

Part B:
Antiretroviral Therapy
Module Overview

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Antiretroviral Therapy



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Module B1

Managing Patients on Antiretroviral Therapy



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Session 1: The Goal and Basic Principles of ART

In this brief introductory session, participants learn about the goal of antiretroviral therapy (ART), management considerations and WHO guidance on scaling up ARV therapies in resource-constrained settings.

Session 2: When to Start ART

Participants learn about the current thinking on why, how and when to start antiretroviral therapy. They discuss the clinical evaluation, lab tests for initiation and monitoring purposes and WHO's recommendations for initiating ART in adults using the WHO Clinical Staging System.

Session 3: Antiretroviral Drug Mechanisms

Participants learn about the drug mechanisms of the major antiretrovirals, including how and when to take them, their form and dosage and how to store them.

Session 4: Drug Interventions and Adverse Drug Reactions: Side Effects and Toxicities

Participants learn about drug interactions and adverse drug reactions (ADRs), as well as side effects, dosing schedules, formulations, toxicity risks and monitoring guidelines for the major antiretrovirals.

Session 5: Recommended First-Line Regimens in Adults

Participants learn about approved antiretroviral agents and WHO-recommended first-line antiretroviral regimens.

Session 6: Patient Follow-up and Monitoring ART

Participants learn about clinical and laboratory monitoring of patients on ART. This session addresses clinical, laboratory and efficacy monitoring; schedules for monitoring; and measures of toxicity and effectiveness.

Session 7: Drug Adherence and Strategies for Compliance

Participants learn about the issues involved in promoting antiretroviral drug adherence.

Session 8: Why and When to Change Therapy

Participants learn about drug resistance, reasons for changing an ART regimen and which second-line regimens to use.

SESSION 1 | The Goal and Basic Principles of ART

PURPOSE

In this brief introductory session, participants will learn about the goal of antiretroviral therapy (ART), management considerations and WHO guidance on scaling up antiretroviral (ARV) therapies in resource-constrained settings.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Describe the goal of ART.
2. List key considerations in the management of chronic HIV illnesses in resource-constrained settings.
3. Briefly describe the overall effects of HIV/AIDS and the effect of ART on the incidence of tuberculosis (TB) in South Africa.
4. Discuss the vast collateral benefits of ART, the obstacles for ART programs in resource-poor countries and the prerequisites for scaling up.
5. Discuss the prerequisites for scaling up, the pros and cons of antiretroviral therapy and what comprises optimal antiretroviral therapy.

TIME:

30 minutes

RESOURCES:

Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach. Geneva: WHO. 2003.

Planning the incorporation of antiretroviral therapy into comprehensive care programs, pp. 52-60 in: *Improving Access to Care in Developing Countries: Lessons from Practice, Research, Resources and Partnerships.* France: UNAIDS/WHO/Ministry of Foreign Affairs. July 2002.

Module 3. ARV Treatments: Planning and Integration into Health Services, in: *Guidance Modules of Antiretroviral Treatments.* WHO/ASD/98.7. Geneva: WHO/UNAIDS. 1987.

Step 1. Explain the purpose and objectives of the session (see above).
(2 minutes)

Step 2. Present the information in 1-10 below.
(15 minutes)

Use the PowerPoint slides on the CD-ROM accompanying this curriculum, if you have the equipment to do so.

1. The goal of highly active antiretroviral therapy (HAART) is to:

- a. Prolong and improve the quality of life for PLHA
- b. Reduce the viral load as much as possible, for as long as possible, in order to halt disease progression and prevent or reduce resistant variants
- c. Achieve immune reconstitution that is quantitative (CD4 count in normal range) and qualitative (pathogen-specific immune response)
- d. Reduce mother-to-child transmission

2. Management of chronic HIV illnesses in resource-constrained settings: key considerations and WHO guidance

- a. The pros and cons of standardized versus individualized diagnosis, treatment and follow-up
- b. Factors determining readiness of patient and clinician to start and continue a long-term relationship for managing HIV with ART
- c. Guidance by WHO and national policies and strategies: what it is and what it is not
- d. Provide an antiretroviral regimen that not only achieves reduction in viral loads, but also:
 - Maintains alternative options in the event of treatment failure AND
 - Is relatively free of side effects AND
 - Is tailored to individual needs for adherence

3. The effect of HIV/AIDS

- a. On life expectancy in Africa
- b. New AIDS cases in Western Europe

4. Effect of ART on the incidence of TB in South Africa

- a. ART reduced the incidence of HIV-associated TB by more than 80 percent

5. Vast collateral benefits of ART

- a. Increases voluntary testing and counseling uptake
- b. Increases awareness of HIV
- c. Increases motivation of health care workers
- d. Increases access to health facilities
- e. Decreases expenses for palliative and OI care
- f. Decreases number of orphans
- g. Keeps households and businesses intact
- h. Has potential to enhance prevention
 - Behavioral: access to prevention education during care encounters
 - Biological: decreased transmission because of lowered viral load

6. Obstacles for ART programs in resource-poor countries

- a. Lack of resources
- b. Procurement of affordable drugs
- c. Available drug supply
- d. Lack of infrastructure
- e. Complicated laboratory monitoring
- f. Lack of trained doctors and nurses
- g. Rapid staff turnover
- h. Stigma

7. Prerequisites for scaling up

- a. Adequate infrastructure
- b. Minimal lab support
- c. Access to OI/symptomatic treatment
- d. Continuous supply of a minimum of ARVs
- e. Patient ready and trained
- f. Physicians and team ready and trained
- g. ARV treatment guidelines in place
- h. Political will to sustain program

8. WHO ARV guidelines

- a. To support and facilitate better management of PLHA using ARV therapy
- b. To standardize and simplify ARV regimens
- c. To scale up ARV treatment programs
- d. To provide scientific evidence for ARV treatment programs

9. Antiretroviral treatment

- a. Advantages: efficacy
- b. Disadvantages:
 - Durability
 - Toxicity
 - Adverse effects
 - Drug interactions
 - Cost

10. Optimal antiretroviral therapy

- a. Prolongs and improves quality of life
- b. Reduces viral load, little risk for resistance
- c. Achieves immune reconstitution
- d. Preserves future therapeutic options
- e. Free of side effects
- f. Tailored to individual needs for adherence
- g. Inexpensive

Step 3. Discuss in-country guidelines and programs for ART.
(10-15 minutes)

SESSION 2 When to Start ART in Adults**PURPOSE**

Participants will learn about the current thinking on why, how and when to start antiretroviral therapy. They will discuss the clinical evaluation, lab tests for initiation and monitoring purposes and WHO's recommendations for initiating ART in adults using the WHO Clinical Staging System.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Discuss the rationale and timing for ART initiation, including the pros and cons of different approaches to this issue.
2. Describe the objectives of the clinical evaluation for ART.
3. Discuss the WHO clinical classification system and its use in deciding when to initiate ART.

TIME:

45 minutes

- Step 1. Explain the purpose and objectives of the session (see above).
- Step 2. Present the objectives of the clinical evaluation and the basic laboratory support needed to decide whether to initiate ART: 1 below. Ask participants which laboratory tests are available in their local situation.
(18 minutes)

1. Rationale and timing of ARV initiation

- a. Typical course of HIV infection and progression of AIDS to death, with and without ART
Refer to PowerPoint slide “Average Progression Without Treatment”
Refer to PowerPoint slide “Impact of Treatment on Viral Load and CD4”
- b. When and how to start ARV therapy
 - A patient needs ART only when he or she is symptomatic and/or there is evidence of significant immune system damage
 - Do *not* start ART if:
 - The patient is not motivated
 - You have not provided intensive counseling
 - Treatment cannot be continued
 - Patient is asymptomatic and there is no information about CD4 count
 - There is poor renal/hepatic function
 - Patient has terminal incurable disease, for example, cerebral lymphoma
 - How to start:
 - Use the simplest, cheapest and most effective three-drug combination as the first-line therapy
 - Then select the next one or two combinations as the second-line therapy

2. Objectives of clinical evaluation before the start of ART

- a. Conduct a clinical evaluation to:
 - Establish presence of HIV infection by means of:
 - History and physical exam
 - Voluntary counseling and testing (results from patient seeking a test while not hospitalized or seeking clinical care)
 - Counseling and testing for diagnostic purposes
 - Establish status of the HIV disease, for example, whether OIs are present
 - Discuss and decide the need for ARV therapy
 - Determine when to start and what to use
 - Discuss adherence and other issues
- b. Obtain basic laboratory support and establish baseline laboratory test results
 - Absolute minimum tests: HIV test, hemoglobin or hematocrit level
 - Basic tests: WBC count, liver function tests (LFTs) and renal function tests (RFTs), blood sugar, lymphocyte count
 - Desirable tests: CD4, amylase, bilirubin, lipids
 - Optional: viral load

c. Do a baseline clinical assessment and prepare the patient

- Baseline medical history

Psychosocial history:

Essential demographic characteristics

Family economic status

Family coping

Length of time since diagnosis of HIV infection, current medications and symptoms

Past medical history including major illnesses (for example, TB), hospitalizations, surgeries, past medications and allergies

For women, pregnancy history (gravida), current or planned pregnancy and access to contraceptive services

Review of systems (respiratory, cardiac, neurological, genitourinary and so on)

- Baseline physical exam:

Vital signs

Weight

Physical exam, documenting abnormalities

Eyes: fundoscopic exam, if possible

Oropharynx

Lymph nodes

Lungs

Heart

Abdomen

Extremities

Nervous system

Genital tract

Step 3. Present the information on when to start therapy and the WHO recommendations in Table 1 below. Ask participants if they have any questions about the recommendations.
(10 minutes)

3. WHO clinical classification system and its use in deciding to start ART

a. Overview of the WHO clinical classification system

Stage I:	Asymptomatic, persistent generalized lymphadenopathy
Stage II:	Weight loss <10 percent, prurigo, fungal nail infection, herpes zoster, recurrent URTIs
Stage III:	Weight loss > 10 percent, chronic diarrhea or fever, oral candidiasis, pulmonary TB, severe bacterial infections
Stage IV:	AIDS defining illnesses: for example, HIV wasting syndrome, PCP, brain toxoplasmosis, candida esophagitis, extrapulmonary TB, CMV retinitis, Kaposi's sarcoma, nonHodgkins lymphoma, and/or performance score 4: bedridden >50 percent of the day during the last month

b. Adults: When to start ART

- WHO stage IV disease (clinical AIDS) irrespective of CD4 cell count (CD4 cell count irrelevant)
- WHO stages I or II HIV disease with a CD4 cell count <200/mm³
- WHO stages II or stage III HIV disease + lymphocyte count <1200/mm³
- WHO stage III HIV disease with a CD4 cell count < 350/mm³

See Table 1 below, Recommendations for Initiating ART in Adults and Adolescents with Documented HIV Infection.

