ho Chi Minh City, Viet Nam, 2006.

Penicillium marneffei: treatment

• Localized	Itraconazole, 8 mg/kg/day for 6–8 weeks (usually recommended 200 mg bid)
• Systemic	Amphotericin, 1.0 mg/kg/day for 14 days; then itraconazole, 8 mg/kg/day for 6–8 weeks

Chronic maintenance therapy required (itraconazole 200 mg/day)

Cryptococcal meningitis

Clinical manifestations: slow onset of headache, fever, fatigue, mental disorders. Meningeal and other uncommon neurological abnormal signs. High CSF opening pressures. CD4 count <100 cells/mm^3

Diagnosis

- Cryptococcal antigen (may not be available)
- India ink stain
- CSF culture

Cryptococcal meningitis: treatment

• Amphotericin (+ flucytosine if available)	0.7 mg/kg/day (100 mg/kg/day)	x 14 days
then		
• Fluconazole	400–800 mg for 8–10 weeks	

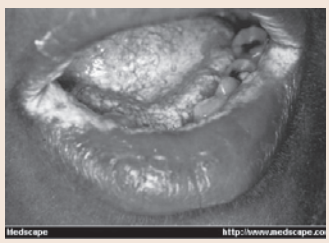
If amphotericin is not available or not tolerated, use high-dose fluconazole (400–800 mg/day)

Chronic maintenance therapy required (fluconazole, 200 mg/day)

Oesophageal candidiasis

CD4 count <200 cells/mm^3
- Painful swallowing
- Bleeding lesions
- Anorexia, weight loss
- Loss of taste

Treatment
-Fluconazole
-Itraconazole
- Amphotericin

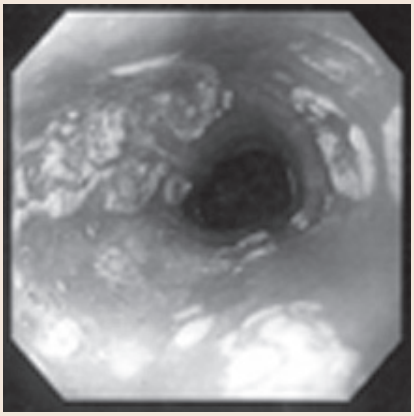


Prophylaxis if:
- CD4 count <200 cells/mm^3 and
- Previous candidiasis

Immune restroration
-Antiretrovirals

Source: Medscape. *Clinical teaching resources*

Candida oesophagitis

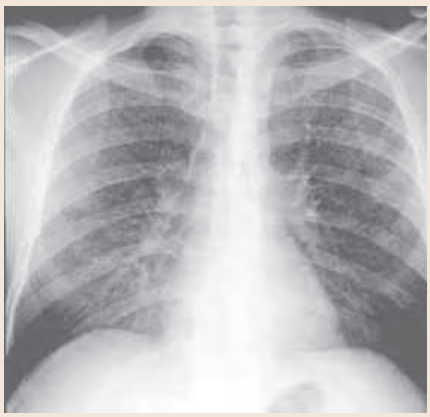


Source: Viet Nam CDC Harvard Medical School AIDS Partnership. *Clinical training*. Ho Chi Minh City, Viet Nam, 2006.

Pneumocystis jiroveci pneumonia

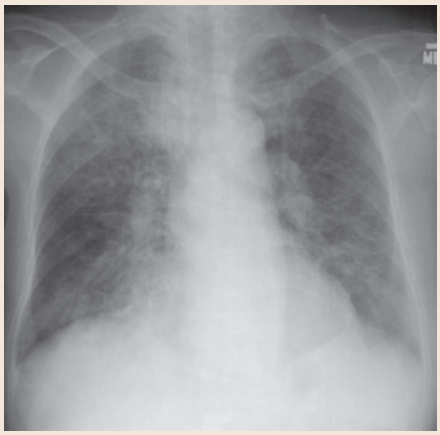
- Manifestations: gradual onset of shortness of breath, dry cough, fever
- Lung sounds: may be clear or have faint crackles
- Hypoxia is common
- CD4 count <200 cells/mm^3 (though occasionally higher)
- CXR:
  - Typical: bilateral diffuse infiltration
  - Atypical: normal or lateral infiltration
  - Pneumothorax is suggestive

The many faces of PCP…



Source: Viet Nam CDC Harvard Medical School AIDS Partnership. *Clinical training*. Ho Chi Minh City, Viet Nam, 2006.

PCP



Source: Viet Nam CDC Harvard Medical School AIDS Partnership. *Clinical training*. Ho Chi Minh City, Viet Nam, 2006.

Pneumocystis jiroveci pneumonia (PCP): treatment

- Trimethoprim – sulfamethoxazole (co-trimoxazole). Dose is based on trimethoprim 15 mg/kg/day in three–four divided doses; usually: 2 double-strength tablets or 4 single-strength tablets every 8 hours for two–three weeks. CTX can be given IV if available.
- For severe cases, add prednisone, 40 mg bid for 5 days then 40 mg qd for 5 days then 20 mg/day for 11 days (21 days total).

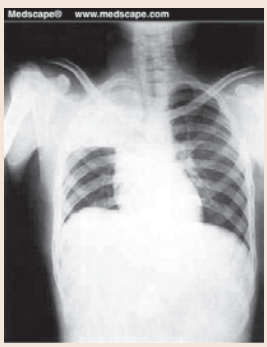
Chronic maintenance therapy required (CTX, 160/800 mg/day)

Lower respiratory infections

"Typical" infections
Pneumoccal pneumonia
- *Strep. pneumoniae*
- High fever, sepsis
- Cough and sputum
- Meningism
- Lobar pattern

Haemophilus influenzae
- Recurrent pneumonia
- Less severe

Staph. aureus (IDUs)
- Very toxic
- Very severe



Source: Medscape. *Clinical teaching resources*

Bacterial pneumonia: empirical treatment

- Benzylpenicillin — 0.4 million U/kg/day (penicillin-sensitive)
- Ampicillin — 200–300 mg/kg/day (penicillin-sensitive)
- Cefotaxime — 200–300 mg/kg/day

Best treatment is based on culture and sensitivity.
Treat for 7–10 days.

Prevention of OIs

- Primary prevention: giving medication to prevent an OI from occurring
- Secondary prevention: (maintenance therapy)
  - Medication is given after an OI is treated to prevent it from recurring.
  - The medication should be continued for life unless the patient is started on ART and has recovery of immune function (increase CD4 count >200 cells/mm^3 for more than three months).

What diseases may be prevented?

- PCP
- Cerebral toxoplasmosis
- Tuberculosis
- Fungal infections
  - Cryptococcosis
  - Penicilliosis
- *Mycobacterium avium* complex (MAC)

When to start CTX (WHO guidelines, 2006)

- WHO stages 2, 3 or 4
- Anyone on TB treatment
- Any WHO stage and CD4 count <300 cells/mm^3
- Dose: 960 mg/day or 960 mg 3x /week
- All symptomatic people with mild, advanced or severe disease

CTX prophylaxis

Can prevent:

- PCP
- Cerebral toxoplasmosis
- *Streptococcus pneumoniae* pneumonia
- Non-typhoid salmonellosis
- Nocardiosis
- Isosporiasis

Benefits of CTX

- Shown to decrease morbidity and mortality even in areas with high background bacterial resistance to CTX
- Inexpensive
- Generally, well-tolerated
- Can be a good way to prepare a patient to take medications on a daily basis and improve adherence prior to beginning ART

Benefits of CTX

Daily CTX prophylaxis given to 509 people with HIV in Uganda. During the CTX treatment period:

- In those with CD4 count <200 cells/mm^3 or stage 3/4 death rate was 46% lower.
- Reports of diarrhoea fell by 35%.
- Hospital admissions fell by 15–30%.
- CTX was well tolerated. Treatment adherence was high.
- CD4+ cell count decline slowed from 203 cells/mm^3 per year to 77 cells/mm^3 per year.

Source: Mermin J et al. *Lancet* 2004

Isoniazid preventive therapy (IPT)

- International "best practice"
- If skin testing available, may reserve for persons with positive tuberculin skin test (>5 mm induration)
- Otherwise, IPT suggested for all HIV-positive patients living in countries with high prevalence of TB
- IPT also suggested for HIV-positive persons exposed to case of active TB
- Give isoniazid (INH), 300 mg per day for 9 months
- EXCLUSION OF ACTIVE TB IS CRITICAL
- Not currently recommended in some countries in Asia (refer to National NTP Guidelines)

Primary prophylaxis for OIs

Disease / Agent	Indication	Primary Prophylaxis	Alternative
Pneumocystis jiroveci	CD4 < 200 cells/µl or WHO stage III or IV disease	CTX (960 mg tab) once daily	Dapsone 100 mg once daily
Toxoplasma gondii	CD4 < 100 cells/µl	CTX (960 mg tab) once daily	Dapsone 50 mg daily plus pyrimethamine 25 mg weekly plus folinic acid 25 mg weekly
Fungal disease	CD4 < 100 cells/µl	Fluconazole 200 mg daily every other day or 400 mg once per week	
Mycobacterium avium	Consider treatment for CD4 < 50 cells/µl	Azithromycin 1200 mg weekly	Clarithromycin 500 mg twice daily
Mycobacterium tuberculosis	Tuberculin skin test ≥5 mm (not currently recommended in Viet Nam)	INH 300 mg daily x 9 months	

Source: Viet Nam CDC Harvard Medical School AIDS Partnership. *Clinical training presentations*. Ho Chi Minh City, Viet Nam, 2006.

Secondary prophylaxis for OIs

Disease / Agent	Indication	Primary Prophylaxis	Alternative
Pneumocystis jirovaci	Prior history of PCP	CTX (960 mg) 1 tablet daily	Dapsone 100 mg daily
Toxoplasma gondii	Prior history of toxoplasma encephalitis	Pyrimethamine 25–50 mg daily plus folinic acid 10-25 mg daily plus sulfadiazine 500-1000 mg 4 times daily	Can substitute clindamycin for sulfadiazine Cotrimoxazole if others unavailable
Mycobacterium avium	Prior history of MAC disease	Clarithromycin 500 mg twice daily plus ethambutol 15 mg/kg/day	Azithromycin 500 mg daily plus ethambutol
Cryptococcus neoformans	Prior history of cryptococcosis	Fluconazole 200 mg daily	
Histoplasma capsulatum	Prior history of histoplasmosis	Itraconazole 200 mg daily	
Penicillium marneffei	Prior history of penicilliosis	Itraconazole 200 mg daily	
Cytomegalovirus	Prior end-organ CMV disease	IV ganciclovir 5 mg/kg/day or IV foscarnet 90-120 mg daily	Oral valganciclovir available

Source: Viet Nam CDC Harvard Medical School AIDS Partnership. *Clinical training presentations*. Ho Chi Minh City, Viet Nam, 2006.

