

Module A4

Antiretroviral Therapy: A Brief Introduction



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Session 1: Setting up the Antiretroviral (ART) Component

In this session, participants learn about setting up a care program with ART including the essential elements of the ART component, the steps involved in developing these essential elements and the critical areas for organization and program development. They also learn about integrating the principles of chronic disease management so that care and treatment are sustainable.

Session 2: Brief Introduction to ART

Participants learn about ART, including the goal and basic principles of therapy and the WHO recommendations on: what therapy to begin with and when to change therapy, the types of therapies and their modes of action, WHO-recommended first-line ARV regimens, adherence issues, monitoring ART and drug interactions. The session also covers treatment options for patients who fail therapy, including WHO-recommended second-line regimens, barriers to treatment and research treatment approaches.

Session 3: Management of Drug Side Effects

Participants review the major side effects of antiretroviral drugs and of some of the drugs given to prevent and treat OIs; they learn how to advise patients in managing these symptoms.

Session 4: Case Studies: Managing Patients with Multiple Issues

Participants will work on two case studies of patients with multiple issues to apply what they have learned in Module 2 about managing patients with HIV-related diseases.

SESSION 1 Setting up the Antiretroviral (ART) Component**PURPOSE**

In this session, participants will learn about setting up a care program with ART, including the essential elements of the ART component, the steps involved in developing these essential elements and the critical areas for organization and program development as well as chronic disease management, so that care and treatment are sustainable.

This session builds on session 4 of Module 1 *Programming Comprehensive Care for People living with HIV/AIDS* (the components of comprehensive care, service delivery across a continuum from facility to community and back and the principles of chronic disease management) by outlining the practical aspects of setting up the ART component of care. A case study of FHI's experience in this area complements this session.

OBJECTIVES:

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

1. Describe the process of setting up the ART component of an HIV care program, including assuring HIV counseling and testing (C&T) services; reorganized service delivery and referrals; trained clinicians; a basic medical records system; access to laboratory services and a secure, consistent supply of affordable antiretroviral drugs.
2. Plan the necessary steps for developing the essential elements of the ART component.
3. Discuss critical areas for program development to ensure sustainability and implement additional components of care and support.
4. Discuss how they might introduce or strengthen an antiretroviral therapy program in the context of comprehensive HIV/AIDS prevention, care and support in their local situations.

TIME:

1 hour and 30 minutes

- Step 1. Explain the purpose and objectives of this session (see above).
- Step 2. Ask participants what they think might be the essential elements of an ART program and write their responses on a flip chart paper. Discuss their responses and add any information they may have missed from A. 1. a-e below.
(12 minutes)

Family Health International, Management Sciences for Health (RPM Plus), John Snow, Inc. (Deliver Project) and others have several tools available, or in development, for assessing a site with respect to the essential elements of an ART program and determining what is needed to prepare the site to deliver ART. Below is a brief outline of what is needed for setting up the ART component of comprehensive care.

A. Setting up the ART component

1. What are the essential elements of an ART program?

- a. **Access to HIV counseling and testing (C&T)** services, either as a voluntary counseling and testing unit within a health facility, as a stand-alone center or integrated into clinical care provision is essential. HIV C&T identifies HIV-infected individuals and provides support in accessing health care services, coping and living positively, and preventing transmission and reinfection.
- b. **Trained clinicians** who can diagnose and treat common HIV-related illnesses and manage ART, observing the principles of chronic disease management and in accordance with national or international guidelines and standards are also required. Health care services include doctors, clinical officers and nurses who diagnose, treat and manage opportunistic infections (OIs) and drug side effects to resolve illness and promote quality of life. They determine the appropriateness of ARVs in terms of the individual's HIV disease status, counsel on treatment adherence, prescribe the regimen, provide continual monitoring of effectiveness and manage secondary effects of the drugs.
- c. **A basic medical records system** that includes access to clinical data, facilitating management of HIV over time (lifetime patient monitoring), as well as access to disease surveillance data
- d. An ART program must have access to **laboratory services** capable of doing routine laboratory tests, such as complete blood count, liver function tests, renal function tests and, if possible, CD4 count or as alternative, total lymphocyte count (TLC). In some situations, the ability to measure viral load will be important. Laboratory tests are used for baseline patient assessment, monitoring the patient's response to ARVs, including treatment effectiveness and adverse drug effects, as well as diagnosis of HIV-related illnesses and treatment response
- e. **A secure, consistent supply of affordable antiretroviral drugs**, as well as drugs to treat HIV-related illnesses, palliation and prophylaxis for certain opportunistic infections is required. ARVs must be taken for life and come as a combination of drugs. Assured drug availability and affordability is necessary for a continuous and ready supply of the prescribed regimens.