Recommendations for Initiating Antiretroviral Therapy in Adults and Adolescents with Documented HIV Infection

Laboratory Axis
<p>If CD4 testing is available:</p> <ul style="list-style-type: none"> • WHO stage IV disease, irrespective of CD4 cell count • WHO stage III disease (including but not restricted to HIV wasting, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, pulmonary TB, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis), with consideration of using CD4 cell counts < 350/mm³ to assist decision-making^a • WHO stage I or II disease with CD4 cell counts ≤ 200/mm^{3b}
<p>If CD4 testing is not available:</p> <ul style="list-style-type: none"> • WHO stage IV disease, irrespective of total lymphocyte count • WHO stage III disease (including but not restricted to HIV wasting, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, pulmonary TB, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis) irrespective of the total lymphocyte count^c • WHO stage II disease with a total lymphocyte count ≤ 1200/mm^{3d}

- a CD4 count advisable to assist with determining need for immediate therapy. For example, pulmonary TB may occur at any CD4 level and other conditions may be mimicked by non-HIV etiologies (e.g. chronic diarrhoea, prolonged fever).
- b The precise CD4 level above 200/mm³ at which ARV treatment should start has not been established.
- c The recommendation to start ART in all patients with stage III disease, without reference to total lymphocyte counts reflects consensus of expert opinion. It took into account the need of a practical recommendation that allows clinical services and TB programmes in severely resource-constrained settings to offer access to ART to their patients. As some adults and adolescents with stage III disease will be presenting with CD4 counts above 200, some of them will receive antiretroviral treatment before the CD4 <200 threshold is reached. However, if CD4 counts cannot be determined, starting ART earlier in these patients was not considered problematic.
- d A total lymphocyte count of ≤ 1200/mm³ can be substituted for the CD4 count when the latter is unavailable and HIV-related symptoms exist. It is not useful in the asymptomatic patient. Thus, in the absence of CD4 cell testing, asymptomatic HIV-infected patients (WHO stage I) should not be treated because there is currently no other reliable marker available in severely resource-constrained settings.

- c. Children: When to start ART (See Module 2, Session 3 for more details)
 - <18 months: Stage III or stages I & II disease + CD4 <20 percent
 - For children >18 months: Stage III or stages I & II disease + CD4 <15 percent. An assessment of viral load is not considered essential to start therapy.

Step 4. **Review the WHO Clinical Staging System and discuss: 3 below.**
 (15-20 minutes)

4. The WHO Clinical Staging System

- a. The WHO Staging System includes a clinical classification system and a laboratory classification to categorize the immunosuppression of adults by their *total* lymphocyte counts.
- b. This staging system has been proven reliable for predicting morbidity and mortality in infected adults.
- c. The WHO Clinical Staging System is based on clinical markers believed to have prognostic significance resulting in four categories. It helps to incorporate a patient performance scale into the system.

Clinical Stage I

1. Asymptomatic infection
 2. Persistent generalized lymphadenopathy (PGL)
- Performance scale I:* asymptomatic, normal activity

Clinical Stage II

3. Weight loss, <10 percent of body weight
 4. Minor mucocutaneous manifestations (for example, seborrheic dermatitis, prurigo, fungal nail infections, oropharyngeal ulcerations, angular cheilitis)
 5. Herpes zoster, within the last five years
 6. Recurrent upper respiratory tract infections (for example, bacterial sinusitis)
- Performance scale II:* symptomatic, normal activity

Clinical Stage III

7. Weight loss, >10 percent of body weight
 8. Unexplained chronic diarrhea, > 1 month
 9. Unexplained prolonged fever (intermittent or constant) >1 month
 10. Oral candidiasis (thrush)
 11. Oral hairy leukoplakia
 12. Pulmonary tuberculosis within the past year
 13. Severe bacterial infections (for example, pneumonia, pyomyositis)
- Performance scale III:* bedridden <50 percent of the day during the last month

Clinical Stage IV

14. HIV wasting syndrome, as defined by the Centers for Disease Control
15. Pncemocystis carinii pneumonia (PCP)
16. Toxoplasma of the brain
17. Cryptosporidiosis with diarrhea >1 month
18. Cryptococcosis, extrapulmonary
19. Cytomegaloviral disease of an organ other than the liver, spleen or lymph node
20. Herpes simplex virus infection, mucocutaneous (>1 month) or visceral (any duration)
21. Progressive multifocal leukoencephalopathy (PML)

- 22. Any disseminated endemic mycosis (for example, histoplasmosis, coccidioidomycosis)
- 23. Candidiasis of the esophagus, trachea, bronchi and lungs
- 24. Atypical mycobacteriosis, disseminated
- 25. Nontyphoid Salmonella septicemia
- 26. Extrapulmonary tuberculosis
- 27. Lymphoma
- 28. Kaposi’s sarcoma (KS)
- 29. HIV encephalopathy, as defined by the Centers for Disease Control

Performance scale IV: bedridden >50 percent of the day during the last month

d. WHO Improved Clinical Staging System

A further refinement of the WHO clinical staging system includes a laboratory axis. The laboratory axis subdivides each category into three strata (A, B, C) depending on the number of CD4 cells. If this is not available, you can use total lymphocytes as an alternative marker.

Laboratory Axis		Clinical Axis			
Lymphocytes*	CD4**	Stage I Asymptomatic PGL	Stage II Early HIV	Stage III Intermediate (ARC)***	Stage IV Late AIDS
A >2000	>500	1A	2A	3A	4A
B 1000-2000	200-500	1B	2B	3B	4B
C <1000	<200	1C	2C	3C	4C

* Reference range total lymphocytes: 1500-4000/mm³

** Reference range CD4 count: 450-1400/mm³

*** ARC: AIDS-related complex

Grey area refers to progression to AIDS

Note: The reference values used for lymphocytes and CD4 count are based on data available from the developed world. There are indications that Africans may have a physiologically higher lymphocyte count. Projects with laboratory equipment to conduct lymphocyte counts in HIV patients should, if possible, collect data about lymphocyte counts and CD4 counts and correlate them with the disease stage.

SESSION 3 Antiretroviral Drug Mechanisms**PURPOSE**

Participants learn about the drug mechanisms of the major antiretrovirals, including how and when to take them, their form and dosage and how to store them.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe how the different classes of ARVs work.
2. Describe dosages and administration of ARVs.
3. Discuss storage and availability in country.
4. Discuss pros and cons and availability of generic drugs in country.

TIME:

1 hour

PREPARATION:

Visual aid for Step 3: Obtain samples of the ARV drugs available locally to show to participants.

- | | |
|---------|---|
| Step 1. | Explain the purpose and objectives of the session (see above).
(3 minutes) |
| Step 2. | Present the mode of action of ARV therapies, administration and storage: 1-2 below using the PowerPoint slides.
(20 minutes) |

1. Antiretroviral therapies: Mode of action

- a. Antiretroviral drugs (ARVs) act on HIV by interfering with its reproductive cycle. The main stages of the cycle where these drugs act to inhibit replication of the virus are:
- Inhibit reverse transcriptase enzyme to interrupt the production of proviral DNA. ARVs prevent formation of proviral DNA. NRTI and NNRTI act here.
 - Inhibit maturation of virion by interrupting the protein processing and virus assembly. During this stage protease enzymes are required, and protease inhibitors act here.

Show PowerPoint slide: HIV-1 Lifecycle, which demonstrates quite clearly where the drugs work in the cycle and slides that demonstrate the mode of action of Zidovudine.

- b. Nucleoside reverse transcriptase inhibitors (NsRTIs):
- Lead to premature termination of the production of the HIV DNA chain
 - Are active against both HIV 1 and 2
 - Resistance develops rapidly if given as single drugs alone (monotherapy)
 - Do not use the following drugs together:

AZT	+	d4T
ddI	+	ddC
d4T	+	ddC
ddC	+	3TC

Also, the combination of ddI and Indinavir is difficult for patients.

Nucleoside reverse transcriptase inhibitors				
Acronym	Generic Name	Trade Name	Unit Dose	Daily Dose
AZT (ZDV)	Zidovudine	Retrovir®	300 mg	2 x 1/d
ddl	Didanosine	Videx® Videx® EC	100 mg 250/400 mg	4 /d 1 /d
ddC	Zalcitabine	Hivid®	0.75 mg	3 x 1 /d
d4T	Stavudine	Zerit®	30/40 mg	2 x 1 /d
3TC	Lamivudine	Epivir®	150 mg	2 x 1 /d
AZT + 3TC	Zidovudine + Lamivudine	Combivir®		2 x 1 /d
ABC	Abacavir	Ziagen®	300 mg	2 x 1 /d
AZT+3TC+ABC	Zidovudine + Lamivudine + Abacavir	Trizivir®		2 x 1 /d

Note: Adapt ARV dose for the following according to body weight:

- Didanosine (Videx®)
 - > 60 kg 400 mg once daily
 - < 60 kg 250 mg once daily
 - Stavudine (Zerit®)
 - > 60 kg 40 mg bid
 - < 60 kg 30 mg bid
- c. Nonnucleoside reverse transcriptase inhibitors (NNRTIs):
- NNRTIs do not work in HIV-2 and HIV-1 group O infection.
 - Delavirdine and nevirapine are antagonistic in action on the HIV reverse transcriptase activity. Do not, therefore, use them together.
 - Interaction with some drugs occurs because of induction and/or inhibition of cytochrome P450 enzymes.

Non-nucleoside reverse transcriptase inhibitors				
Acronym	Generic Name	Trade Name	Unit Dose	Daily Dose
NVP	Nevirapine	Viramune®	200 mg	1/d x 14d then 2/d
EFZ	Efavirenz	Stocrin® Sustiva®	200 mg or 600 mg	3/d 1/d
DLV	Delavirdine	Rescriptor®	200 mg	Two tabs 3x a day

d. Protease inhibitors (PIs)

- HIV protease enzyme is responsible for cleaving various polyproteins in the process of producing mature infectious virions. PIs interfere with the production of HIV protease enzyme; this leads to a reduction of the virus in the body that is sometimes sufficient to lead to undetectable levels of virus.
- Rapid resistance will develop if PIs are used as single agents.
- PIs are associated with multiple drug interactions because of their inhibition of cytochrome P450 enzymes. For example, PIs increase the metabolism of rifampicin and decrease its effectiveness in treating TB.
- Take indinavir with plenty of water to prevent kidney stones.
- If a patient develops diabetes during PI treatment, it is best to stop the PIs if there is another alternative.

Protease inhibitors				
Acronym	Generic Name	Trade Name	Unit Dose	Daily Dose
IDV	Indinavir	Crixivan®	200/400 mg	3 x 2/d
RTV	Ritonavir	Norvir®	100 mg	2 x 6/d
NFV	Nelfinavir	Viracept®	250 mg	3 x 3/d or 2 x 5/d
SQV	Saquinavir HG	Invirase®	200 mg	3 x 6/d
	Saquinavir SG	Fortovase®	200 mg	2 x 8/d
APV	Amprenavir	Agenerase®	150 mg	2 x 3/d
LPV/RTV	Lopinavir/Ritonavir	Kaletra®	400/100 mg	1 x 2/d

e. Nucleotide Reverse Transcriptase Inhibitor (NRTI)

- Tenofovir disoproxil fumarate (TDF)
 - First nucleotide RTI with durable activity against some nucleoside-resistant strains of HIV with significant HIV RNA reductions
 - Favorable safety profile
 - If available, add TDF either to d4T/ddI or to ABC/ddI or substitute for either d4T or ABC in these combinations.
 - When ddI is given with TDF, reduce the dosage of ddI and give the ddI with food.
 - A possible side effect is Fanconi syndrome.
 - You may use tenofovir and/or nevirapine cases of high cholesterol and triglyceride levels.
 - Currently restricted availability in resource-limited settings

Nucleotide reverse transcriptase inhibitors				
Acronym	Generic Name	Trade Name	Unit Dose	Daily Dose
TDF	Tenofovir	Viread®	300 mg	Once daily

2. Administration and storage of ARVs:

- a. Take on an empty stomach—1h before or 2h after a meal
 - Didanosine
 - Indinavir (except if given with ritonavir)
- b. Take with food
 - Nelfinavir, ritonavir, lopinavir, saquinavir
 - Tenofovir
 - ddI, when given with tenofovir
- c. Take with or without food
 - ZDV, D4T
 - Nevirapine
 - Efavirenz, but avoid high fat food
- d. Administer crixivan with liquids, with or without a light meal, one hour before or two hours after a regular meal.
- e. Storage of ARVs in the refrigerator
 - Ritonavir (Note: Patients without access to a refrigerator can be given a two to four week supply of Ritonavir.)
 - ddI suspension
 - d4T solution
 - Lopinavir/ritonavir capsules and solution
- f. Storage of ARVs in glass jars
 - ZDV syrup
 - d4T syrup

Step 3: Present the information on the use of generic ARVs: 3. a-b below. Discuss any issues or concerns the participants may have.
(10 minutes)

3. Discussion on the use of generic antiretrovirals

- a. Overview: Generic antiretrovirals are now being produced in India, Brazil, Argentina and Thailand using ingredients produced largely by Indian companies. These companies often provide ingredients to the pharmaceutical companies that make branded antiretrovirals.