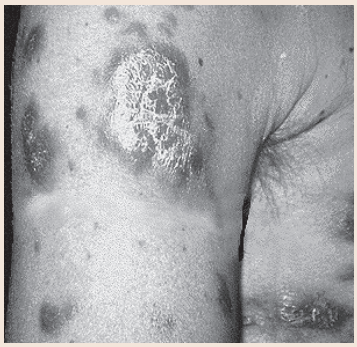
When is it safe to stop?

- PCP: if CD4 count ≥200 cells/mm^3 for six or more months, it is safe to discontinue primary and secondary prophylaxis.
- Toxoplasmosis: discontinue if CD4 counts are ≥ 200 cells/mm^3 for six months and no signs of toxoplasmosis
- MAC: discontinue primary prophylaxis if CD4 counts ≥100 cells/mm^3 for >3 months; secondary prophylaxis stops when counts ≥100 cells/mm^3 for >6 months, 12 months of treatment have been completed and patient asymptomatic for MAC.

AIDS-defining neoplasms

- Kaposi sarcoma
- Non-Hodgkin lymphoma
- Primary CNS lymphoma
- Invasive cervical carcinoma

Kaposi sarcoma



Source: Viet Nam CDC Harvard Medical School AIDS Partnership. *Clinical training*. Ho Chi Minh City, Viet Nam, 2006.

Cervical cancer

- Rates of cervical dysplasia in HIV-infected women are 10–11 times greater than in HIV-seronegative women
- In 1993 CDC added invasive cervical cancer as an indicator condition in the definition of AIDS
- Pap smears are important for screening in women with HIV

Activity 4 – Group discussion: the follow-up visit

- Hoa comes back to see you one day later than you planned.
- Her laboratory tests are back. Her CD4 count is 150 cells/mm^3, her Hb is 11.1g/dl and her ALT is 75 IU/L. She is HBsAg positive and hepatitis C positive. CXR and sputum were clear.
- What do you need to think about next?

Activity 4: Following up Hoa

- Reinforce that she has come back to the clinic to see you.
- Ask if anything new has come up since she was in last week.
- Ask if she had any questions or worries about anything you discussed last week.
- Discuss results.
- Discuss need for CTX prophylaxis.
- Talk about HBV and HCV status
- How you will monitor from now on
- Seen drug substitution counsellor?
- Any further questions – make appointment, give handout on CTX and HBV, refer to support group, condoms, needles, etc.

Conclusion

- The first visit to the outpatient clinic will set the groundwork for future care.
- Development of a treatment partnership from the very beginning will improve the chances of treatment success.

Annex 3

Presentation 6.3: The use of ARV drugs for the HIV-infected IDU

ARV drugs for the HIV-infected IDU

Session objectives

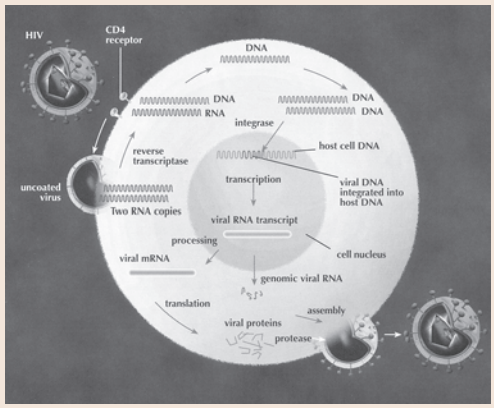
- Revise how ARVs drugs work
- Review the goals of ART
- Examine the ARV drugs and regimens recommended by the revised 2006 WHO ARV guidelines

Activity 1: Small groups

How do ARV drugs work?

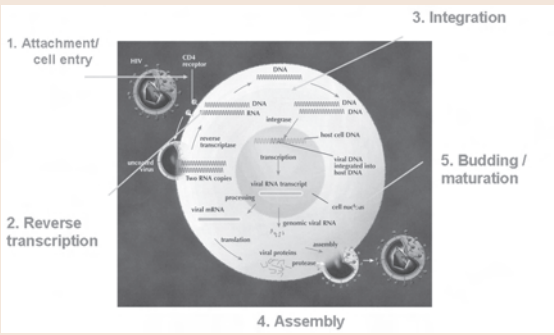
Group work: Draw on flipchart paper the replication cycle of HIV and where each different class of ARV drugs acts

Replication cycle of HIV-1



Source: Carey D. *ASHM Short course in HIV medicine.*

HIV – points for intervention



Source: Carey D. *ASHM Short course in HIV medicine.*

Antiretroviral therapy

- Maximal and durable suppression of HIV replication
- Maintains and restores immune function
- Delays disease progression and prolongs survival
- Improves quality of life
- Prevents emergence of drug-resistant virus
- Reduces HIV transmission

What antiretroviral drugs are available?

FDA-approved ARV classes

Nucleoside/nucleotide RTI	Non-nucleoside RTI	Protease inhibitors (PIs)
AZT	Nevirapine	Saquinavir
ddI	Delavirdine	Ritonavir
ddc	Efavirenz	Indinavir
d4T		Nelfinavir
3TC	Entry/fusion inhibitors	Amprenavir
ABC	**Enfuvirtide**	Lopinavir/ritonavir
AZT/3TC		Atazanavir
AZT/3TC/ABC		Fos-amprenavir
Tenofovir		Tipranavir
Emtricitabine		Darunavir
3TC/ABC		
TDF/FTC		

Several combination drugs are also available

AZT + 3TC = Combivir, Duovir, Lamzidivir

AZT + 3TC + ABC = Trizivir

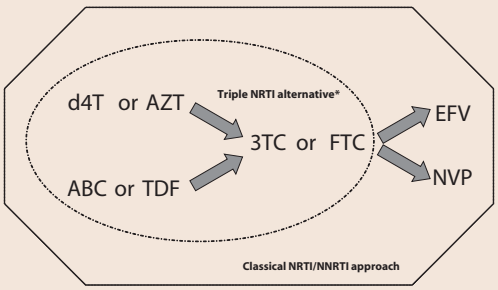
d4T + 3TC + nevirapine = Triamune, GPOvir, SLN

TDF + FTC (2004) = Truvada

ABC + 3TC (2004) = Epzicom, Kivexa

TDF + FTC + EFV (2006) = Atripla

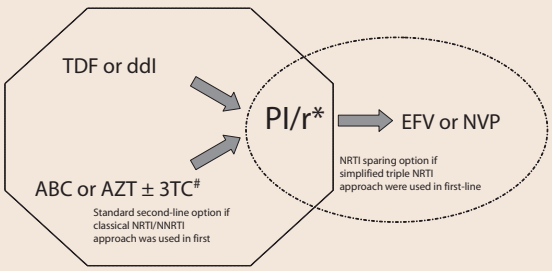
First-line ARV drugs in adults and adolescents: WHO guidelines, 2006



* Triple NRTI should be considered as a simplification strategy for first-line therapy as suggested above, mainly for situations where NNRTI options provide additional complications (e.g. pregnancy, viral hepatitis coinfection, TB coinfection, women who wish to become pregnant or who have CD4 counts >250 cells/mm^3; NVP or EFV grade 4 serious adverse events; HIV-2 or HIV- 0; adolescents).

Source: WHO guidelines, 2006.

Second-line ARV drugs in adults and adolescents: WHO guidelines, 2006



* Ritonavir boosted PIs are considered as the key component in second line regimens and their use should be reserved for this situation LPV/r has been recommended as the preferred RTV boosted PI as it is available as a FDC and a new formulation that does not need refrigeration was recently launched but other boosted PIs (ATV/r SQV/r fos APV/r and IDV/r) can be substituted based on individual programme priorities In the absence of a cold chain and where the new LPV/r formulation is not available unboosted ATV or NFV can be employed as the PI component but it is considered less potent than an RTV boosted PI

ZDV + 3TC are listed here for "strategic" use as resistance to both drugs is predicted to be present following fa lure on the respective first line regimen listed ZDV may prevent or delay the emergence of the K65R mutation; 3TC will maintain the M184V mutation which may decrease viral replicate capacity as well as induce some degree of viral desensitization to ZDV It must be stressed that the clinical efficacy of this strategy in this situation has not been proven

Source: WHO guidelines, 2006.

The new first- and second-line ARV drugs recommended by WHO

- **d4T:** 30 mg (<60 kg) 40 mg (>60 kg) twice a day
- **AZT:** 300 mg twice a day
- **3TC:** 150 mg twice a day (can be taken as 300 mg once a day)
- **FTC:** 200 mg once a day
- **ABC:** 300 mg twice a day (can be taken as 600 mg once a day)
- **TDF:** 300 mg once daily

The new first and second-line ARV drugs recommended by WHO

- *ddI: EC 400 mg (>60 kg), 250 mg (<60 kg) once daily
- *ddI : 125 mg twice a day or 250 mg once a day (<60 kg), 200 mg twice daily or 400 mg once a day (>60 kg)
- NVP: 200 mg twice daily
- *EFV: 600 mg once daily
- Boosted PI:* LPV 400 mg/RTV 100 mg (twice daily), *SQV 1000 mg/RTV 100 mg (twice daily), *fos-APV 700 mg/RTV 100 mg (twice daily), *ATZ 300 mg/RTV 100 mg (once a day), IDV 800 mg/RTV 100 mg (twice daily)

*once-daily dosing possible.

Exercises 6.3.1 – 6.3.4 Small groups

Use all resources you have plus your own knowledge and experience to fill in a matrix summarizing the major features of the ARV drugs that your group has been assigned (total 14 drugs).

1. Class of drug
2. How it works
3. Dosing recommendations
4. Food effect
5. Minor side-effects
6. Major toxicity
7. Drug interactions with methadone and buprenorphine
8. Drug interactions with ARVs and other drugs

Review presentations

- NRTIs and NtRTIs
- NNRTIs
- PIs

Annex 4

Presentation 6.4: Selecting a first-line regimen

Selecting a first-line regimen

Acknowledgements: Viet Nam CDC HIV AIDS Partnership

Dr E. Pontali, Prison of Genoa and WHO

Session objectives

- Understand the issues that need to be addressed before an HIV-positive IDU is able to start ART
- Appreciate and understand the complexity of factors influencing the choice of ART regimens for HIV-positive IDUs who require ART
- Demonstrate a detailed understanding of all the ART regimens included in the revised WHO guidelines, 2006
- Analyse the most important aspects of the clinical and social history of an HIV-positive IDU and choose a suitable regimen for this client

Principles of treatment and care for HIV/AIDS in IDUs

- ART is as effective in IDUs as in other PLWHA
- Given appropriate support, former and active IDUs can adhere to ART and should have equal access to it
- Current or past drug use is not a criterion for deciding on prescribing ART
- Special attention is required in relation to substance dependence and co-morbidities when administering ART

Principles of ART in IDUs

- Provision of good-quality OST is a desirable HIV care component and is highly effective in addressing opioid dependence and supporting ART adherence.
- IDUs who are not enrolled in an OST programme are three times less likely to be receiving ART than IDUs enrolled in a programme
- The absence of OST should not be a barrier to starting ART in patients who need it. Additional adherence support strategies may be required for IDUs who cannot access OST.
- The basic WHO-recommended first-line ARV drug formulary is suitable for most IDUs.