Step 3. Present the information on the necessary planning steps to start ART: 2. a-e below. Answer any questions participants may have.
(10 minutes)

2. What are the necessary planning steps to start ART?

The following questions raise issues to consider. They are not necessarily sequential and can occur simultaneously.

- a. Is there a referral system between HIV counseling and testing services and clinical care provision?
 - If accessible C&T services do not exist, identify, or, if necessary, create the capacity to diagnose HIV.
 - Create linkages to refer HIV-infected individuals needing care and support to appropriate services.

- b. Does the health care staff have the capacity (knowledge, skills and attitude) to provide HIV care that includes managing opportunistic infections and the safe and effective use of ARVs?
 - Provide training to staff, including physicians, nurses, counselors, pharmacists, laboratory technicians and nutritionists on ART, management of HIV disease and adherence counseling.
 - Provide follow-up supervision.

- c. Does a functional medical records system exist?
 - Provide technical assistance for developing a data-management system for long-term patient monitoring according to the principles of chronic disease management.
 - Is it easy for the clinician to retrieve the patient's record at the time of the patient's visit?

- d. What facility has laboratory services with the capacity to perform the essential tests for ART management?
 - Finalize an agreement for lab services with this facility, including a mechanism for the safe and timely transport of lab specimens and specifications for timely reporting of lab results.

- e. Is there a drug management system in place that includes a mechanism for ordering, storing, securing and distributing ARVs?
 - If yes, finalize an agreement to procure ARVs, including procedures for ordering, securing storage, assuring consistent supply, monitoring of supply and dispensing drugs to patients.
 - If not, investigate preferential pricing for ARVs and establish a system for reliable procurement, storage and dispensing of drugs.

- f. Is the clinic site set up to accommodate patient appointments and continuity of care?
 - Is there a system that allows for following a patient by the same team over time, or at a minimum, by the same physician?
 - Are there regular clinic days and a consistent location for HIV care? Is there a place that ensures privacy for the patient-physician interaction?

Step 4. Ask participants what other elements they think are critical for comprehensive HIV care. List their responses on a flip chart sheet. Discuss their responses and add any elements they may have missed from 3. a-g below.
(10 minutes)

3. As a health care site develops the essential elements of ART, what other elements are critical for comprehensive HIV care?

As health care facilities develop the essential elements outlined to provide ART, initiate plans to assure sustainability and to implement additional components of care and support. Critical areas for program development are:

- a. Involve PLHA and community groups throughout the process: have advisory committees and stakeholder groups participate in developing community treatment preparedness and care services.
- b. Develop national standards and guidelines for clinical HIV management, including C&T, prevention and management of OIs (including tuberculosis) and use of ART, if guidelines do not exist.
- c. Establish policies on charges for laboratory tests, clinic visits, OI drugs and ART.
- d. Develop standard operating procedures for HIV testing and counseling, universal precautions, post-exposure prophylaxis, ART eligibility, patient follow-up and referrals within and across services.
- e. Create or expand a functional referral system between clinical care and community support services to link clients and PLHA. The objective is to achieve a continuum of care and address a variety of needs, including nutrition, mental health, legal and economic support, palliative care and psychosocial and spiritual support.
- f. Strengthen capacity of health care system based on initial assessments; for example, improve data management and health commodity management, upgrade infrastructure and expand HIV services.
- g. Develop and implement a monitoring and evaluation plan.
- h. Maintain continual capacity building and support of staff through training, monitoring and supervision.

Step 5. Present the ART program examples using FHI's experience in introducing antiretroviral therapy (ART) in resource-poor settings. See HANDOUT, Table 1 at the end of the session.