Thailand and Brazil have promised to assist several African countries in making generic versions of ARVs.

China, Vietnam and Indonesia also have pharmaceutical companies that have announced their intention to produce and supply these drugs.

In theory, generic antiretrovirals are attractive because their price is often much lower than the lowest price offered by the manufacturer of the branded equivalent. While there continue to be arguments about how much of an obstacle patents pose to treatment access, there is substantial evidence that countries that make their own generic versions of drugs are also able to secure better prices for branded versions.

Some have argued that patents are not a serious barrier to treatment access because relatively few drugs are patented in the countries with the most PLHA and the least access to drugs. Thus, the major factor limiting access would be political will and commitment on the part of national governments and international funders.

Médecins Sans Frontières has compared the effectiveness of three strategies for reducing prices across six countries (Senegal, Honduras, Cameroon, Uganda, Brazil and Thailand). The organization found that countries that allowed generic competition, and especially those with local generic manufacture, had substantially lower prices for affected drugs than countries that got drugs exclusively from proprietary drug companies.

In Brazil, generic drugs have been a key factor in controlling the cost of ARV treatment. There was a 43 percent reduction in the cost of triple drug combinations (including a PI or NNRTI) from 1997 to 2000, and a 34 percent reduction of quadruple drug combinations (using ritonavir-boosted PIs). Through the period, the number of patients on treatment in Brazil has increased in a linear fashion by 1,400 per month; the average individual cost was US\$13.3 per day in 2002.

b. Concerns

Quality control: Generic producers must carry out biological equivalence studies in healthy volunteers to show that their product has a pharmacokinetic profile equivalent to the branded product. So far, little information is available about the bioequivalence studies that Indian manufacturers have conducted, although it is reported that Cipla has carried out studies on eight antiretrovirals: Ranbaxy on seven and Hetero on five drugs or combinations of drugs. Any license application will include a review of this bioequivalence data as a requirement for use of the drugs outside India.

Before the World Health Organization lists antiretrovirals, WHO officials must inspect the manufacturing processes. Generic producers should also receive a certificate of Good Manufacturing Practice to show that their equipment and procedures meet minimum industry standards.

The International Dispensary Association, the world's largest nonprofit supplier of essential medicines to resource-limited countries, is inspecting Indian antiretroviral manufacturing during 2002.

Manufacturing issues: Generic producers must take a finished product and try to trace back how it was made. Each step, or chemical reaction, could lead to impurities or loss of efficacy. With some drugs, notably the nucleoside analogues AZT (zidovudine) and d4T (stavudine), the process of reverse engineering is relatively simple; but for others, such as 3TC (lamivudine), nevirapine and efavirenz, the process is tricky. Protease inhibitors take more time to make because they involve many more stages than nucleoside analogues. So far, Indian manufacturers have been unable to bring the cost of their generic protease inhibitors down below the cost price of the manufacturer of the branded product.

- Step 4. Discuss the availability of ARV drugs (including generics, if available) in their local situation and what forms they come in. Discuss drug management issues and possible strategies to address these, including in-country guidelines.
- Show samples of drugs available locally; discuss the different formulations, as well as such features as strength and taste. Doing this is especially important for those participants who are learning about ARVs for the first time.
- (30 minutes)

SESSION 4 Drug Interactions and Adverse Drug Reactions: Side Effects and Toxicities**PURPOSE**

In this session, the participants will learn about drug interactions and adverse drug reactions (ADRs), as well as side effects, dosing schedules, formulations, toxicity risks and monitoring guidelines for the major ARVs.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe the important drug interactions among various ARVs and discuss the significance of these interactions.
2. List various toxicities and common side effects of each drug.
3. Discuss monitoring and management of toxicities and side effects.
4. Describe class adverse drug reactions, including class-specific and ARV-specific adverse effects of ART.

TIME:

2 hours

PREPARATION:

Steps 3 and 4: On a large piece of flip chart paper, create a blank chart as shown on the blank table in this session.

Create a handout with the same chart on letter-size or legal-size paper, and make copies for the small discussion groups.

REFERENCE:

For further information and details on drug interactions and adverse drug reactions: side effects and toxicities, refer to: WHO. *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach*. Annexes 11A & B, pp. 128-141.

Note: You may wish to make copies of these annexes to hand out to the participants.

- | | |
|---------|---|
| Step 1. | Explain the purpose and objectives of the session (see above). |
| Step 2. | Describe the various drug interactions and introduce the information in Tables below. 1. a-f
(25 minutes) |

1. Antiretroviral drug interactions

a. Introduction

Pharmacokinetic interactions occur when one drug alters the serum or tissue concentration of another by changing its absorption, distribution, metabolism or elimination. Such interactions can result in clinically significant changes in drug concentration; this may require modifying the dose of one or more drugs or may necessitate the use of an alternative drug or drugs.

b. Changes in drug absorption

- Alterations of gastric pH

If a drug changes the gastric pH, it can affect the absorption and hence the concentration of other drugs that have specific pH requirements for absorption.

For example, ddI requires a higher gastric pH for optimal absorption and is administered with an antacid buffer that raises the gastric pH. Thus, ddI decreases the absorption of drugs whose absorption requires low gastric pH, such as ketoconazole, itraconazole, tetracycline, quinolone antibiotics, IDV and LPV/r. If coadministration occurs, give these drugs two hours apart from ddI.

- Presence or absence of food

Food can enhance or decrease the bioavailability of a drug, often because of its effect on gastric acidity. Therefore, you should administer some drugs, such as ddI and IDV, one hour before or two hours after eating.

Additionally, the bioavailability of lipid-soluble drugs, such as efavirenz, may be enhanced when administered with a high-fat meal.

- Chelation

The binding of two drugs or compounds to form insoluble complexes that cannot be absorbed can change the absorption of a drug.

For example, chelation, with calcium in milk products, or with cations such as those of aluminum, magnesium, iron or zinc found in antacids or multivitamins significantly decrease the absorption of the fluoroquinolone drugs.

c. Changes in distribution

- Protein-binding

Things that alter the protein-binding of a drug affect the amount of free drug that is available to produce the necessary therapeutic effect.

For example, warfarin is 99 percent protein-bound and, if given with other protein-bound drugs such as EFZ, can be displaced from its protein sites. This places the patient at risk for bleeding and requires monitoring of the prothrombin time.

- Hypoalbuminemia

Patients with low albumin levels can experience an increased therapeutic effect and/or risk for toxicity of drugs that are highly protein-bound, such as warfarin or phenytoin.

2. Changes in metabolism

- Metabolism in the liver cytochrome P450 system

The induction or inhibition of various P450 enzymes by one drug can significantly alter the serum concentration of another drug that is metabolized by the same P450 enzyme.

The PIs and NNRTIs are primarily metabolized by the same P450 CYP3A4 isoenzyme and can inhibit or induce this isoenzyme, resulting in increases or decreases in concentration of concomitantly administered drugs. Moreover, other drugs that inhibit or induce this isoenzyme can bring about increases and decreases in the concentration of concomitantly administered PIs and/or NNRTIs. Each PI and NNRTI has a different drug interaction profile, depending primarily on its potency as an inducer or inhibitor of CYP3A4 and/or other P450 enzymes.

- Ritonavir is the most potent CYP3A4 inhibitor and consequently has the largest amount of drug interactions and contraindications.
- NVP is a CYP3A4 inducer.
- EFZ is both an inducer and inhibitor of CYP3A4.
- Rifampicin is a potent inducer of hepatic metabolism and significantly decreases the concentration of PIs to subtherapeutic levels.

NFV, RTV and the NNRTIs can significantly decrease the estrogen levels in contraceptives. Consequently, women taking these drugs cannot rely on oral contraceptives and should use another or an additional method of contraception.

PIs and EFZ can raise the serum concentration of cisapride and of nonsedating antihistamines (astemizole, terfenadine), which can lead to cardiotoxicity. They can also increase the serum concentration benzodiazepines, and this can result in prolonged sedation. Therefore, do not administer PIs and these other drugs concomitantly.

e. Changes in elimination

- Kidney function

The inhibition of the tubular secretion of one drug by another that is eliminated by the kidney can result in changes in drug concentration.

For example, probenecid can increase levels of ZDV.

3. Summary

- Do not combine indinavir (crixivan[®]) and nelfinavir (viracept[®]) with:
Rifampin (rifadin[®])
Terfenadine (triludan[®])
Astemizole (hismanal[®])
Cisapride (cyprid[®], prepulsid[®])
- Interactions with ritonavir

Do not use ritonavir with:		Possible Alternatives	
Generic Name	Brand Name	Generic Name	Brand Name
Piroxican	Feldene [®]	Aspirin	
Auriodarone	Cordarone [®]		
Artemizole	Hismanal [®]	Loratidine	Claritin [®]
Terfenadine	Triludan [®]		
Cisapride	Prepulsid [®]		
Alprazolam	Xanax [®]	Temazepam	Euhypnos [®]
Chlorazepate	Tranxene [®]	Lorazepam	Temesta [®]
Diazepam	Valium [®]		
Midazolam	Dormicum [®]		
Triazolam	Halcion [®]		

- Protease inhibitors and antituberculous treatment

	Rifampicin	Rifabutin
Saquinavir	Mixed Case (NO)*	NO
Indinavir	NO	1/2 dose
Ritonavir	NO	NO
Nelfinavir	NO	1/2 dose

*can be given when boosted with ritonavir

- Adapt ARV dose because of drug interactions. (See tables below for further information.)

Nevirapine 400 mg/d (no change)
 Indinavir 3 x 1000 mg/q 8h

Efavirenz 600 mg/d (no change)
 Indinavir 3 x 1000 mg/q 8h

Nevirapine 400 mg/d (no change)
 Lopinavir/ritonavir 2 x 500/100 mg/bid

- The tables below summarize drug interactions between NNRTIs and PIs and relevant drug interactions involving NNRTIs and PIs.