When should you start ART in an HIV-infected IDU?

When to start

WHO clinical staging	CD4 count available	CD4 count not available
1	Treat if <200 cells/mm^3 (Consider treatment if below 350, particularly if closer to 200–250 cells/mm^3).	No treatment
2	Treat if <200 cells/mm^3 (Consider treatment if below 350 cells/mm^3, particularly if closer to 20–250 cells/mm^3).	Treat if TLC <1200 cells
3	Treat but consider CD4 values for better management and decision making in some situation (e.g. TB)	Treat irrespective of TLC
4	Treat irrespective of CD4 count	Treat irrespective of TLC

Source: WHO. *ART for HIV infection in adults and adolescents in resource-limited settings.* Geneva, WHO, 2006.

Activity 1: Large group discussion

What factors do we need to take into consideration when selecting a first-line regimen for HIV-positive IDUs?

Selecting a first-line regimen: general principles

- **Efficacy:** potency and durability
- **Convenience:** pill burden, food restriction, heat-stable and easy to carry
- **Safety**
  - Short-term
  - Long-term: cardiovascular system, lipid profile, body shape changes, diabetes
- **Drug interactions**
- **Special conditions:** pregnancy
- **Cost**
- **Availability**

When selecting a first-line regimen for IDU clients you also need to pay special attention to:

- Frequent co-morbidities: TB, HBV and HCV,
- Pregnancy
- Frequent co-treatments:
  - TB treatment (rifampicin-based regimens)
  - Interferon/ribavirin treatment in hepatitis
  - OST
- Regimens that optimize adherence (e.g. once daily, suitable for DOT, low pill burden, minimal side-effects)

Baseline clinical assessment

1. Staging of HIV disease including CD4 count where available
2. Major medical conditions and coinfections (TB, HBV, HCV, stability of OST, major psychiatric illness)
3. Pregnancy
4. Previous ART
5. Current medications, including OST and traditional therapies
6. Assess for current OIs
7. Baseline laboratory tests – including TB screening
8. Baseline weight and functional status

Baseline tests prior to starting ART

- HIV test (if no prior confirmation is available)
- CBC (including TLC)
- HBV, HCV serology (if available)
- Rapid plasma reagin (RPR) if available
- LFT, renal function
- Pregnancy test
- CD4 count or TLC if CD4 count not available
- CXR and sputum x 3 (if clinical suspicion of TB)

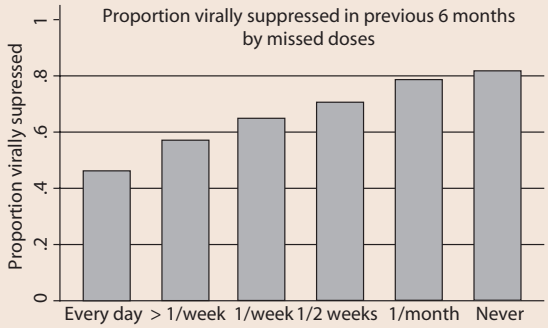
Guiding principles of ARV use in the setting of an acute OI

- Always treat the acute OI first
- Begin ART when the patient is clinically stable
- Be vigilant for drug interactions and overlapping toxicities
- Beware of immune reconstitution inflammatory syndrome (IRIS)
- Do not start OI prophylaxis at the same time as ART

Patient stability and potential adherence barriers assessed

- Client actively involved in treatment decisions and developing ART adherence plan
- Assessment of current drug use or enrolment in substance dependency treatment programme
- Stable living conditions
- Dealing with psychiatric conditions
- Family, community and peer support
- Availability of treatment support person/ treatment supervisor

Missed doses and viral suppression



Source: Liu H et al. *Journal of Acquired Immune Deficiency Syndromes*, 2006.

Is the client well-informed about and committed to ART?

- Demonstrated understanding of HIV/AIDS, ART and need for lifelong treatment
- Demonstrated understanding of the importance of adherence
- Demonstrated understanding of the side-effects
- Demonstrated understanding of the need for follow up post-treatment
- Prior history of treatment/prophylaxis adherence for OIs, regular attendance or participation in training courses

Counselling on side-effects

- Clinicians and counsellors must provide careful counselling to patients when starting ART (and any new medication)
- Patients will be more likely to continue medications if:
  - They know what to expect
  - They know how to avoid and manage side-effects
  - They are able to contact someone if side-effects occur

Guiding principles of OST and ART

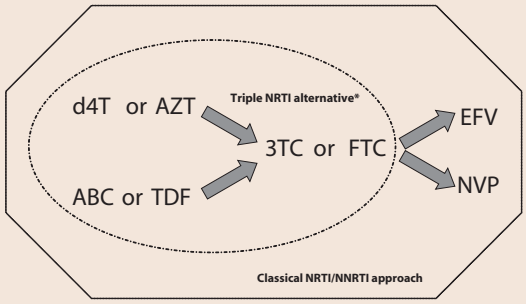
- Make sure client is stable on OST
  - Days not attended
  - Recent changes in dosing
- Ascertain concurrent substance abuse
- Ensure client understands adherence
- Ensure client is well educated about potential side-effects of ARVs
- Ensure client is well educated about potential interactions between OST and ART

Make sure all relevant health workers know that a client is starting ART

- Clinicians need to discuss potential drug interactions with patients receiving methadone/ buprenorphine – possibility of withdrawal symptoms and increased dose
- Clinicians need to report prescribed ART regimen (and changes in regimen) to patients on OST
- Clinicians on both sides will need to carefully monitor IDUs on ART and drug substitution for symptoms or withdrawal or overdose

Which antiretroviral regimen should you use?

First-line ARV drugs in adults and adolescents: WHO guidelines, 2006



* Triple NRTI should be considered as a simplification strategy for first-line therapy as suggested a mainly for situations where NNRTI options provide additional complications (e.g. pregnancy, viral hepatitis coinfection, TB coinfection, women who wish to become pregnant or who have CD4 counts >250 cells/mm^3; NVP or EFV grade 4 serious adverse events; HIV-2 or HIV- 0; adolesce

Source: WHO guidelines, 2006.

Possible first-line regimens

- d4T, 3TC, EFV
- AZT, 3TC, EFV
- d4T, 3TC, NVP
- AZT, 3TC, NVP
- TDF, 3TC, EFV
- TDF, 3TC, NVP
- AZT, 3TC, ABC (limited efficacy)
- AZT, 3TC, TDF (limited efficacy)

* Can substitute FTC instead of 3TC in all regimens although 3TC is cheaper and more readily available

Issues impacting on choice of ARV regimen in IDUs – 1

Co-morbidity factors

- If chronic hepatitis B is present, 3TC, FTC and TDF are active against both infections.
- NVP may not be used if there is coexisting significant liver disease (HCV, HBV, alcohol).
- EFV may not be used in individuals with serious psychiatric disorders.
- In alcohol users, the potential for pancreatitis and peripheral neuropathy is increased with d4T.
- Pregnant women or those who wish to become pregnant should avoid EFV.

Issues impacting on choice of ARV regimen in IDUs – 2

Co-treatment factors

- If the treatment of TB includes rifampicin, EFV should be chosen rather than NVP as it is less likely to cause hepatotoxicity
- If the treatment of TB includes isoniazid, avoid d4T as the risk of peripheral neuropathy is much higher if both drugs are used
- Interactions with methadone/ARVs
- Interactions with buprenorphine/ARVs
- EFV and PEG-INF (possible severe depression)

Activity 2: Small group work

Exercise 6.4.1.
Examine profile of each potential first-line ART regimen and list advantages and disadvantages in relation to:

1. Adherence factors
2. Co-morbidities – HBV, HCV, TB, pregnancy, psychiatric illness, alcoholism
3. Co-treatment interactions – HBV, HCV, TB, methadone, buprenorphine

Choosing NRTI backbone

- **d4T**
  - Can be used for most patients – well-tolerated
  - Twice-daily dosing
  - Long-term mitochondrial toxicity (lactic acidosis and lipoatrophy)
  - Should not be used if neuropathy or on other neurotoxic drugs
  - Increased risk of pancreatitis/neuropathy if heavy alcohol intake
  - No interaction with methadone
- **AZT**
  - Preferred for use in pregnant women
  - Twice-daily dosing
  - Preferred for use in patients with a history of neuropathy
  - Can cause anaemia and pancytopenia
  - Should be avoided in cases of severe anaemia (Hb <8 g/dl)
  - More minor side-effects than other NRTIs
  - Methadone – increased AZT toxicity

Choosing NRTI backbone

- **ABC**
  - Well-tolerated
  - Hypersensitivity reaction
  - Less mitochondrial toxicity than d4T, AZT
  - No interaction with methadone/buprenorphine
- **TDF**
  - Once-daily dosing
  - Well-tolerated
  - Cannot be used if underlying renal disease
  - Limited mitochondrial toxicity
  - No interaction with methadone/buprenorphine

NVP versus EFV?

- **NVP**
  - Avoid if LFTs are >2.5 normal
  - Avoid if patient taking rifampicin
  - Avoid if CD4 count >250 cells/mm^3 (women) and CD4 count >400 cells/mm^3 (men)
  - No food restrictions
  - Can use in pregnant women
  - Interaction with methadone
- **EFV**
  - Can be used in patients with a history of hepatitis
  - Once-daily dosing
  - Food restriction – should be taken on an empty stomach
  - Avoid in women of childbearing age and never use in pregnancy
  - Can be used with rifampicin
  - Minor CNS side-effects common
  - Caution if patient has a history of psychiatric illness
  - Interaction with methadone

When to use triple NRTIs

- Triple NRTIs should be considered as a simplification strategy for other first-line drugs where NNRTIs provide additional complications.
  - For example: pregnancy, viral hepatitis coinfection, TB coinfection, women who wish to become pregnant or who have CD4 count >250 cells/mm^3; NVP or EFV grade 4 SAE
- The rate of failure with triple NRTI regimens is high, thus this strategy should only be used if strictly necessary.