Table B1, 4.1: Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors

	Nevirapine (NVP)	Efavirenz (EFZ)	Indinavir (IDV)	Lopinavir (LPV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
Nevirapine	No effect on NVP EFZ AUC decreased 22 percent Recommendation: Standard dosing	NVP increased twofold IDV decreased 28 percent Recommendation: Change IDV dose to 1000 mg three times daily No change NVP	No effect on NVP LPV trough decreased 55 percent Recommendation: Consider LPV/r 533 mg/133 mg twice daily No change NVP	No effect on NVP NFV levels increased 10 percent Recommendation: Standard dosing	No effect on NVP SQV decreased 25 percent Recommendation: Standard dosing	
Efavirenz	No effect on EFZ IDV decreased 31 percent Recommendation: Change IDV dose to 1000 mg three times daily No change EFZ	No effect on EFZ LVP AUC decreased 40 percent Recommendation: Consider LPV/r 533 mg/133 mg twice daily No change EFZ	No effect on EFZ NFV increased 20 percent Recommendation: Standard dosing	EFZ decreased 12 percent SQV decreased 62 percent Recommendation: Do not coadminister (SQV/r boosting may be possible)		
Indinavir			No effect on LPV IDV AUC and trough increased Recommendation: Change IDV dose to 600 mg twice daily No change LPV	NFV increased 80 percent IDV increased 50 percent Recommendation: Limited data for IDV 1200 mg twice daily with NFV 1250 mg twice daily	SQV increased fourfold to sevenfold No effect on IDV Recommendation: Insufficient data to provide recommendation	
Lopinavir				No data	SQV AUC/trough increased Recommendation: SQV 800 mg twice daily No change LPV/r	
Nelfinavir					SQV increased twofold to fivefold NFV increased 20 percent Recommendation: Fortovase 1200 mg twice daily No change NFV	

Source: *Scaling Up Antiretroviral Therapy in Resource Limited Settings: Guidelines for a Public Health Approach*. Geneva: WHO, 2002, pp. 112-113.

B1, 4.1 (cont.)

	Nevirapine (NVP)	Efavirenz (EFZ)	Indinavir (IDV)	Lopinavir (LPV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
Antifungal						
Ketoconazole	NVP increased 15-30 percent Ketoconazole decreased 63 percent Recommendation: Do not coadminister	No data	IDV increased 68 percent Recommendation: Change IDV to 600 mg three times daily	LPV decreased 13 percent Ketoconazole increased threefold Recommendation: None	No dose adjustment	SQV increased threefold Recommendation: Standard dosing
Antimycobacterials						
Rifampin	NVP decreased 37 percent Recommendation: Use with caution only if no alternatives available	EFV decreased 25-33 percent Recommendation: Consider EFV 800 mg daily	IDV decreased 89 percent Recommendation: Do not coadminister	LPV AUC decreased 75 percent Recommendation: Do not coadminister	NFV decreased 82 percent Recommendation: Do not coadminister	SQV decreased 84 percent when given without RTV Recommendation: If using SQV/RTV rifampin can be used at 600 mg/day or two or three times weekly
Rifabutin	NVP decreased 16 percent Recommendation: Standard dosing	EFV unchanged Rifabutin decreased 35 percent Recommendation: Increase rifabutin dose to 450-600 mg daily (or 600 mg two or three times weekly); EFV no change	IDV decreased 32 percent Rifabutin increased twofold Recommendation: Decrease rifabutin dose to 150 mg daily (or 300 mg two or three times weekly); IDV dose change to 1000 mg three times daily	Rifabutin AUC increased threefold Recommendation: Decrease rifabutin dose to 150 mg daily; LPV/r no change	NFV decreased 32 percent Rifabutin increased twofold Recommendation: Decrease rifabutin dose to 150 mg daily (or 300 mg two or three times weekly); NFV dose increase to 1000 mg three times daily	SQV decreased 40 percent (RTV increases rifabutin levels fourfold) Recommendation: If using SQV/RTV, use rifabutin 150 mg two or three times weekly
Clarithromycin	NVP increased 26 percent Clarithromycin decreased 30 percent Recommendation: Standard dosing	EFV unchanged Clarithromycin decreased 39 percent Recommendation: Do not coadminister	Clarithromycin increased 53 percent Recommendation: Standard dosing	No data	No data	Clarithromycin increased 45 percent SQV increased 177 percent Recommendation: Standard dosing

B1, 4.1 (cont.)

	Nevirapine (NVP)	Efavirenz (EFZ)	Indinavir (IDV)	Lopinavir (LPV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
Antimycobacterials						
Oral contraceptives	Estradiol decreased 20 percent Recommendation: Use alternative or additional methods	Estradiol increased 37 percent; no data on other components Recommendation: Use alternative or additional methods	When used with RTV: estradiol decreased Recommendation: Use alternative or additional methods	Estradiol decreased 42 percent Recommendation: Use alternative or additional methods	Estradiol decreased 47 percent; norethindrone decreased 18 percent Recommendation: Use alternative or additional methods	When used with RTV: estradiol decreased Recommendation: Use alternative or additional methods
Methadone	Methadone decreased significantly Recommendation: Opioid withdrawal reported; may require increase in methadone dose	Methadone decreased significantly Recommendation: Opioid withdrawal reported; may require increase in methadone dose	No change, but there may be a decrease if given with low-dose RTV Recommendation: When IDV is given with low-dose RTV: opioid withdrawal possible; may require increase in methadone dose	Methadone AUC decreased 53 percent Recommendation: Opioid withdrawal possible; may require increase in methadone dose	May decrease methadone levels Recommendation: Opioid withdrawal possible; may require increase in methadone dose	No data but may decrease if given with low-dose RTV Recommendation: When given with low-dose RTV: opioid withdrawal possible; may require increase in methadone dose
Anticonvulsant						
Phenobarbital	Unknown	Unknown		Unknown, but may decrease LPV levels substantially Recommendation: Monitor anticonvulsant levels	Unknown, but may decrease NFV levels substantially Recommendation: Monitor anticonvulsant levels	Unknown, but may decrease SQV levels substantially Recommendation: Monitor anticonvulsant levels
Lipid-lowering agents: Simvastatin Lovastatin Atorastatin	No data	No data	Potential for large increase in statin levels (except pravastatin) Recommendation: Do not coadminister except pravastatin; no dose adjustment	Potential for large increase in statin levels Recommendation: Do not coadminister	Potential for large increase in statin levels Recommendation: Do not coadminister	Potential for large increase in statin levels Recommendation: Do not coadminister

Step 3. Ask participants to break into groups. Distribute the handout of the blank chart to each group; ask them to discuss the drugs available to them in each category, their side effects and toxicities, and how to monitor for these toxicities. Have one recorder fill in the blanks in the handout. (Or give them flip chart paper to use in recording their answers during discussion.) Give them 15 minutes to complete this task.

Step 4. Hang the blank chart you created on the wall, and ask the recorder of each group to help fill in the blanks. Discuss the answers, and compare them to the information in 4. below.
(15 minutes)

Note: The success of this exercise will depend on the background and level of knowledge of the participants. If they do not have the necessary knowledge and experience to complete the chart, you may choose to create a chart that shows the side effects and toxicities, leaving the how-to-monitor column blank, and ask the groups to discuss how they would manage and monitor the listed side effects and toxicities.

Drug Name	Side Effects and Toxicity (toxins are italicized)	How to Monitor
Nucleoside reverse transcriptase inhibitors (NsRTIs)		
Nucleotide reverse transcriptase inhibitors (NtRTIs)		
Protease inhibitors (PIs)		

4. Common side effects and toxicities, and how to monitor

Drug Name	Side Effects and Toxicity (toxicities are italicized)	How to Monitor
Nucleoside reverse transcriptase inhibitors (NsRTIs)		
ZDV, AZT	• GI intolerance, asthenia, headache, <i>anemia, leukopenia</i>	• Full blood count
ddI	• GI intolerance: <i>pancreatitis, peripheral neuropathy, lactic acidosis</i>	• Foot pain, paresthesias, deep tendon reflexes, abdominal pain
d4T	• <i>Peripheral neuropathy, pancreatitis, lactic acidosis</i>	• Foot pain, paresthesias, deep tendon reflexes
3TC	• Generally well tolerated: <i>lactic acidosis</i>	
ABC	• Hypersensitivity reaction (HSR)— symptoms of fever, rash, GI, respiratory problems, <i>lactic acidosis</i>	• Educate patient on signs and symptoms of HSR and what to do; check history for prior reaction.
Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)		
TDF		• Liver function tests (LFTs)
Nonnucleotide Reverse Transcriptase Inhibitors (NNtRTIs)		
NVP	• <i>Extensive rash, fulminant hepatitis</i>	• Liver function tests q 2 wks x 2, then q mo x 12, then q 3 mo.
EFX	• CNS— <i>dissociated state x 2 to 3 weeks</i> ; rash Avoid pregnancy	• Liver function tests
Protease Inhibitors (PIs)		
SQV • Fortovase (FTV) • Invirase (INV)	• <i>GI intolerance, lipodystrophy</i>	• Liver function tests • Lipid profile
RTV	• <i>GI intolerance, paresthesias, hepatitis, lipodystrophy</i>	• Liver function tests • Lipid profile
IDV	• GI intolerance, <i>nephrolithiasis</i> , benign increase in bilirubin, lipodystrophy	• Lipid profile • Liver function tests • UA
NFV	• <i>Diarrhea, lipodystrophy</i>	• Liver function tests • Lipid profile
LPV/r	• <i>GI intolerance (esp. diarrhea), asthenia, lipodystrophy</i>	• Liver function tests • Lipid profile

Step 5. Explain that there are certain general adverse class effects known as ADRs. Present the following information on ADRs and discuss.
(20 minutes)

5. Class adverse drug reactions (ADRs)

- a. Lipodystrophy: fat distribution
 - Diagnosis
 - Fat accumulation: abdomen, dorsal neck, (*buffalo hump*), breasts
 - Fat atrophy: Extremities, buccal fat, buttocks
 - Measurement
 - Waist-hip ratio >0.85 (women) or >0.95 (men)
 - Patient perception
 - Intervention
 - Results with changing therapy, including use of different classes, are inconclusive

- b. Hyperlipidemia
 - Evaluation
 - Baseline for patient at risk for cardiovascular disease and prior to ART
 - Triglycerides
 - Normal levels: <150 mg/dl
 - Elevated levels: 200-499 mg/dl
 - Very high levels requiring immediate intervention to prevent pancreatitis and reduce risk of cardiovascular disease: >500 mg/dl
 - Drug selection
 - ACTG expert panel recommendations for statins with concurrent PI or NNRTI: Atorvastatin or Pravastatin
 - Therapeutic switch
 - PIs, and possibly NNRTI agents, appear to be associated with increases in blood lipids, including cholesterol, LDL cholesterol, and triglycerides. Use of nonPI-containing regimens may reverse these changes. Changing from PI-based regimens to an NRTI/NNRTI regimen may improve lipid profile.

- c. Diabetes
 - Risk is associated with the use of all drugs classified as PIs
 - Frequency: 3-17 percent of diabetic patients on PIs have a reaction that occurs at median of 60 days
 - Cause: Peripheral insulin resistance
 - Monitoring: Fasting blood glucose at pre-ART baseline; some recommend fasting blood sugar at 3 to 4 month intervals for the first year of PI therapy; subsequent measurements based on baseline measurements and risks
 - Treatment: Insulin sensitizers (metformin or glitazones) preferred over insulin or sulfonyl-ureas, based on mechanism of diabetes; most do not recommend changes in ART unless there is severe diabetes

- d. Mitochondrial toxicity: lactic acidosis ± steatosis
 - Rate: 1.3 per 1,000 patient years
 - Risk: Prolonged NRTI use, obesity, female sex, pregnancy, d4T > AZT, ddl > ABC, 3TC

- Symptoms: Fatigue, nausea, vomiting, wasting, abdominal pain, dyspnea, diarrhea, anorexia, weakness, myalgias, parasthesias, hepatomegaly. May cause respiratory failure requiring ventilator therapy.

	2DV	3TC	d4T	ddC	ddl
Neuropathy			++	++	++
Myopathy	++				
Cardiomyopathy	+			+	+
Pancreatitis		++	+		++
Hepatitis	+	+	+		
Lactic acidosis	+	+/-	+		+
Bone marrow depression	++	+/-		+	+

- Lab: Lactic acid—obtain without tourniquet, fist-clenching or stasis; use prechilled fluoride-oxalate tubes
Transport on ice for processing within four hours.
 - <2 mmol/mL: normal
 - 2-5 mmol/mL: d/c NRTI, if symptomatic (after ruling out other cause of symptoms; at this low level may be something else)
 - >5 mmol/mL: d/c NRTI
 - >10 mmol/mL: potentially lethal
 - Other lab: Variable ↑ CPK, LDH, lipase, amylase, ALT4 anion gap, ↓ HCO₃, CT scan or echo—fatty liver; liver biopsy—steatosis
 - Management: Discontinue NRTI, or switch to NRTI with reduced frequency of lactic acidosis (ABC, AZT, tenofovir). NRTI-sparing regimens with established efficacy: LPV/RTV, EFV/IDV ± RTV, SQV/RTV, APV/RTV/EFV
 - Recovery: Mean time to normal lactic acid levels after stopping NRTIs is 50 days
- e. Hepatotoxicity
- Definition: ALT or AST elevation to 3-4 x the upper limits of normal that is not otherwise explained
 - Frequency with ART: 2 percent to 18 percent
 - Mechanism: NRTI—mitochondrial toxicity; PI and NRTI—unclear; liver biopsy usually not helpful
 - Agents: All retroviral agents, especially RTV and NVP.
Note: NVP-associated hepatitis usually occurs in the first 12 weeks of therapy; may be asymptomatic and in rare cases may progress to hepatic necrosis and death. Monitor ALT levels.
 With PIs the hepatotoxicity may occur at any time during treatment; stop the implicated drug when the ALT is 5 x the upper limits of normal.
 - Risk: chronic hepatitis (HCV, HBV), d4T use, alcoholism and increased baseline transaminase levels. With HCV or HBV coinfection, the increased ALT may result from immune reconstitution rather than drug toxicity.
 - Dose modification (decrease dose) with hepatic failure (any cause): AZT, all PIs, all NRTIs
- f. Osteoporosis
- Risk: Osteopenia in 25-50 percent of ART recipients; osteoporosis in 5-10 percent
 - Routine screening: Not indicated
 - Treatment: Increase intake of calcium and vitamin D, plus weight bearing exercises
- g. Avascular necrosis
- Rate: 0.3 percent to 1.3 percent
 - Risks: ETOH abuse, hyperlipidemia, steroid use, hypercoagulability, hemoglobinopathy; relationship with ART is unclear

- Diagnosis: MRI or CT scan
- Most frequent sites: femoral head, shoulder

h. Rash

- Most common with NNRTIs: NVP, DLV, EFV; frequency—10 percent to 20 percent
Most are cutaneous and can be treated with antihistamines.
Severe or life threatening reactions include Stevens-Johnson syndrome and DRESS (drug rash, eosinophilia and systemic symptoms with fever, and multiple organ involvement).
- Indications to D/C NNRTI: Symptoms of DRESS or rash with fever, desquamation, mucous membrane involvement, blistering or arthritis (1 percent to 2 percent)
- Safety of alternative NNRTIs: Unknown; chemical structures of NNRTIs are very different and limited experience shows that a switch from NVP to EFV for rash is safe
- PI most likely to cause rash: APV—22 percent (sulfonamide)
- NRTI most likely to cause rash: ABC

i. Summary

- ARVs : Potential problems in tropical countries
AZT (retrovir®): Be careful if anemia, for example, caused by HIV, malaria, ankylostomiasis, malnutrition, cotrimoxazole, hydroxyurea
ddI (videx®) d4T (zerit®): Be careful if polyneuritis, caused by HIV, isoniazid, dapsone, vitamin deficiency, ethylism, diabetes
- NRTIs: Adverse effects

AZT (zidovudine)	Retrovir®	Anemia Neutropenia Nausea Myopathy Headache
3TC (lamivudine)	Epivir®	Neutropenia Polyneuritis
ddI (didanosine)	Videx®	Pancreatitis, polyneuritis
ddC (zalcitabine)	Hivid®	Pancreatitis Polyneuritis Oral ulcerations
d4T (stavudine)	Zerit®	Pancreatitis Polyneuritis
ABACAVIR	Ziagen®	Rash, fever Shock Nausea

- NNRTIs: adverse effects

Nevirapine	Viramune®	Rash Hepatotoxicity
Efavirenz	Sustiva® Stocrin®	Neuropsychiatric disorders Sleep abnormalities Dizziness Rash

- Protease inhibitors: adverse effects

Indinavir	Crixivan®	Nephrolithiasis Arthralgias, paronychia, Dry skin, hair loss ↑ bilirubin
Ritonavir	Norvir®	Diarrhea Nausea Oral paresthesia
Saquinavir	Invirase® Fortovase®	Diarrhea
Nelfinavir	Viracept®	Diarrhea

- Long-term adverse effects of protease inhibitors
 - Hepatitis
 - ↑ Cholesterol
 - ↑ Triglycerides
 - Diabetes
 - Lipodystrophy (60-65 percent of patients)
 - Sexual dysfunction?
 - Atherosclerosis? Coronary insufficiency?
- ART adverse effects

	Class specific	ARV specific
NRTI	Mitochondrial toxicity (lactate acidosis, lipoatrophy?)	Nail pigmentation (ZDV) Hypersensitivity (abacavir)
NNRTI	Rash	CNS dysfunction (efavirenz) Severe hepatitis (nevirapine)
PI	Metabolic abnormalities Lipodystrophy Bleeding in hemophiliacs	Nephrolithiasis (indinavir) Diarrhea (nelfinavir, ritonavir, lopinavir) Rash (amprenavir)

Step 6. Discuss the management of particular adverse effects associated with certain drugs: 4. below. Use the algorithms in PowerPoint slides 28-34.
(20 minutes)

4. Management of side effects: see PowerPoint slides for algorithms on management of:

- ZDV-associated anaemia
- Didanosine-associated pancreatitis
- Nevirapine-associated rash
- Stavudine-associated polyneuropathy
- Efavirenz-associated rash
- Indinavir-associated nephrotoxicity
- Efavirenz-associated CNS effects
- Nelfinavir/ritonavir associated diarrhea:
 - Loperamide, calcium carbonate (500mg bid), psilium
 - Dietary advice: good fluid intake; food that may worsen diarrhea: coffee, alcohol, spicy food, high fat food, lactose rich food
 - Take into account patients' experience.
- Adequate hydration is essential to healthy body function.
Patients taking crivivan™ should drink at least 1.5 L (approximately 48 oz) of water or other liquids every day.

Step 7. Ask participants to break into small groups and discuss the following case studies using the questions as a guide. Ask one participant to record the main points from the discussion on a flip chart paper. Give them 15 minutes to break into groups and discuss the two cases.

Bring the participants together and ask each recorder to report on his or her group's discussion. Discuss any questions they may have.

(15 minutes)

CASE STUDIES

Case 1

A 45-year-old man with a previous history of seizure disorder is seen at the clinic. For the past two years he has been on combivir (lamivudine and zidovudine), one tablet two times a day, nevirapine 200mg bid and phenobarb 30mg in the morning and 60mg at night.

Recently the lab results show a fall in the CD4 count and a rise in the viral load. You decide to change therapy to stavudine 40mg bid, didanosine 400mg daily, nelfinavir 1.25mg bid and phenobarb as before. Two weeks later on review, the patient's wife complains to the doctor that the man is sleeping all the time and unable to work.

- a. *What might be the cause of patient's problem?*
- b. *What would you do?*

Case 2

A 35-year-old patient on 20 units of humulin (insulin) is started on zidovudine, lamivudine and indinavir. Three months later, on review, you observe the fasting blood sugar has gone up from 3.8mmol/l to 10mmol/l.

- a. *What do you think is happening?*
- b. *What would you do?*
- c. *Did the patient receive optimal treatment?*

ANSWERS

Case 1

- a. Nelfinavir(PI) is an inhibitor of cytochrome P-450 system, unlike nevirapine, which is an inducer. The high blood levels of phenobarb are a result of reduced activity of cytochrome system.
- b. Reduce dose of phenobarb and review.

Case 2

- a. Insulin resistance from the indinavir
- b. NNRTI; adapt insulin needed
- c. No, patient did not. Generate discussion on putting diabetics on PIs.

SESSION 5 Recommended First-Line Regimens in Adults

PURPOSE

In this session, participants will learn about approved antiretroviral agents and WHO-recommended first-line antiretroviral regimens.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Identify the drugs to be included in several first-line ARV regimens.
2. Discuss use of these regimens in reference to in-country guidelines and availability.

TIME:

45 minutes

Step 1. Discuss what therapy to begin with and how to begin: **1 and 2** below. Review the WHO guidelines of recommended therapies. Ask participants if these agents are available in their local situation and how the WHO guidelines compare with their country-specific guidelines. Discuss the differences.
(10 minutes)

1. What therapy to begin with:

- a. The only regimens potent enough to reduce viral replication drastically and to prevent the emergence of resistance and treatment failure for a significant amount of time involve a *combination of at least three antiretrovirals*.
- b. There are currently 16 approved ART agents for the treatment of HIV-1 infection (in the U.S.). These include six nucleoside reverse transcriptase inhibitors (NtRTI), three nonnucleoside reverse transcriptase inhibitors (NNRTIs) and six protease inhibitors (PIs). Thirteen of the drugs have been incorporated into WHO's guidelines: See Table B1, 5.1 below.