Exercise 6.4.2 Activity 3: Case studies

- *Outline your first preferred ART regimen for this client*
- *Why did you choose this regimen?*
- *What would be an alternative to this regimen?*
- *What other issues do you need to consider?*
- *What are the major issues you would need to counsel and educate each patient on for this regimen?*

Special considerations for clients who are IDUs

Treatment situation	First-line preferential	First-line alternatives
IDU without other significant clinical co-morbidities or co-treatments but needs ART	AZT+3TC+NVP or EFV	TDF or d4T can be substituted for AZT
IDU with HIV/HBV with indication to treat HBV and ART	AZT+3TC+ NVP or EFV	TDF or d4T can be substituted for AZT
IDU with TB/HIV using TB regimens with rifampicin and needs ART	AZT+3TC+EFV	TDF or d4T can be substituted for AZT; NVP can be substituted for EFV (caution)

Source: Pontali E, 2006.

Summary principles for ART in IDUs

- Treat OIs first
- Stabilize first if on OST
- Co-morbidities and co-treatment interactions should be taken into consideration in ARV selection
- Involve client and other relevant health workers in decision-making about ART – educate ALL about potential for side-effects and interactions with OST
- Use specific strategies (use of FDC/blister packs, once-daily drugs, DOT/supervised treatment) to support adherence
- Provide careful ongoing monitoring and support – side-effects, interactions with OST and adherence support

Annex 5

Presentation 6.5: Monitoring IDUs on ART and managing side-effects

Monitoring IDUs on ART and managing side-effects and toxicities within the first year

Acknowledgements: Viet Nam CDC HIV AIDS Partnership

Session objectives

- Know what to expect in the first year of treatment
- Understand the routine monitoring processes
- Understand the monitoring that is required when a toxicity arises
- Understand the impact of OST on routine monitoring
- Understand the impact of OST on drug interactions, side-effects and toxicities
- Be able to deal with minor side-effects
- Understand the management of major side-effects that may occur in the first year of treatment
- Understand when and how to switch ARV drugs in the first-line regimen in the event of toxicity

What to expect in the first six months of ARV therapy

- Clinical and immunological recovery: CD4 count may take some time to increase and not be very dramatic if very immunosuppressed
- Early ARV toxicity – rash, NVP hypersensitivity, anaemia and neutropenia
- IRIS: at 2–13 weeks. Affects 10–25% of those with CD4 count <50 cells/mm^3
- Mortality on ART: overall mortality is 2–10% and approximately 60–70% of these deaths occur within the first six months of treatment (greater risk if CD4 count <50 cells/mm^3 and disseminated TB/other OIs)

Monitoring ART when resources are limited

Activity 1: Large group discussion

- What are the important things we need to monitor when an IDU client is on ART?
- What are we monitoring for?
- What implications do the "usual timing of side-effects and toxicities" have on routine monitoring?

Monitoring

- Routine monitoring depends on what model of ART dispensing is used.
- We need to monitor:
  - Minor side-effects (clinical evaluation)
  - Toxicities (laboratory and clinical evaluation)
  - Adherence (self-report, pill count, visual aids)
  - Stability of OST (clinical evaluation)
  - Efficacy of the ART regimen (laboratory and clinical evaluation)
- Additional monitoring should take place when there are side-effects and symptoms of toxicity, issues with adherence, or stability of OST.

Schedule of basic ART monitoring

First 3 months
- Weekly follow up of adherence and side-effects
- Monthly: full adherence review
- Bloods at 2 and 4 weeks: LFT (if on NVP) and CBC (if on AZT)
- Opioid withdrawal symptoms and need to stabilize dose (if on OST)
- Clinician review weekly–fortnightly in first month and then every month thereafter
- Dispense ARV drugs daily or weekly
- HBC team visits
- PLWHA visits
- Phone calls
- Text messages

Schedule of basic ART follow up

At three months (if stable) and then every three months thereafter (earlier if problems)
- Full clinical assessment
- Labs – FBC, LFT, renal function (if on TDF)
- CD4 count every six months
- Full adherence review (recommended each month)
- OST reassessment
- Case manager review
- Education – prevention messages

Plus HBC support, PLWHA peer support groups, "on-ARV" support groups

Monitoring OST in someone on ART

- In the first month of ART (esp. NNRTIs) – very important to monitor for withdrawal – often need to increase methadone dose
- Make sure client is stable on OST
  - Days not attended
  - Recent changes in dosing
- Ascertain concurrent substance abuse
- Other adherence factors
- Reinforce information about adherence and side-effects of ARVs
- Reinforce information about potential interactions between OST and ART

Side-effects on ART

- Is the condition a side-effect or something else?
- Differential diagnosis
  - New OI
  - IRIS
  - Side-effect from another medication
  - Withdrawal from methadone
  - Non-HIV related clinical condition
- Need to grade the severity of the side-effect
- Consider whether the ARV drug in question or the entire regimen needs to be stopped

Grading the severity of the side-effect

Grade 1	**Mild.** *Transient or mild discomfort, no limitation in activity, no medical intervention/therapy required*
Grade 2	**Moderate.** *Limitation in activity - some assistance may be needed; no or minimal medical intervention/ therapy required*
Grade 3	**Severe.** *Marked limitation in activity, some assistance usually required, medical intervention/therapy required, hospitalization possible*
Grade 4	**Severe life-threatening.** *Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care*

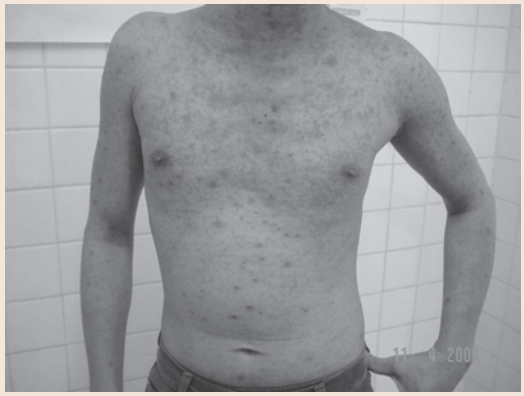
Exercise 6.5.1 Activity 2: Case studies

- Break up into small groups
- Use Exercise 6.5.1

Major toxicities of ARVs that present within the first year of ART

- Major toxicities within the first four weeks of starting ART
- Major toxicities within two to six months of starting ART
- Major toxicities that can occur after six months of ART

NNRTI rash



Source: Dr Nguyen Thanh Liem, Binh Thanh Outpatient Clinic, Binh Thanh District, Ho Chi Minh City, Viet Nam

NNRTI rash

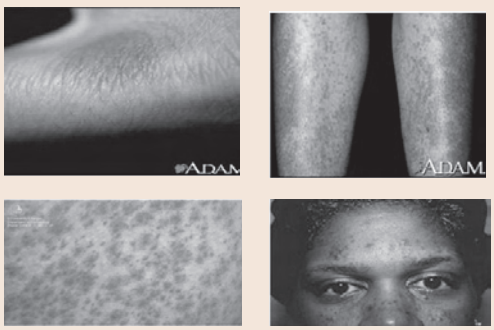
- Between 17% and 25% of patients will have some form of rash on NVP usually in the first 2–6 weeks of treatment
- Incidence is reduced by the 2-week lead-in dosing with once-daily NVP therapy (200 mg once daily for 2 weeks)
- The rash is usually erythematous and maculopapular, may or may not be itchy. Located on trunk, face and extremities
- Rash on EFV occurs in 5–10% (recent Thai study states that NVP rash = EFV rash) but Stevens –Johnson syndrome rare

Grading the rash

Grade 1: Mild
- Erythema, with or without pruritis

Grade 2: Moderate
- Diffuse maculopapular rash, or
- Dry desquamation, or
- Typical target lesions without blistering, vesicles or ulceration, and
- No systemic symptoms

Moderate rash



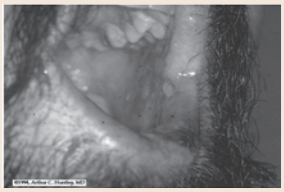
Source: Viet Nam CDC Harvard Medical School AIDS Partnership. *Clinical training*. Ho Chi Minh City, Viet Nam, 2006.

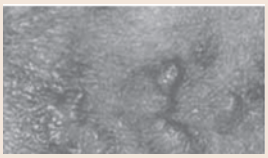
Grading the rash

Grade 3: Severe
- Vesiculation
- Moist desquamation
- Ulceration
- Diffuse rash and serum sickness-like reactions (fever, lymphadenopathy, edema, muscle and/or joint pain)
- Diffuse rash and systemic symptoms (fever, blistering, elevated transaminases)

Grade 4: Potentially life-threatening
- Mucous membrane involvement
- Suspected Stevens–Johnson syndrome (toxic epidermal nurolysis [TEN])
- Erythema multiforme
- Exfoliative dermatitis

Severe rash





Source: Dr Nguyen Thanh Liem, Binh Thanh Outpatient Clinic, Binh Thanh District, Ho Chi Minh City, Viet Nam

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

- 7% of all rashes will require discontinuation of the drug.
- Indications to discontinue NVP are rash with fever, blisters, mucous membrane involvement, conjunctivitis, edema, arthralgia, malaise.
- Another indication is hepatotoxicity with rash.
- SJS and TEN are classified according to the percentage of body surface area affected – SJS <10%, TEN >30%.

Source: Dr Nguyen Thanh Liem, Binh Thanh Outpatient Clinic, Binh Thanh District, Ho Chi Minh City, Viet Nam

Management of NVP rash

- Assess the severity of the rash
- Assess for hepatotoxicity
- Increase monitoring frequency
- If mild – manage with mild steroid cream and NSAIDs (50% of mild to moderate rash improves)
- If mild to moderate (grade 1 or 2) – switch to EFV (if not available continue on once-daily dosage for 1–2 weeks, symptomatic treatment)
- If severe (grade 3 or 4) – stop all ARV drugs. Grade 3 – switch to EFV but if grade 4 – do not change from NVP to EFV but change to a different ARV class

Hepatotoxicity and ART – 1

General principles:

- Up to 50% of patients taking ART will have transient elevations in LFT
- Most patients are asymptomatic and LFT will return to normal without stopping the responsible ARV (even with grade 3–4 elevation)
- Fewer than 5% of patients will need to stop ART or change ARVs due to hepatotoxicity
- Diagnosing the cause of hepatotoxicity can be very difficult

Hepatotoxicity and ART – 2

Common causes of hepatotoxicity:

- NNRTI (NVP)
- Lactic acidosis due to NRTIs
- IRIS in patient with HBV or HCV
- ABC hypersensitivity
- Coinfection with hepatitis B or C increases the risk for hepatotoxicity

Hepatotoxicity in Thailand

Risk factor	Relative risk
HBsAg +	3.20
HCV +	3.00
NNRTI	9.75

Source: Law WP et al. *AIDS*, 2003.