Table B1, 5.1: Approved Antiretroviral Agents Included in WHO's ARV Guidelines^a

Nucleoside reverse transcriptase inhibitors (NsRTIs)	Nucleotide reverse transcriptase inhibitor (NtRTI)	Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	Protease inhibitors (PIs)
Zidovudine (ZDV, AZT) ^b	Tenofovir disoproxil fumarate (TDF)	Nevirapine (NVP) ^b	Saquinavir (SQV) ^b
Didanosine (ddI) ^b		Efavirenz (EFZ) ^b	Ritonavir (RTV) (as pharmacoenhancer) ^b
Stavudine (d4T) ^b			Indinavir (IDV) ^b
Lamivudine (3TC) ^b			Nelfinavir (NFV) ^b
Abacavir (ABC) ^b			Lopinavir/ritonavir (LPV/r) ^b
a Approved and generally available in industrialized countries as of January 2002		b Approved for inclusion in WHO's Essential Drug List as of April 2002	

1. How to start therapy

- a. Use the simplest (that is, few pills a few times a day) cheapest and most effective (that is, potent enough to make a difference with the least number of side effects) three-drug combination as the first line therapy.
- b. Then select the next one or two combinations on the list as the second-line therapy to be used if or when the first line drugs fail.
- c. WHO's recommended first line therapies are as follows:

Table B1, 5.2: Recommended First-line Antiretroviral Regimens in Adults and Adolescents with Documented HIV Infection

Regimen	Pregnancy Considerations	Major Toxicities
d4T/3TC/NVP	Yes	d4T-related neuropathy, pancreatitis and lipoatrophy; NVP-related hepatotoxicity and severe rash
ZDV/3TC/NVP	Yes	ZDV-related GI intolerance, anaemia and neutropenia; NVP-related hepatotoxicity and severe rash
d4T/3TC/EFV	No	d4T-related neuropathy, pancreatitis and lipoatrophy; EFV-related CNS toxicity and potential for teratogenicity
ZDV/3TC/NVP	No	ZDV-related GI intolerance, anaemia and neutropenia; EFV-related CNS toxicity and potential for teratogenicity

Step 2. Ask participants to break into small groups and discuss the following case studies using the questions as a guide. Ask one participant to record the main points from the discussion on a flip chart paper. Give them 15 minutes to break into groups and discuss the cases.
(15 minutes)

CASE STUDIES

Case 1

A 35-year-old truck driver comes to the clinic complaining of persistent diarrhea that started five months ago. You conduct a lab test and stool exam and find that his lymphocyte count is 1200/mm³; cryptosporidium is found in the stool exam.

- a) How would you classify this patient?
- b) Would you start this patient on ARV therapy? Why or why not?
- c) If so, which regimen would you put him on?

Case 2:

A 24-year-old student presents for anonymous HIV testing. She was raped three months ago. Two months ago, she was seen in the clinic for fever, malaise, fatigue and swollen lymph nodes. At that time, she was diagnosed with influenza. Presently she has no complaints or symptoms. Her HIV test is positive. Her CD4 count is 550.

- a) How would you classify this patient?
- b) Was the diagnosis she received two months ago correct? If not, what would you assume the diagnosis to have been?
- c) Would you start this patient on ARV therapy? Why or why not?
- d) If yes, which regimen would you put her on?

Case 3:

A young woman who is three months pregnant comes to the clinic complaining of fever for over a month. From her previous record, you see that six months ago she weighed 54 kg. She now weighs 46 kg. She has a history of herpes zoster. You have no facilities to test the woman for HIV or do a CD4 count or lymphocyte count.

- a) How would you classify this patient and why?
- b) Would you start this patient on ARV therapy? Why or why not?
- c) If so, which regimen would you start her on?

- Step 3. Bring the participants together again and ask each recorder to report on his or her group's discussion. Discuss any questions they may have.
(20 minutes)

SESSION 6 Patient Follow-up and Monitoring ARV Therapy

PURPOSE

In this session, participants will learn about clinical and laboratory monitoring of patients on ART. This session addresses clinical, laboratory and efficacy monitoring; schedules for monitoring; and measures of toxicity and effectiveness.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Discuss clinical monitoring, including clinical and laboratory parameters to follow, barriers, specimen transport and personnel capacity.
2. Describe how to monitor for tolerability, efficacy, toxicity and resistance to ARV therapy.
3. Discuss recommended protocols for clinical monitoring.

TIME:

1 hour

PREPARATION:

Prepare a case study from your own experience of a patient with drug toxicity.

- Step 1. Explain the purpose and objectives of the session (see above).
(1 minute)
- Step 2. Present the information on clinical, laboratory and efficacy monitoring: 1. 1-b below.
(10 minutes)

1. Monitoring ARV therapy

Gather the following information:

- Clinical symptoms
- Detailed past and present history
 - Other medical problems
 - Other drugs, including herbs
- Thorough and regular physical examination

b. Laboratory

- Absolute minimum tests: HIV test, hemoglobin or hematocrit level
- Basic tests: WBC count, liver function tests (LFTs) and renal function tests (RFTs), blood sugar, lymphocyte count
- Desirable tests: CD4, amylase, bilirubin, lipids
- Optional: viral load
- Efficacy

Look for:

- Decrease or disappearance of symptoms
- Gain in body weight
- Decrease in frequency or severity of OIs
- Decrease of Kaposi's lesions
- Increase in total lymphocyte count
- Increase in CD4 count
- Sustained suppression of VL, if available

- Step 3. Present the information on how to carry out monitoring: 2. a below.
Stress the importance of conducting a physical exam at every visit.
Discuss the schedule for clinical monitoring. Ask participants if this is feasible in their local situation and what barriers or constraints they might encounter.
(10 minutes)
- Step 4. Present the information on laboratory monitoring for ART tolerance: 2. b below. Ask participants what laboratory tests for monitoring ARV therapy are available in their local situation. List these on a flip chart. In light of the responses, discuss the resources available and the limitations.
Discuss the lab resources and limitations, issues of specimen transport and personnel capacity. Based on this discussion, decide on a monitoring plan that works in their local situation.
(30 minutes)

Recommended Tiered Laboratory Capabilities for ARV Monitoring in Limited-Resource Settings^a

Primary health care centers (level 1)	District hospitals (level 2)	Regional referral centers (level 3)
Rapid HIVab testing	Rapid HIVab testing	Rapid HIVab testing
Hemoglobin (if ZDV is being considered for use) ^b	Capability to resolve indeterminate rapid HIVab test by second serological method	FBC and differential
Pregnancy testing ^d	FBC and differential	CD4+ cell count ^c
Referral for sputum smear for TB (if microscopy not available)	CD4 + cell count ^c	Full serum chemistries (including but not restricted to electrolytes, renal function, liver enzymes, lipids)
	ALT	Pregnancy testing ^d
	Pregnancy testing ^d	Sputum smear for TB
	Sputum smear for TB	Viral load testing ^e

a This table only considers testing that is desirable for proper monitoring of ARV toxicity, efficacy and two prominent concomitant conditions (pregnancy and TB). It is not meant to be comprehensive with respect to other diagnostic capabilities that are important in the comprehensive care of HIV-infected persons. Other resources are available for these considerations.

b In primary health care centers where laboratory facilities are not available or in the absence of laboratory-based haemoglobinometry, the WHO hemoglobin color scale can be used together with clinical signs to evaluate anaemia (more details at www.int/bct/)

c Scale-up of AAT under the 3-by-5 Plan does not require uniform CD4 testing availability but, because of the value of this test in patient monitoring, WHO will work with Member States to make this a reality.

d EFV should not be given to women of childbearing potential unless adequate contraception is assured, nor to women in the first trimester of pregnancy.

e Because of the cost and technical issues associated with viral load testing, this test is not currently recommended as part of the present treatment guidelines. However, it is hoped that more cost-effective technologies will allow regional referral centers to acquire this capability, given its utility in assessing treatment failure.

2. How to monitor

- a. For clinical and efficacy monitoring, it is very important to examine the patient at every visit. The monitoring schedule should be as follows:
 - First follow-up after one week, or earlier if there are side effects
 - Monthly visits thereafter, or more, if needed
 - At each visit, ask about symptoms, adherence, HIV and nonHIV-related problems, quality of life
 - Physical examination, body weight
- b. Laboratory monitoring for tolerance and toxicities of ART

Basic laboratory monitoring for recommended first-line ARV regimens at primary health care centres (level 1) and district hospitals (level 2)

Regimen	Laboratory assessment at baseline (pretherapy)	Laboratory assessment on therapy
d4T/3TC/NVP	Desirable but not required: CD4	Symptom-directed determination of ALT for toxicity CD4 q6-12 months, if available, for efficacy
ZDV/3TC/NVP	Recommended: Hgb Desirable but not required: FBC, CD4	Symptom-directed determination of Hgb, WBC, ALT for toxicity CD4 q6-12 months, if available, for efficacy
d4T/3TC/EFV	Pregnancy test (mandatory) Desirable but not required: CD4	Symptom-directed testing but none routinely required for toxicity CD4 q6-12 months, if available, for efficacy
ZDV/3TC/NVP	Pregnancy test (mandatory) Recommended: Hgb Desirable but not required: FBC, CD4	Symptom-directed determination of Hgb, WBC for toxicity CD4 q6-12 months, if available, for efficacy

- Frequency of blood chemistries
 - ALT after two weeks and one month, if NVP treatment or if abnormal ALT at baseline, or if the patient develops symptoms; in other cases, every three months
 - Hb every three months, or more frequently, if clinically indicated
 - Creatinine, glucose, amylases and lipids, when clinically indicated
- Desired CD4 and viral load changes during ART
 - Viral load decline of 1.5-2.0 logs in first month
 - Viral load decline to <50 copies/ml in 80-90 percent of patients at 24 weeks

Some clinicians use the following rates of CD4 increase to assess success of therapy, but these are only suggestive, and there is much individual variation. In patients with severe immune deficiency, it is likely that the rate of increase will be slower than that indicated.

 - Median CD4 increase 100-200 in first year
 - Median CD4 increase 100 in next years
- Total lymphocyte/CD4 count
 - Total lymphocytes: baseline and then every three months
 - CD4 count: at baseline and then every six months (this might vary according to national/site protocols)
- Viral load
 - Only when suspicion of treatment failure unrelated to nonadherence

Recommendations for Initiating ART in Infants and Children

CD4 testing	Age	HIV diagnostic testing	Treatment recommendation
If CD4 testing is available	< 18 months	HIV virological testing not available but infant is HIV antibody-seropositive (Note : HIV antibody test must be repeated at the age of 18 months to obtain definitive diagnosis of HIV infection)	WHO Pediatric Stage II and III disease with CD4 < 20% ^a WHO Pediatric Stage III (i.e. AIDS) irrespective of CD4 %
		Positive HIV virological test ^b	WHO Pediatric Stage II disease, with consideration of using CD4 < 20% to assist in decision-making ^{a,c}
	≥ 18 months	HIV antibody-seropositive	WHO Pediatric Stage I disease (i.e. asymptomatic), CD4 < 20% ^{a,d} WHO Pediatric Stage III disease, irrespective of CD4 %
		HIV antibody-seropositive	WHO Pediatric Stage II disease, with consideration of using CD4 < 15% to assist in decision-making ^{a,c} WHO Pediatric Stage I disease with CD4 < 15% ^{a,d}
If CD4 testing is not available	< 18 months	HIV virological testing not available but infant is HIV antibody-seropositive	Treatment not recommended ^e WHO Pediatric Stage III, irrespective of total lymphocyte count
		Positive HIV virological test	WHO Pediatric Stage II disease, with consideration of using total lymphocyte count < 2500/mm ³ to assist in decision-making ^f
	≥ 18 months	HIV antibody-seropositive	WHO Pediatric Stage III irrespective of total lymphocyte count WHO Pediatric Stage II disease, with consideration of using total lymphocyte count < 1500/mm ³ to assist in decision-making ^f
		HIV antibody-seropositive	

a A CD4 cell percentage < 20% corresponds to an absolute CD4 count of approximately < 1000/mm³ for children aged < 12 months and < 750/mm³ for children aged 12-18 months; CD4 < 15% corresponds to < 500/mm³ for children aged 1- 5 years and to < 200/mm³ for children aged > 6 years.

b HIV DNA PCR or HIV RNA amplification assays or immune complex dissociated p24 antigen assays.

c CD4 cell percentage is advisable to assist with determining the need for immediate therapy.

d If a child is asymptomatic and treatment is being initiated on basis of CD4 criteria, consideration should be given to performing a confirmatory CD4 assay if resources permit.

e Many of the clinical symptoms in the WHO Pediatric Stage II and III disease classification are not specific for HIV infection and significantly overlap those seen in children without HIV infection in resource-limited settings; thus, in the absence of virological testing and CD4 cell assay availability, symptomatic HIV-seropositive infants < 18 months of age should only be considered for ARV therapy in exceptional circumstances (e.g. child with a classic AIDS-defining opportunistic infection such as Kaposi's sarcoma, Pneumocystis carinii pneumonia or cryptococcal meningitis). If ARVs are given to a symptomatic HIV-seropositive infant in the absence of a definitive virological diagnosis, HIV antibody testing should be repeated at the of age 18 months to confirm infection status; ARV therapy should only be continued in infants with confirmed HIV infection.

f A total lymphocyte count of <2500/mm³ for children aged < 18 months or of <1500/mm³ for children aged ≥ 18 months can be substituted for CD4 % when the latter is unavailable and HIV-related symptoms exist. Its utility in asymptomatic children is unknown. In the absence of CD4 cell testing, therefore, asymptomatic HIV-infected children (WHO Pediatric Stage I) should not be treated because no other reliable marker is currently available in severely resource-constrained settings.