Hepatotoxicity: differential diagnosis

ARV Toxicity
- **Hepatotoxicity (NNRTIs, PIs)**
- **Hypersensitivity reactions**
  - NNRTI (NVP, EFV)
  - ABC (abacavir)
- **Lactic acidosis with hepatic steatosis**
  - NRTI

Non-ARV drugs
- **TB drugs** – pyrazinamide (PZA), rifampicin, isoniazid (INH)
- **Antifungal drugs**
  - Fluconazole, itraconazole, ketoconazole
- **Others** – co-trimoxazole – paracetamol
- **Alcohol**

Infectious diseases
- **Viral**: CMV, HAV, HBV, HCV, HDV, HEV, dengue
- **Bacterial**: TB, MAC, sepsis
- **Fungal**: Penicilliosis

Other causes
- **IRIS** (HBV; less HCV)
- **Steatosis** (fatty liver)
- **Tumour**: lymphoma, Kaposi sarcoma

Grading hepatotoxicity

GRADE		↑ LFT >ULN	↑ LFT > patient baseline
mild	1	1.25–2.50	1.25–2.50
mild	2	2.60–5	2.60–3.50
severe	3	5–10	3.50–5
severe	4	>10	>5

Two types of NNRTI-related hepatotoxicity

1. Early: hypersensitivity reaction (NVP only)
- Usually occurs in the first 1–2 months of treatment
- Higher risk: female CD4 count >250 cells/mm^3, male CD4 count >400 cells/mm^3
- AST/ALT >5–10 x ULN plus rash, fever, bodyache, mucous membrane involvement (features of SJS)

2. Late: elevations in AST/ALT
- 5–10% of patients on NNRTIs will have grade 3–4 elevation in AST/ALT
- Most patients are asymptomatic and can continue to take the medications
- Increased risk with HBV or HCV coinfection
- NVP has greater risk than EFV

Treatment: NNRTI hepatotoxicity

Mild: LFT <5 x ULN, no symptoms
- Continue ART. Follow closely with LFT every 1–2 weeks
- Can switch from NVP to EFV (if EFV available)

Moderate: LFT 5–10 x ULN and patient has moderate symptoms
- Stop the NNRTI, continue 2 NRTI for 1 week. Restart EFV when the symptoms resolve and LFT <5 x ULN

Severe: LFT >10 x ULN or Stevens–Johnson syndrome
- Stop all ART and other drugs
- Do not use NNRTI again
- Restart 2 NRTI + PI when the patient is stable

AZT-related anaemia and pancytopenia

- Bone marrow suppression is related to the marrow reserve, dose and duration of treatment
- Anaemia usually occurs within 4–6 weeks
- Neutropenia usually occurs after 12–24 weeks
- Avoid by not initiating AZT in those with low Hb
- Avoid by careful monitoring – check FBC at 2 weeks and 4 weeks and then every 3 months (more frequently, if symptomatic)
- Avoid by not using AZT when other myelosuppressive drugs are being used
- Manage by stopping AZT and switching to another suitable NRTI (± transfusion, erythropoietin, G-CSGSF)

d4T-related peripheral neuropathy

- Frequency of peripheral neuropathy (PN) is 5–15% (up to 24%)
- Related to mitochondrial toxicity
- Worse when d4T is combined with ddI
- Onset is after 2–6 months
- Resolves if d4T is stopped promptly but recovery is slow
- Do not use d4T if baseline PN or on neurotoxic drugs (e.g. isoniazid)

ABC hypersensitivity – 1

- ABC hypersensitivity: 3–5% of patients
  - Fever
  - Malaise, myalgias
  - Rash
  - GI symptoms
  - Dyspnea, pulmonary infiltrates
- Onset usually in first 2–6 weeks of therapy, although late cases reported

ABC hypersensitivity – 2

- ABC hypersensitivity appears to be T-cell mediated
- Associated with HLA B57.1 (class I) HLA B57.1 (rare in Asian races)
- Usually presents within first 6 weeks of treatment
- Symptoms: rash, fever, nausea, vomiting, fatigue, arthralgia, headache, abdominal pain, dyspnoea, cough
- Laboratory: AST/ALT, lymphocytes, creatine phosphokinase (CPK)
- Never rechallenge if this is suspected
- Rechallenge associated with cardiovascular collapse and death

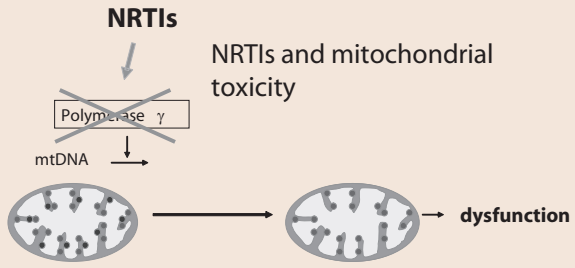
Source: *Martin Am. PNAS*, 2004.

Lactic acidosis

- Lactic acidosis ± hepatic steatosis is related to mitochondrial toxicity caused by NRTIs
- Relatively rare: 1–14/1000
- Can occur any time between 1 and 20 months of treatment
- Symptoms: can develop slowly, usually after several months of ART
  - Mild: fatigue, bodyache, nausea, vomiting, diarrhoea, weight loss
  - Severe: wasting, dyspnoea, abdominal pain, coma

NRTI: mitochondrial toxicity and lactic acidosis

- NRTIs inhibit mitochondrial DNA polymerase gamma
- Decreased ability to use oxygen to produce energy from glucose and fatty acids
- Anaerobic metabolism leads to build up of fat in the liver and lactic acid in the blood
- Risk of lactic acidosis:
  d4T+ddI > d4T > ddI > AZT
- Very low risk: 3TC, TDF, ABC



Source: Cecilia M, Shikuma MD, 2006.

Lactic acidosis

- Diagnosis
  - Elevated lactic acid levels (>2.5) plus abnormal LFT and hepatic steatosis on liver ultrasound
  - Lactic acid testing only available at large hospitals: must draw blood without tourniquet, use flouride-oxalate tube, and deliver blood to lab on ice within four hours
- If lactic acid levels not available:
  - Increased anion gap [Na-(Cl+HCO_3)] >16, HCO_3 >20
  - ↑LFT, ↑CPK, ↑LDH, ↓pH, ↓HCO_3
  - Ultrasound: fatty liver
- Treatment
  - Mild symptoms: stop NRTI and/or switch to NRTI with less mitochondrial toxicity (TDF, ABC)
  - Severe symptoms or lactic acid >10: hospitalize, stop ART, hydration, bicarbonate IV, dialysis
  - IV riboflavin (50 mg/day) or IV vitamin C may be beneficial

Switching therapy due to toxicity

- Substitute a drug in the same ARV class but with a different side-effect/toxicity profile (exception being severe rash and hepatotoxicity of NVP)
- Drug substitutions should be limited to grade 3 and grade 4 toxicities (exception being rash and hepatotoxicity of NVP)
- Grade 3 toxicity: substitute ARV drug immediately
- Grade 4 toxicity: discontinue all ART until the patient is stable and the toxicity has resolved

ARV substitution options in instances of toxicity

ARV DRUG	Common associated toxicity	Suggested substitute
ABC	Hypersensitivity reaction	AZT or TDF or d4T
AZT	Severe anaemia[a] or neulropenia[b] Severe gastrointestinal intolerance[c]	TDF or d4T or ABC
	Lactic acidosis	TDF or ABC [d]
d4T	Lactic acidosis Lipoatrophy/metabolic syndrome[e]	TDF or ABC[d]
	Peripheral neuropathy	AZT or TDF or ABC
TDF	Renal toxicity (renal tubular dysfunction)	AZT or ABC or d4T
EFV	Persistent and severe control nervous system toxicity[i]	NVP or TDF or ABC (or any PI[h])
	Potential teratogenicity (first trimester of pregnancy or women not using adequate contraception)	NVP or ABC (or any PI[h])
NVP	Hepatotoxicity	EFV or TDF or a PI
	Hypersensitivity reaction	TDF or ABC (or any PI[h])
	Severe or life-threatening rash (Stevens–Johnson syndrome)[g]	

Immune reconstitution inflammatory syndrome (IRIS)

What is IRIS?

- An inflammatory response occurring as a result of an improved ("reconstituted") immune system as a result of taking ART
- Worsening of clinical or laboratory parameters despite improved HIV markers (increased CD4 count or reduced viral load)
- Estimated to occur in 10–25% of those on ART
- Commonly occurs within the first 1–12 weeks of ART
- Can occur with any infectious antigen (TB, MAC, cryptococcosis, toxoplasmosis, CMV)
- It does not mean a therapeutic failure of ART

IRIS: pathogenesis

Restored pathogen immune response leads to:

1. Regression of OI (protective) but may also result in
2. Immune reconstitution inflammatory syndrome (immunopathological)

IRIS: pathogenesis – two presentations

- **Early** (first several months): unmasking and/or recognition of an ongoing infection due to improved immune response (usually occurs soon after ART)
- **Late**: reconstituting immune system leads to reaction to previously treated infection or non-replicating antigens (may occur later after starting ART)

IRIS: common associated pathogens

- Mycobacteria:
  - **TB and MAC**
  - BCG in children
- Fungal: *Cryptococcus*, PCP, *Histoplasma*
- Viral: CMV, VZV, HBV, HCV, JC virus (PML)
- Autoimmune: psoriasis, alopecia, thyroiditis

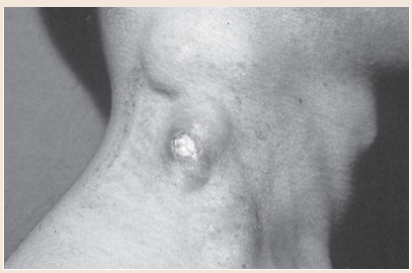
IRIS: management

- Treat the OI
- Avoid interruption of ART
- Treat with antimicrobials if new infection is suspected, continue previous therapy
- Anti-inflammatory medications
  - NSAIDs
  - Corticosteroids: prednisone 1 mg/kg/day with tapering over several weeks if severe (e.g. cerebral edema from toxoplasmosis or dyspnoea or dysphagia caused by TB-related lymphadenopathy)
- Therapeutic aspiration used in some places to reduce bulk in TB lymphadenitis

Case presentation

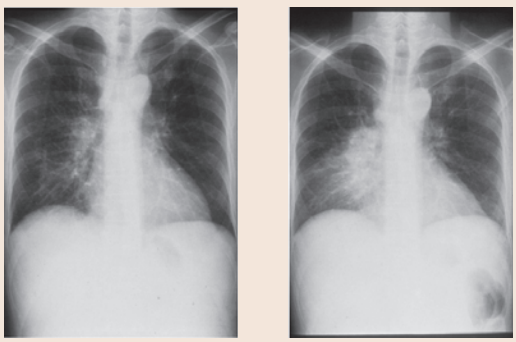
- Anh Ha, diagnosed HIV+ two years ago
- Previous OIs: herpes zoster three years ago, oral thrush two months ago
- On CTX prophylaxis for one year
- Started ARVs (d4T/3TC/NVP) six weeks ago
- Haemoglobin: 12 g/dl. Last CD4 count: 75 cells/mm^3 (5%) three months ago
- Presents with history of two weeks of persistent cough, fever, night sweats and 2 kg weight loss. Current weight 57 kg
- On examination: large right cervical lymph node (3 cm diameter)
- Chest X-ray: bilateral lower lobe infiltrates with enlargement of mediastinal lymph nodes

IRIS



Source: Rachel Burdon, 2006.

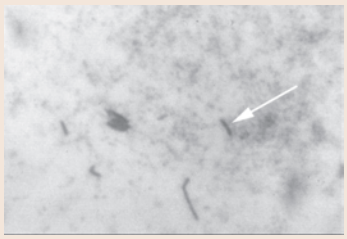
Inflammation at site of treated TB after commencing ART



Source: Mina John, Martyn A H French. *Medical Journal of Australia,* 1998.

Case presentation

- Sputum microscopy is negative for *Mycobacterium tuberculosis* but
- Lymph node puncture reveals acid-fast bacilli (AFB)



Source: Viet Nam CDC Harvard Medical School AIDS Partnership. *Clinical training*. Ho Chi Minh City, Viet Nam, 2006.

Case presentation

Management:

- Treat for TB: HREZ
- Give NSAIDs
- Continue ART
- Switch from NVP to EFV to avoid interactions between rifampicin and NVP
- To avoid added neurotoxicity (d4T,INH), switch d4T to AZT, give Vit B6 (pyridoxine)
- New ARV regimen: AZT + 3TC + EFV
- Aspirate lymph nodes if purulent

Presentations of TB IRIS

- Fever (87.5%)
- Lymphadenopathy (~70%)
- Worsening respiratory symptoms (28%) sometimes with pulmonary infiltrates
- Gastrointestinal disease (caecum)
- Splenic abscess (rupture may occur)
- Arthritis or osteomyelitis
- Other: psoas abscess, skin, CNS…

Source: Lawn S et al. *Lancet Infectious Diseases* 2005.

Can *Mycobacterium tuberculosis* IRIS be predicted?

- IRIS can occur with:
  - Lower CD4+ T-cell count, especially <50 cells/mm^3 at baseline
  - May see rapid increase in CD4 cell count
  - Always associated with rapid decline in plasma HIV RNA level
  - Strongly associated with starting ART within the first two months of anti-TB therapy

IRIS and hepatitis B

- In patients with severe immunosuppression, the body is not able to mount a reaction against HBV
- With immune reconstitution and restoration of cellular immunity (T-cell mediated), immune cells are able to recognize liver cells harbouring the HBV antigens (HBsAg) and will destroy these hepatocytes leading to:
  - Immune-mediated hepatitis with elevation of liver enzymes
  - Other possible symptoms: fever and rash, fatigue, etc.
  - Differential diagnosis: drug-related hepatotoxicity

Immune reconstitution hepatitis management

- If liver enzymes less than 10 x ULN values and patient only has mild symptoms:
  - Continue ART, but you might want to switch to less hepatotoxic drugs to avoid added toxicity
  - Monitor LFT closely
  - Consider adding TDF and 3TC to regimen
- Liver enzymes should slowly return to normal
- There is a risk of rebound (flare) hepatitis B if you stop an ARV regimen that includes 3TC and TDF

Immune reconstitution inflammatory syndrome

...is not treatment failure

Exercise 6.5.2
Activity 3: Case studies

- This exercise should take 30 minutes.
- Break up into small groups.
- Use Exercise 6.5.2.

Annex 6

Presentation 6.6: Treatment failure, second-line therapy and long-term toxicities

Treatment failure, second-line therapy and long-term toxicities

Acknowledgements: Viet Nam CDC HIV AIDS Partnership

Session objectives

- Demonstrate an understanding of **resistance** and its role in treatment failure, including the role of adherence and missed doses in creating drug resistance
- Evaluate when it is necessary to **switch a client to second-line** therapy
- Demonstrate an understanding of the **side-effects and major toxicities of second-line ART drugs** and how to manage these when they arise
- Understand the **routine monitoring** processes that should be carried out for all HIV-positive IDUs on second-line ART, including the difference between routine monitoring, monitoring of OST, and monitoring that is required when a toxicity arises
- Demonstrate an understanding of the **long-term toxicities** of both the first-line and second-line ARV drugs including how these impact on lifestyle and adherence

Terms used to describe resistance

- Wild-type virus
  - HIV that is replicating freely in the body, without the influences of ARV agents
- Resistant virus
  - HIV that has developed the ability to replicate in the presence of medications
- Drug resistance
  - Any property of a virus that allows it to grow better in the presence of a drug
- Drug cross-resistance
  - Resistance to one drug that also confers resistance to a second drug, when exposure to the second drug may not have occurred

What is resistance?

- HIV reproduces itself very quickly, making 60 billion copies of new virus every day.
- Since the virus often makes mistakes when copying itself, each new generation differs slightly from the one before.
- These tiny structural differences are called mutations.
- Mutations change the genetic code of the HIV, including the enzymes used in the lifecycle.
- If the enzyme (target of ART drugs) genetic code is altered, the ARV drug may no longer work.
- This can result in strains of HIV that have reduced sensitivity to the drugs. These HIV strains are called drug-resistant.

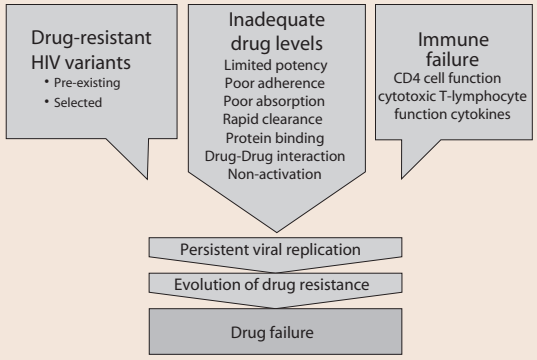
Causes of resistance and treatment failure

1) Patient factors (related to adherence)
- Patients forget (travel, work, daily routine changes), patients start to feel better, stop due to side-effects, substance use

2) Prescribing factors
- Incorrect combinations or doses
- Incorrect drugs if ARVs have been used in the past and resistance a possibility
- Drug interactions if other medications (e.g. TB medications)

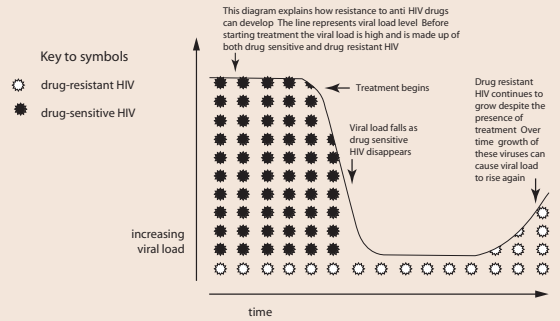
3) Viral factors (beyond the control of the patient and health worker)
- Patients may have been infected with virus that is already resistant to the first-line regimen that they have been started on
- Over time the virus can mutate and drug-resistant strains appear even with perfect adherence

Pathways to resistance and drug failure



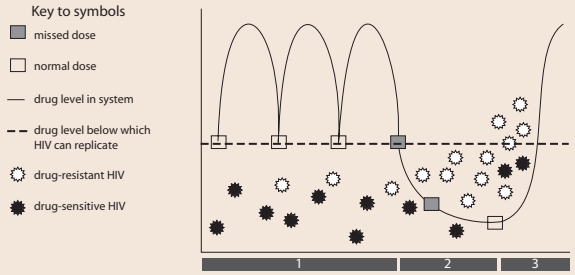
Source: Hirsch et al. *Journal of the American Medical Association*, 2000.

Development of resistance to HIV drugs



Source: NAM. *What is resistance*. AidsMAP – patient booklets, p. 2

Missed doses and resistant virus



Source: NAM. *What is resistance*. AidsMAP – patient booklets, p. 7

Resistance mechanisms to NRTIs

- HIV does not allow the nucleotide analogue to incorporate itself into the DNA.
- The nucleoside analogue is removed from the HIV before it can stop the production of the DNA.

Source: Clavel F, Hance AJ. *New England Journal of Medicine*, 2004.

Resistance mechanisms to NNRTIs

- NNRTIs attach directly to the reverse transcriptase enzyme. This decreases its ability to produce DNA.
- Resistance appears when the NNRTI can no longer attach directly to the enzyme.

What is treatment failure?

- **Treatment failure:** when the ART regimen does not adequately suppress replication of HIV.
- HIV has become "resistant" to all the medications in the ART regimen.
- There is laboratory or clinical decline of the client due to increased viral replication and worsening immunosuppression.

Treatment failure

The decision on when to switch from first-line to second-line therapy is critical.

- If the decision is made too early, the months or years of potential further survival benefit from any remaining first-line therapy effectiveness is lost.
- If the decision is made too late, the effectiveness of second-line therapy may be compromised and the patient is put at additional and appreciable risk of death.