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3. HIV drug resistance

- a. Refers to a reduction in the ability of a drug, or a combination of drugs, to block HIV reproduction in the body. This reduction occurs because of the changes (or mutations) in the genetic structure of HIV resulting from the rapid and often inaccurate reproduction of new viral copies.
The best way to avoid the development of drug resistance is to keep HIV under control. The less virus there is in the body, the less likely it is that the virus will reproduce and mutate.
- b. Factors that can prevent HIV medications from controlling the virus are poor treatment adherence, poor drug absorption and varying pharmacokinetics (the individualized absorption, distribution, metabolizing and removal of drugs from the body).
- c. Testing for resistance
 - There are two ways to test for HIV drug resistance:
 - Genotypic testing: identifies mutations that are linked to the reverse transcriptase and protease genes of a person's HIV
 - Phenotypic testing: measures the growth of HIV in the presence of HIV drugs
 - Weaknesses and drawbacks
 - The tests measure only the dominant HIV strains that exist at the time of testing, not *minority* strains or strains that may be hiding in, for example, resting cells.
 - The tests should be performed when the patient is taking ARVs and no later than three weeks from stopping treatment (otherwise, the virus will likely have reverted to *wild type*).
 - The tests are difficult to interpret and often present conflicting results, particularly in patients who have had multiple regime failures.
 - The tests are costly.

Step 5. Present the information on drug level monitoring: 4. a-c below. Begin by stating that drug level monitoring is probably unavailable in their local situations, but it is important to understand that high peak levels or high drug exposure can be associated with toxicities.
(5 minutes)

4. Drug level monitoring

- a. At present, therapeutic drug monitoring (TDM) is infrequently performed outside research settings. Since this is a new and investigational area of HIV management, it seems unlikely to become widely available very quickly. Currently, British treatment guidelines recommend TDM in circumstances where providers are using doses other than those recommended by the manufacturer. You should also use TDM in cases of severe liver impairment and to manage toxicity. In patients with high peak levels, but no current evidence of toxicity, dosage reduction may be a strategy to prevent toxicity from developing.
- b. High peak levels or high drug exposure with the following drugs are associated with toxicities:
 - Ritonavir and triglyceride elevations, circumoral paraesthesia, diarrhea
 - Indinavir and kidney stones, colic and other urinary tract or kidney problems associated with indinavir crystals
 - Efavirenz and central nervous system toxicities such as vivid dreams, anxiety, feeling *stoned*High drug levels have not been clearly linked to other adverse effects of therapy.
- c. Summary: testing drug levels
 - Poor treatment adherence is a major cause of poor drug levels.
 - Interactions between drugs can influence drug levels.
 - Some people's bodies get rid of drugs faster than others.
 - Low drug levels in the blood may cause treatment to fail.
 - A small number of treatment centers are testing drug levels in people taking protease inhibitors.
 - Higher drug levels may mean greater anti-HIV activity but more severe and more frequent side effects.

Step 6. Present the case of drug toxicity that you have prepared (if you have time) and discuss.
(10 minutes)

SESSION 7 Drug Adherence and Strategies for Compliance

PURPOSE

In this session, participants will learn about the issues involved in promoting ARV drug adherence.

OBJECTIVES:

By the end of this session, the participants will be able to:

1. Describe the importance of good adherence and the consequences of poor adherence.
2. Describe effective strategies to promote adherence and discuss how to help patients cope with nontoxic side effects of ARVs.
3. Demonstrate ways to counsel patients about adherence.
4. Develop a tool or questionnaire to measure adherence in their local context.

TIME:

1 hour and 40 minutes

PREPARATION:

- 1) For the exercise in Step 4, on the factors influencing adherence, prepare four flip chart papers with the following headings:

Patient-Related Factors	Provider-Related Factors
Regimen-Related Factors	Other Factors
- 2) For Step 6, make copies of the role play, and cut the page so that the three roles are on separate pieces of paper. Make enough copies for each person to have a copy of the particular role he or she will be playing.

REFERENCES:

Bartlett, J.A. *Addressing the Challenges of Adherence*. JAIDS Vol 29, Supp1, Feb 1, 2002.

Mildmay International/FHI. *Antiretroviral Therapy: A Course for Doctors*. Sept. 2002.

British HIV Association/Medical Society for the Study of Venereal Diseases. *Guidelines on Provision of Adherence Support to Individuals Receiving Antiretroviral Therapy*. Draft 2002.

WHO. *Scaling Up Antiretroviral Therapy in Resource Limited Settings: Guidelines for Public Health Approach*. June 2002.

- | | |
|---------|--|
| Step 1. | Explain the purpose and objectives of the session (see above).
(2 minutes) |
| Step 2. | Present the definitions and information on measuring adherence, including the general comments: 1-3 below.
(15 minutes) |

1. Definitions of adherence and compliance

- Adherence is the term used to describe the patient's taking drugs correctly in terms of dose, frequency and time.
- In adherence, the patient is involved in deciding whether or not to take the drugs.
- Compliance means the patient does what he or she has been told to do by the doctor/pharmacist.

2. Measuring adherence

- Directly Observed Therapy (DOT): theoretically associated with 100 percent adherence; labor intensive and impractical outside institutional setting
- Electronic pill bottle monitoring, for example, Medication Event Monitoring Systems (MEMS) is expensive. A patient can remove doses but then not take them. It cannot be used on blister packs.
- Patient self-report: convenient and inexpensive
- Pill count: labor intensive
- Plasma drug levels: objective measure
- Pharmacy records/prescription refill monitoring
- Viral load assay: not a primary measure of adherence; surrogate marker; can be helpful when used with patient self-reports

3. Adherence: general comments

- One of the key determinants of success
- Poor adherence leads to virologic failure, evolution of drug resistance, and subsequent immunologic and clinical failure.
- Important to counsel patients carefully before initiating ART; involves clinicians, nurses, pharmacist, family, and others
- Do not start ART on first clinic visit. You need to counsel patient in treatment adherence to maximize the adherence.
- Once treatment has started, you need to monitor and provide support continuously.

- | | |
|---------|--|
| Step 3. | Tape or place the prepared flip chart papers with the four factors affecting adherence on the wall at the front of the room. Ask each participant to name one factor that may influence adherence. Write the responses on the appropriate flip chart. Add any factors from the lists below that participants may have missed. Discuss any questions or comments they may have.
(15 minutes) |
|---------|--|

4. Factors affecting adherence

- a. Patient-related factors
 - Patient readiness and commitment
 - Forgetfulness
 - Being away from home
 - Lifestyle
 - Depression
 - Cultural elements
 - Socioeconomic elements
 - Patient's lifestyle and fitting ARVs into it
- b. Provider-related factors
 - Provider readiness (knowledge, skills)
 - Counseling
 - Patient education
 - Medication alerts, for example, charts and diaries
 - Adherence team
 - Provider support
- c. Regimen and drug-related factors
 - Pill burden
 - Frequency of dosing (No more than twice-daily regimens)
 - Side effects
 - Food restrictions
 - Drug interactions
 - Storage
 - Packaging of pills (Use coblister packs when available.)
- d. Other factors
 - Cost

Step 4. Present the information on adherence intervention strategies: 5 below. Ask participants to contribute examples of how they could implement each strategy in their setting.
(20 minutes)

5. Adherence intervention strategies

Educate and motivate, provide basic drug information, and discuss importance of adherence, timing of medications, drug interactions and the like

- Simplify regimen
- Tailor treatment to patient's lifestyle
- Prepare for and manage side effects
- Use an adherence team
- Address patient-related issues
- Recruit an adherence monitor
- Provide adherence promoting devices
- Use home-based care staff to promote adherence
- Use adaptation of directly observed therapy for a time to be determined

- Step 5. Ask participants to break into groups of three to practice counseling the patient on adherence using the role play below. One person should play the client, one the clinician and one the observer. Give a copy of the appropriate text to each one. Tell them they have 30 minutes for this activity.
(30 minutes)
Note: Adherence counseling involves not only being able to convey the technical aspects of adherence, but having the skills to make patients relax, feel comfortable and have confidence in a provider. The latter may require more time.
- Step 6. Bring the groups back together and discuss, from each person's point of view, what worked and didn't work, the problems they encountered and suggestions for improving their counseling skills.
(20 minutes)
(Total time: 50 minutes)

Role Play: Setting the Stage for Adherence

CLIENT

You are a 43-year-old schoolteacher. You were diagnosed as HIV positive three years ago. You have not wanted to think about it, so you have not returned to the clinic for checkups as advised, and you have been well—until last week. Today you want to see a doctor because for the past week, you have been having difficulty swallowing and you noticed that there are sores in your mouth.

You are feeling anxious, but you want help. You fear you will have to take many pills, something you have never liked to do and something that might mean you will have to tell your wife you are HIV positive.

CLINICIAN

The patient is a 43-year-old schoolteacher who was diagnosed with HIV three years ago. He has not been to see a doctor in three years. He says he has been feeling healthy. On examination, he has oral thrush and his history revealed he has had difficulty swallowing.

You prescribe fluconazole for the oral/esophageal candidiasis. You also think he should start on zidovudine, lamivudine and efavirenz. You plan to order the lab work and to have him come back next week.

Before you begin, think about the following:

1. How should you begin the discussion about the drugs and issues that would affect adherence?
2. What do you say to start the discussion?
3. What issues do you bring up during the discussion?
4. What follow-up do you recommend?

OBSERVER

1. What are the verbal and nonverbal skills demonstrated by the clinician?
2. What might the clinician use that he or she did not?
3. What is the client's reaction to the clinician's approach?
4. What major points are addressed that are important to compliance? (See points under "Strategies" in # 5, above.)
5. What major points are missed?
6. Develop a locally appropriate adherence measure instrument.

Validated patient questionnaires have proven to be one of the more reliable, easily instituted tools for monitoring adherence in the outpatient setting. The questionnaire should record information about tolerance, side effects and toxicity.