Diagnosing treatment failure

Treatment failure can be diagnosed:

- **Clinically:** by assessing disease progression and WHO staging
- **Immunologically:** by using trends in CD4 counts over time
- **Virologically:** by measuring HIV viral load (plasma HIV-1 RNA levels)

Treatment failure: WHO guidelines 2006

Clinical failure	New or recurrent WHO stage 4 conditions
CD4 cell failure	• Fall of CD4 count to pre-therapy baseline (or below); or • 50% fall from the on-treatment peak value (if known); or • Persistent CD4 levels below 100 cells/mm^3
Virological failure	Plasma viral load above 10 000 copies/ml

Definition: clinical treatment failure

- Clinical HIV disease progression despite ART
- The development of a new or recurrent WHO stage 3 or 4 condition after six months of treatment
- Treatment failure should not be diagnosed clinically
  - There has been a reasonable trial of first-line therapy lasting at least to 6–12 months
  - Adherence has been assessed and optimized
  - Intercurrent OIs have been treated and resolved
  - IRIS has been excluded

Diagnosing clinical treatment failure

- Development of a new or recurrent WHO stage 3 or 4 condition on treatment after at least six months of ART
- Remember TB can occur at any CD4 level and does not necessarily indicate ART failure
- The response to TB therapy should be used to evaluate the need to switch ART. If there is a good response to TB therapy the decision to switch ART can be postponed
- This applies to any severe and/or recurrent bacterial infections or oesophageal candidiasis
- If it is unclear whether clinical failure should be diagnosed, a one-off CD4 count may assist the diagnosis (do not switch if CD4 count >200 cells/mm^3)

New or recurrent event on ART	Recommendations	Additional management options
Asymptomatic (T1)	Do not switch regimen	• Maintain scheduled follow-up visits, including CD4 monitoring (if available) • Continue to offer adherence support
Stage 2 event (T2)	Do not switch regimen	• Treat and mange staging event • Assess and offer adherence support • Check if on treatment for at least six months • Assess continuation or reintroduction of OI prophylaxis • Schedule earlier visit for clinical review and consider CD4 (if available)
Stage 3 event (T3)	Consider switching regimen	• Treat and manage staging event and monitor response • Assess and offer adherence support • Check if on treatment for at least six months • Check CD4 cell count (if available) • Assess continuation or reintroduction of OI prophylaxis • Institute more frequent follow-up
Stage 4 event (T4)	Switch regimen	• Treat and manage staging event and monitor response • Check if on treatment for at least six months • Assess continuation or reintroduction of OI prophylaxis • Check CD4 cell count (if available) • Assess and offer adherence support

Definition: immunological treatment failure

- Progressive severe immunodeficiency demonstrated by a declining CD4 cell count over time
- Definitions of immunological failure are:
  - CD4 count below 100 cells/mm^3 after six months of therapy (some argue it should be 50 cells/mm^3)
  - A return to, or a fall below, the pre-therapy CD4 baseline counts after six months of therapy; or
  - A 50% decline from the on-treatment peak CD4 count (if known)

Diagnosing immunological treatment failure

- Ideally, a CD4 count should be repeated and confirmed before any switch to second-line ART.
- Infections can result in transient CD4 count decrease. Treatment failure should not be diagnosed until intercurrent infections are treated and recovery made – then CD4 count should be repeated.
- It can be difficult to track the true peak of a CD4 count when they are only done every six months – difficult to diagnose *"a 50% decline from the on-treatment peak CD4 value".*
- CD4 cell count can also be used to determine when not to switch therapy. In general, switching is not recommended if the CD4 cell count is above 200 cells/mm^3.

Diagnosing virological treatment failure

- Virological success is defined as a plasma HIV-1 RNA level <400 or <50 copies/ml after six months.
- When viral load is undetectable, ART should not be switched, regardless of the CD4 count/clinical stage.
- WHO guidelines 2006 define virological failure as plasma HIV-1 RNA level >10 000 copies/ml after six months of therapy and adequate adherence.
- 10 000 copies/ml is the level associated with clinical progression and CD4 cell count decline.

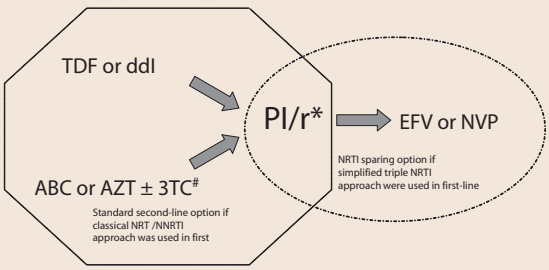
Difficulties in diagnosing treatment failure in resource-limited settings

- If clinical correlates alone are used, it is likely that many patients will switch with advanced disease, at appreciable risk of death from OIs, and will have high viral loads with extensive drug resistance.
- The value of immunological monitoring in defining ART failure largely depends on having a baseline CD4 count before commencing ART and on having longitudinal CD4 measurements on ART.
- One-off (spot) CD4 counts on ART are difficult to interpret when making decisions about treatment success or failure.
- Viral load, the most sensitive way to diagnose treatment failure, is not accessible in most resource-limited settings.

Principles of second-line therapy

- WHO recommends that the entire regimen be changed if treatment failure occurs.
- A second-line regimen should ideally include a minimum of three active drugs, one of them drawn from at least one new class.
- In resource-limited settings, the PI class is usually reserved for second-line treatment, preferably supported by two new NRTIs.
- Remember resistance to one NNRTI confers resistance to all NNRTIs (i.e. cannot use NVP if failed on EFV and vice versa).

Second-line ARV drugs in adults and adolescents: WHO guidelines, 2006



* Ritonavir boosted PIs are considered as the key component in second ine regimens and their use should be reserved for this situation LPV/r has been recommended as the preferred RTV boosted PI as it is available as a FDC and a new formulation that does not need refrigeration was recently launched but other boosted PIs (ATV/r SQV/r fos APV/r and DV/r) can be substituted based on individual programme priorities In the absence of a cold chain and where the new LPV/r formulation is not available unboosted ATV or NFV can be employed as the PI component but it is considered less potent than an RTV boosted PI

ZDV + 3TC are listed here for "strategic" use as resistance to both drugs is predicted to be present following failure on the respective first line regimen listed ZDV may prevent or delay the emergence of the K65R mutation; 3TC will maintain the M184V mutation which may decrease viral replicate capacity as we l as induce some degree of viral desensitization to ZDV It must be stressed that the c inical efficacy of this strategy in this situation has not been proven

Source: WHO guidelines, 2006.

Possible combinations

First -line regimen		Second-line regimen	
		RTI component	PI component
Standard strategy	AZT or d4T + 3TC + NVP or EFV	ddI + ABC or TDF + ABC or TDF + 3TC (± AZT)	PI/r
	TDF + 3TC + NVP or EFV	ddI + ABC or ddI + 3TC (± AZT)	
	ABC + 3TC + NVP or EFV	ddI + 3TC (± AZT) or TDF + 3TC (± AZT)	
Alternative strategy	AZT or d4T + 3TC + TDF or ABC	EFV or NVP ± ddI	

Second-line ART regimens: WHO guidelines, 2006 – 1

- RTV-boosted PIs are considered as the key component in second-line regimens, and their use should be reserved for this situation.
- LPV/r has been recommended as the preferred RTV-boosted PI as it is available as an FDC and a new formulation that does not need refrigeration.
- Other boosted PIs (ATV/r, SQV/r, fos-APV/r and IDV/r) can be substituted based on individual programme priorities and availability.

Second-line ART regimens: WHO guidelines, 2006 – 2

- In the absence of a cold chain and where the new LPV/r formulation is not available, unboosted ATV or NFV can be employed as the PI component but they are considered less potent than a RTV-boosted PI.
- ZDV + 3TC are listed here for "strategic" use as resistance to both drugs is predicted to be present following failure on the respective first-line regimen listed.
  - Slows down the selection of thymidine analogue mutations (AZT/d4T)
  - Can reverse resistance to specific ARVs – *M184V* + *L74V or M184V* + *K65R* mutations permit AZT, d4T and TDF to be effective AGAIN

Second-line ART for IDUs: common treatment situations

Treatment situation	Second-line preferential	Second-line alternatives
IDU without other significant clinical co-morbidities or co-treatments but needs ART	ABC + ddI+ LPV/r (or other boosted PI).	NFV can be substituted for LPV/r or other boosted PI. EFV or NVP can be substituted for ABC or ddI if none of both were used in first line.
IDU with HIV/HBV with indication to treat HBV and ART	ABC + ddI+ LPV/r (or other boosted PI) and maintenance of 3TC and/or TDF.	AZT, 3TC, TDF plus LPV/r (or other boosted PI). EFV or NVP can be substituted for ABC or ddI if neither were used in first line.
IDU with TB/HIV using TB regimens with rifampicin and needs ART	ABC + ddI+ LPV/r and additional dose RTV (or other boosted PI).	Maintain the PI and substitute rifampicin for rifabutin (if available)in TB regimen with adjustments in ARV dose if needed.

Source: Pontali E, 2006.

Activity 1: Group work

Review side-effects and toxicities of second-line ARV drugs:

- Minor side-effects and when they are likely to occur
- Major toxicities that are likely to occur within the first year of ART (and when they are likely to occur)
- Interactions with methadone and buprenorphine
- Longer-term toxicities

Side-effects and toxicities of second-line ART within the first year of treatment

ddI

Minor side-effects

- GI intolerance is common (especially with buffered formulation)

Major toxicities within the first year

- Peripheral neuropathy, usually at 2–6 months in 5–12%
- Pancreatitis 1–9% (avoid ddI with d4T, heavy alcohol use)
- Lactic acidosis and hepatic steatosis (any time from 1 to 20 months)

Major long-term toxicities

- Lactic acidosis and hepatic steatosis
- Lipoatrophy

Remember

- Food restrictions with ddI
- Interaction with methadone. Cannot use buffered ddI as methadone decreases ddI by 64%. However ddI-EC can be used.

Protease inhibitors

	Indinavir	Saquinavir	Nelfinavir	Lopinavir/r	Atazanavir	Fosamprenavir
Minor side effects	Gastrointestinal intolerance (10 15%) Dry skin paronychia alopecia	Gastrointestinal intolerance (10 20%) Headache	Gastrointestinal intolerance (10 30%) Skin rash (20%)	Gastrointestinal intolerance	Gastrointestinal intolerance	Gastrointestinal intolerance Skin rash (19%)
Major toxicity within first year	Nephrolithiasis and nephrotoxicity Abnormal LFTs	Abnormal LFTs	Abnormal LFTs	Abnormal LFTs	Indirect Bilirubin Jaundice or scleral icterus Abnormal LFTs Prolonged PR interval	Abnormal LFTs
Long term toxicity	Lipodystrophy	Lipodystrophy less lipid effect insulin resistance	Lipodystrophy hyperlipidaemia insulin resistance	Lipodystrophy hyperlipidaemia insu in resistance	Lipodystrophy insulin resistance Minimal lipid changes	Lipodystrophy
Interaction with methadone	IDV alone no interaction but boosted IDV may need to increase methadone	Saq alone minimal effect but boosted Saq may need to increase methadone	No interaction but conflicting data (monitor)	Methadone levels decrease may need to increase methadone	No interaction reported	Sma l reduction in methadone (monitor) Methadone may decrease FPV levels

PIs commonly cause asymptomatic hepatotoxicity especially with HBV and HCV co infection Change therapy if symptomatic or LFT > 5 10 ULN

Activity 2: Managing ART toxicities

- Small group discussion of four case studies
- Use Exercise 6.6.1

Implications for monitoring strategies

- Baseline tests: fasting BSL (OGTT is better) and fasting lipids
- Ongoing monitoring: three-monthly LFT, annual fasting BSL (or OGTT) plus fasting lipids – can change to annual depending on risk assessment
- Very careful monitoring of OST – many more interactions with methadone (less is known for buprenorphine)

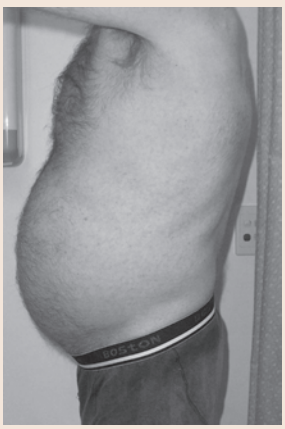
Activity 3: Managing long-term toxicities

- Use Exercise 6.6.2

Longer-term toxicities related to first- and second-line ART

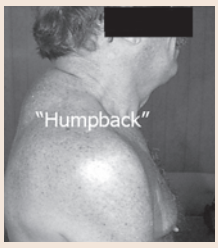
Lipodystrophy syndrome

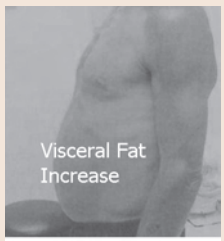
1: Fat redistribution
Lipohypertrophy
Lipoatrophy
2: Hyperlipidaemia
3: Insulin resistance and hyperglycaemia



Source: Cecilia M, Shikuma MD. Bangkok 2006.