Each country and/or health center may develop its own brief, culturally appropriate questionnaire; one standardized tool may not be applicable to all regions and cultures.

- Step 7. With the whole group, discuss developing a tool to measure adherence. Record their ideas and suggestions on a flip chart; then discuss the pros and cons of each one. Tools may include:
- Three-day recall
 - One-week recall (patient self-report)
 - Pharmacy records to support patient self-report
 - A questionnaire that records information about tolerance, side effects and toxicity

(10 minutes)

SESSION 8 Why and When to Change Therapy

PURPOSE

In this session, participants will learn about drug resistance, reasons for changing an ART regimen and which second-line regimens to use.

OBJECTIVES:

By the end of this session, participants will be able to:

1. Discuss the reasons for changing therapies.
2. Identify choices for second-line ARV regimens.
3. Describe what limitations there may be to selecting alternative therapy.

TIME:

1 hour and 30 minutes

- | | |
|---------|--|
| Step 1. | Explain the purpose and objectives of the session (see above).
(3 minutes) |
| Step 2. | Present the information on when to change therapy: 1 below.
Ask the participants if they have any questions or comments.
(15-20 minutes) |

1. Situations in which regimen or individual drug should be changed

a. Treatment failure

- Defined as:
 - **Clinical failure:** clinical disease progression signaled by the development of new symptoms, symptoms that do not disappear, or an OI or malignancy when the drugs have been given sufficient time to induce a protective degree of immune restoration
 - **Immunologic failure:** a fall in the CD4 counts > 30 percent from the peak value or a decline equivalent to or less than the pretherapy baseline
 - **Virologic failure:** failure to achieve undetectable viral load levels after 3-6 months; repeated, continual, detectable viremia indicative of incomplete viral suppression; the reappearance of a detectable viral load
- Reasons for treatment failure:
 - ARV potency is insufficient
 - Drug levels are insufficient (including cellular mechanisms)
 - Poor adherence
 - Preexisting viral drug resistance
 - Poor prescribing

Clinical and CD4+ Cell Count Definitions of Treatment Failure in HIV-Positive Adults and Adolescents

Clinical signs of treatment failure	CD4 cell criteria for treatment failure
<ul style="list-style-type: none"> • Occurrence of new opportunistic infection or malignancy signifying clinical disease progression. This must be differentiated from the immune reconstitution syndrome which can occur in the first three months following the initiation of ART.^a The latter does not signify treatment failure, and the opportunistic infection should be treated as usual, without changes in the antiretroviral regimen. • Recurrence of previous opportunistic infection.^b • Onset or recurrence of WHO Stage III conditions (including but not restricted to HIV wasting, chronic diarrhea of unknown etiology, prolonged fever of unknown etiology, recurrent invasive bacterial infections, or recurrent/persistent mucosal candidiasis). 	<ul style="list-style-type: none"> • Return of CD4 cell to pre-therapy baseline or below without other concomitant infection to explain transient CD4 cell decrease.^c • > 50% fall from therapy CD4 peak level without other concomitant infection to explain transient CD4 cell decrease.^c

a Immune reconstitution syndrome (IRS) is characterized by the appearance of signs and symptoms of an opportunistic disease a few weeks after the start of potent antiretroviral therapy in the setting of advanced immunodeficiency, as an inflammatory response to previously subclinical opportunistic infection. It is also possible that this immunologic reconstitution may lead to the development of atypical presentations of some opportunistic infections.

b Recurrence of TB may not represent HIV disease progression, as reinfection may occur. Clinical evaluation is necessary.

c If patient is asymptomatic and treatment failure is being defined by CD4 cell criteria alone, consideration should be given to performing a confirmatory CD4 cell count if resources permit.

- What to do in the case of treatment failure:
 - Check treatment regimen
 - Check adherence with ARVs
 - Perform resistance testing, if available
 - Monitor therapeutic drug, if possible

Adherence	Undetectable viral load after 3 months
> 95 percent	100 percent
90-95 percent	64 percent
80-90 percent	50 percent
70-80 percent	25 percent
<70 percent	6 percent

b. Toxicity:

Plasma drug levels: objective measure

- Drug causing the toxicity cannot be identified, and/or low-grade, intolerable side effects compromise adherence. (See session 4 on drug interactions and ADRS: side effects and toxicities, for details.)
- Clearly-defined toxicity to a single drug

This permits drug substitution without compromising the overall regimen. For example, you can substitute d4T for ZDV when ZDV-related symptoms or anemia appear or NVP for EFV when EFV-related central nervous system symptoms are unremitting.

If an interruption in therapy is indicated to permit resolution of toxicity, suspend the entire regimen temporarily to prevent the emergence of drug resistance.

Major Potential Toxicities of First-Line ARV Regimens and Recommended Drug Substitutions

Regimen	Toxicity	Drug substitution
d4T/3TC/NVP	<ul style="list-style-type: none"> • d4T-related neuropathy or pancreatitis • d4Y-related lipoatrophy • NVP-related severe hepatotoxicity • NVP-related severe rash (but not life-threatening) • NVP-related life-threatening rash (Stevens-Johnson syndrome) 	<ul style="list-style-type: none"> • Switch d4T → ZDV • Switch d4T → TDF or ABC^a • Switch NVP → EFV (except in pregnancy) • Switch NVP → EFV • Switch NVP → PI^b
ZDV/3TC/NVP	<ul style="list-style-type: none"> • ZDV-related persistent GI intolerance or severe hematological toxicity • NVP-related severe hepatotoxicity • NVP-related severe rash (but not life-threatening) • NVP-related life-threatening rash (Stevens-Johnson syndrome) 	<ul style="list-style-type: none"> • Switch ZDV → d4T • Switch NVP → EFV (except in pregnancy; in this situation switch to NFV, LPV/r or ABC) • Switch NVP → EFV • Switch NVP → PI^b
d4T/3TC/EFV	<ul style="list-style-type: none"> • d4T-related neuropathy or pancreatitis • d4T-related lipoatrophy • EFV-related persistent CNS toxicity 	<ul style="list-style-type: none"> • Switch d4T → ZDV • Switch d4T → TDF or ABC^a • Switch EFV → NVP
ZDV/3TC/NVP	<ul style="list-style-type: none"> • ZDV-related persistent GI intolerance or severe hematological toxicity • EFV-related persistent CNS toxicity 	<ul style="list-style-type: none"> • Switch ZDV → d4T • Switch EFV → NVP

^a Switching off d4T typically does not reverse lipoatrophy but may slow its progression. TDF and ABC can be considered as alternatives, but availability is currently limited in resource-constrained settings. In the absence of TDF or ABC availability, ddI or ZDV are additional alternatives to consider.

^b PI can be LPV/r or SQV/r. IDV/r or NFV can be considered as alternatives.

- Step 3. Ask participants to name a second-line regimen and write this regimen on a flip chart. Go around the room until you have all their answers.
(5 minutes)
- Step 4. Describe the WHO-recommended second-line regimens given below and compare them to the participants' responses. Note and discuss any differences. Ask them what their in-country guidelines are for these therapies.
(15 minutes)
- Step 5. Briefly discuss the limitations to selecting alternative therapy: 3 c below.
(5 minutes)
Total time: 25 minutes

2. Recommended second-line regimens in adults and adolescents

a. Reasons for altering an initial ART regimen include:

- Side effects interfering with activities of daily living and leading to poor adherence
- Drug toxicity
- Occurrence of active tuberculosis or pregnancy
- Treatment failure
- WHO-recommended second-line regimens (See Table B1, 8.1 below.)

Table B1, 8.1: Recommended Second-Line Regimens in Adults and Adolescents

For failure on:	Change to:
d4T or ZDV	TDF or ABC
+	+
3TC	ddl ^a
+	+
NFV or EFV	LPV/r or SQV/r ^b

a. Dose of ddl should be reduced from 400 mg to 250 mg when coadministered with TDF.

b. LPV/r and SQV/r require secure cold chain. NFV can be considered as an alternative in resource-limited settings without cold chain.

c. Limitations to selecting alternative therapy

- Drug resistance:
 - If you do not use viral load and resistance monitoring to define treatment failure, virological failure is likely to have been present for an extended period by the time you detect it.
 - Viral replication over time leads to the evolution of more drug resistant mutations, and it will be difficult to know which drugs have been compromised without drug resistance testing.
- How to avoid drug resistance:
 - Triple therapy
 - Optimal adherence
 - Monitoring for treatment failure
 - Switch all ARVs in the case of treatment failure
- Stop ARVs in the presence of:
 - Serious adverse effects
 - Inefficient treatment, for example, monotherapy
 - Nonadherence
- Remember:
When ARVs are stopped, viral load will increase, leading to an increased risk of HIV transmission.

Step 6. Ask participants to break into small groups and discuss the following case studies using the questions as a guide. Ask one participant to record the main points from the discussion on a flip chart paper. Give them 15 minutes to break into groups and discuss the cases.
(15 minutes)
Bring participants together to review the group discussion.
(20 minutes)

CASE STUDIES

Case 1

A 34-year-old man has been on stavudine, lamivudine and nevirapine for the past four years. On his last visit, the CD4 count had fallen from 300 cell/mm³ to 200 cells/mm³ and the viral load had risen from undetectable levels to 50,000 copies/ml.

- a. What do you think is happening to the patient?
- b. What possible regimen can you give to the patient, based on your local situation?

Case 2

A 30-year-old teacher comes to you; he was recently diagnosed with HIV infection. He complains of difficulty in swallowing and loss of weight. He has no other complaints and no fever.

Medical History

Herpes zoster, six years ago

Findings on physical exam

Weight loss < 10 percent of body weight

Dysphagia from oral candidiasis

Lab test results

No CD4 lymphocyte count available

Hemoglobin 9mg/dl

Leukocytes 5200 10⁹/l

Lymphocytes 15 percent

Total lymphocytes 780 10⁹/l

ALT 200 U/l

Plan

You give him fluconazole 200mg x 14 days to treat the oral candidiasis.

Start him on a regimen of efavirenz/stavudine/epivir (EFZ/d4T/3TC).

- a. Is this an appropriate regimen to begin with?
- b. Why or why not?

Continuing case situation

After one month, he is experiencing nausea and has no appetite. His lab results show:

Hemoglobin 9.2 mg/dl

AST 450 U/l

ALT 465 U/l

- a. What do you think is happening to this patient?
- b. What would you do next?

Continuing case situation

You decided to stop efavirenz and continue stavudine epivir for three days.

You do a control liver test after one month, with the following test results:

ALT: 120 U/l

AST: 130 U/l

a. What do these lab results tell you?

b. What do you do next?

Continuing case situation

You start the patient on indinavir and continue with stavudine/epivir. After one month, you repeat the lab tests, with the following results:

ALT: 125 U/l

AST: 140 U/l

a. What is your conclusion?

ANSWERS

Case 1:

What do you think is happening to the patient?

There may be a problem with adherence. If patient is adherent, then it comes from treatment failure.

What possible regimen can you give to the patient based on your local situation?

PI-containing regimen with completely new NRTIs

Case 2:

What do you think is happening to this patient?

This may be a toxic effect from NNRTI or an immune reconstitution syndrome.

What is your conclusion?

The abnormal liver tests were probably a toxic effect of the NNRTI and not an immune reconstitution syndrome in a patient with HIV/hepatitis coinfection.

References

PART A: MODULE B1

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