Lipohypertrophy (fat accumulation)





- Fat accumulation in truncal/abdominal area and in the dorsal cervical area
- Fat accumulation in truncal area largely due to increase in visceral fat

Source: Cecilia M, Shikuma MD. Bangkok 2006.

Lipoatrophy (peripheral fat wasting)

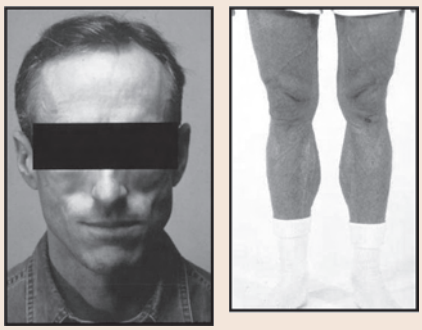
Treatment failure can be diagnosed:

- Fat wasting peripherally in the face, arms, legs and buttocks
- Lipoatrophy is the only body shape change that is unique to HIV disease

Source: Bacchetti P. *Journal of Acquired Immunodeficiency Syndromes*, 2005, 40:121–131.

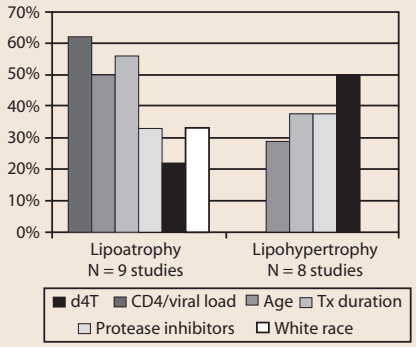
Lipoatrophy

- Subcutaneous fat loss



Courtesy of Michael Polis, MB, NIAID.

Risk factors for lipoatrophy and lipohypertrophy



Source: Lichtenstein KA. *Journal of Acquired Immune Deficiency Syndromes*, 2005, 39:395-400.

Fat redistribution

- Lipoatrophy appears most associated with d4T or d4T/ddI +/- AZT.
- PIs can exacerbate NRTI-related lipoatrophy.
- Fat accumulation more closely associated with PIs. Changes may occur with or without hyperlipidaemia.

Treatment of fat redistribution

- Lipoatrophy
  - May be slowly reversible by substituting ABC or TDF for d4T (or AZT if these ARV drugs are not available)
  - Thiazolidinediones or glitazones (extremity wasting)
  - Poly-L-lactic acid injections (cheeks)
- Lipohypertrophy
  - Change PIs for NNRTI or NRTI
  - Exercise and diet
  - Metformin
  - Thiazolidinediones or glitazones
  - Growth hormone
  - Liposuction (recurrence frequent)

Terms to describe hyperlipidaemia

Low-density lipoprotein (LDL)

- Elevated serum levels of this lipid are a strong risk factor for cardiovascular disease.
- The number of cardiac risk factors determines when to start treatment to lower LDL.

Triglycerides (TG)

- There is an increasing body of data that elevated TG also leads to cardiovascular disease.

Hyperlipidaemia

- Incidence of 47–75% in patients on PIs
  - May take a few weeks to months to appear
- Implications of hyperlipidaemia
  - Cholesterol and LDL-cholesterol: increased risk of atherosclerosis and coronary artery disease
  - Triglycerides: increased risk of pancreatitis and atherosclerosis
- Screening
  - Baseline fasting lipid level before starting ART regimen and then every 3–6 months on patients taking PIs
  - Yearly fasting lipids in patients on d4T

Hyperlipidaemia: ARV-specific laboratory findings

- All PIs (except ATZ)
  - Elevated LDL, total cholesterol (TC) and TG
  - Low HDL
- RTV
  - Elevated TG >> LDL and TC
- d4T
  - Elevated TG, occasional elevation of LDL and TC
- EFV or NVP
  - NVP: elevated HDL, occasionally increase in TG
  - EFV: can cause elevated LDL, occasionally increase in TG

Managing hyperlipidemia

- Diet and exercise (modest effect)
- Smoking cessation
- Weight loss
- Control blood pressure
- Control BSL if abnormal
- Statins (atorvastatin 10–40 mg, pravastatin 20–80 mg most commonly used: care with side-effects – baseline creatine kinase [CK])
- Fibrates (gemfibrozil 600 mg BD)
- Consider switching off PI or shift to ATZ

Insulin resistance and diabetes

- Frank diabetes found in 3–5% of patients on ART, but insulin resistance can be found in up to 90% of those on PIs
- PIs vary in their effect on glucose tolerance – ATZ and APV have minor effect on insulin sensitivity
- Insulin resistance less commonly associated with long-term exposure to NRTI (particularly d4T and 3TC)
- Other factors:
  - Previous hyperglycaemia
  - Family history of diabetes
- Laboratory diagnosis
  - Fasting serum glucose >126 mg/dl (7 mmol/l)
  - 2-hour post-prandial serum glucose >200 mg/dl (11.1 mmol/l)

Insulin resistance and diabetes

- Treatment
  - Balanced diet, low in simple sugars, carbohydrates
  - Regular excercise
  - Diabetic agents (metformin, glitazones, sulfonylurea, insulin)
  - Switch PI for NNRTI or NRTI
  - Replace current PI with ATZ or fos-APV

Source: WHO: *Report of a WHO consultation. Part 1: Diagnosis and classification of diabetes mellitus*. Geneva, World Health Organization, 1999; American Diabetes Association. *Diabetes Care* 2005, 28(supp 1)S4–S36.

Mortality in the era of ART

- Mortality in HIV-infected patients with good initial response to ART is still higher than in the general population.[1]
- More than 50% of deaths (where ART is extensively available) are now due to non-AIDS related causes.[2]
- Of particular concern is an increase in cardiac deaths.

1 Van Dighem A. *Journal of Acquired Immune Deficiency Syndromes*, 2005, 40:212–218.

2 Le Moing V et al. 45 ICAAC Abstract H-516, Dec 2005.

Cardiac risk factors

- Tobacco
- Male sex
- Older age
- Hyperlipidaemia
- Hypertension
- Diabetes mellitus
- Family history of premature coronary artery disease (CAD)
- Patient already with a history of CAD

The relative risk (RR) of cardiac and cerebrovascular events by cardiac risk factors and exposure to ART

Variable	RR (95% CI)	P value
Cholesterol, by mmol or higher	1.1 (1.03–1.19)	0.008
Triglycerides, by $\log_2$ mmol or higher	1.3 (1.12–1.51)	0.0006
Diabetes	2.22 (1.46–3.37)	0.0002
Hypertension	1.79 (1.25–2.56)	0.001
Use of ART, per year of exposure	1.26 (1.14–1.38)	0.0001

n = 207 of 23,468 PLWHAs

Adapted from *AIDS*. 2004,18:1811-1817 from the Data Collection on Adverse Event of Anti-HIV Drug (DAD) Study

Management of cardiovascular complications of ARV

- Early diagnosis and use of pharmacological therapies for the prevention/treatment of cardiac risk factors (hypertension, lipids)
- Behavioural changes:
  - Diet
  - Regular physical exercise
  - Smoking cessation
- Diminish further risks from ARV by:
  - Using NNRTIs or ATZ for PI
  - Using NRTIs, avoiding d4T

Osteonecrosis – 1

- Ischaemic death of the cellular components of bone, normally at the epiphyseal or subarticular regions
- 85% of cases are at one or both femoral heads, but may affect any bone
- Often insidious with subtle symptoms and joint pains
  - Patient may report pain on movement or on weight-bearing

Osteonecrosis – 2

Risk factors:

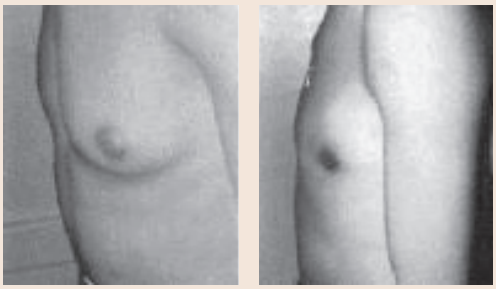
- Diabetes
- Prior history of prolonged steroid use
- Older age
- Excessive use of alcohol
- Hyperlipidaemia
- Use of PIs

Source: Glesby MJ. *Clinical Infections Diseases*, 2003.

Gynaecomastia

- An increase in size of the mammary gland
- Clinical presentation – unilateral pain, swelling of the breast
- Differential diagnosis
  - Hypogonadism (testicular tumours)
  - Pseudo-gynaecomastia (fatty deposit such as in lipodystrophy)
  - Medications (INH, ketoconazole, metronidazole)
  - Breast cancer

Gynaecomastia



Normal breast

Source: Viet Nam CDC Harvard Medical School AIDS Partnership. *Clinical training*. Ho Chi Minh City, Viet Nam, 2006.

ARV-associated gynaecomastia

- Prevalence in a cohort of patients on ART was 2.8% after two years
- Higher incidence in patients on regimen containing EFV – 8.1%

Other long-term complications

- Do not forget late IRIS
- Changes in adherence
- Changes in OST
- Some patients simply get fed up with taking long-term medication and want to stop

Activity 4: Small group work

- Break up into small groups for 15 minutes
- Use Exercise 6.6.2

What makes patients want to stop?

- Gastrointestinal side-effects
- Rash
- Malaise
- Body composition changes – lipoatrophy, lipodystrophy
- Neuropathy and pain
- Desire for drug holiday
- Depression

Summary

- The challenges to providing for the health of the HIV-infected patient currently do not end with access to potent ART regimens.
- Optimal care requires attention to screening, monitoring, prevention and therapy of complications induced by HIV and/or its therapies.
- First- and second-line ART is as successful in IDUs as non-IDUs; however, interactions of ARVs with OST and co-morbidities need careful monitoring.

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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