(20 minutes)

Step 6. If you have a very large group or you have several participants from different countries or localities, you could ask them to break into small groups and discuss the questions. Then have them come together and present their plans to the entire group.

Ask participants how they might introduce or strengthen an antiretroviral therapy program in the context of comprehensive HIV/AIDS prevention, care and support in their local situations. Ask them to select a location they think is appropriate and discuss how they would go about setting up an ART program there, using the following questions as a guide:

What facilities are available in this location?

What initial sources of drugs are available to you?

What services are currently available in this location?

Are any guidelines in place?

In addition to the intervention facilities, what other resources are available to you?

(40 minutes)

Total time: 60 minutes

PROGRAM EXAMPLE

Introducing antiretroviral therapy programs in the context of comprehensive HIV/AIDS prevention, care and support: an example of what is being done in three African countries

1. Family Health International (FHI) has set out to introduce antiretroviral therapy (ART) in resource-poor settings within the context of comprehensive HIV/AIDS prevention, care and support.
 - a. The first ART learning sites are in Ghana, Kenya and Rwanda.

Each program is geographic in focus, allowing multiple entry points to care and treatment. Each fosters a close collaboration between national, district and private sector entities and coordinates activities among clinical care facilities, community support systems and NGOs in the selected communities. The U.S. Agency for International Development (USAID) is the primary funder; additional support comes from FHI and the U.K. Department for International Development (DFID).

- b. The guiding principles in each program include:
 - Making a commitment to community preparedness
 - Facilitating communication among the government, NGOs, PLHA and clinical care sectors
 - Ensuring comprehensive care that addresses client needs along a continuum of care
- c. The programs involve various levels of the health care system
 - In Kenya, the program is in an urban and a semiurban area and involves a provincial tertiary care referral hospital, a government referral hospital, and two semiprivate and government primary care clinics.
 - In Rwanda, the program is at a mission hospital, an urban mission health clinic and will reach eight rural health centers.
 - In Ghana, the program is at a district government hospital and a mission hospital, both in a semirural area near the capital city; it will soon expand to teaching hospitals in Accra and Kumasi.

VCT was operational in the Kenya and Rwanda settings when the treatment program was introduced, whereas in Ghana, part of the program's task was to set up VCT services in the district. Prevention of mother-to-child transmission (PMTCT) services are operational in all three sites.

- d. In all three sites, national guidelines on opportunistic infections (OIs) and ART have only recently been developed. Standard operating procedures for each site are consistent with the national guidelines; in Kenya and Ghana the programs played a collaborating role in developing the guidelines.

The following tables summarize the program details in Kenya, Ghana and Rwanda.

HANDOUT Table A4, 1.1: Summary of FHI's Antiretroviral Therapy Programs

	Ghana	Kenya	Rwanda
Location	Manya Krobo and Yilo Krobo Districts (semirural districts in the eastern region)	Mombasa (coastal city)	<ul style="list-style-type: none"> Kabgayi District (rural) Kigali (capital city)
Facilities	<ul style="list-style-type: none"> Atua Government Hospital: district hospital Semiurban: 123 beds, 162 staff St. Martin's Catholic Hospital: mission hospital Semiurban: 84 beds, 100 staff Korle-Bu Teaching Hospital: major university/teaching hospital in Accra Komfo Anokye Teaching Hospital: major university/teaching hospital in Kumasi 	<ul style="list-style-type: none"> Coast Provincial General Hospital: provincial tertiary referral hospital Urban: 700-bed, 395 HCWs on staff Port Reitz District Hospital: government referral hospital Mkomani-Bomu Clinic: semiprivate primary health care clinic Semiurban: outpatient clinic, 11 HCWs on staff Magongo Health Center: local government primary health care clinic Semiurban: ambulatory care, 6 HCWs on staff 	<ul style="list-style-type: none"> Kabgayi District Hospital: mission hospital Urban: 400-bed Health centers (8) in the rural district of Kabgayi Biryogo Medical and Social Center Mission health clinic serving the poorest in Kigali
HIV Prevalence	National: 4 percent (UNAIDS, 2002) Site Prevalence: 8-14 percent	National: 15 percent (UNAIDS, 2002)	National: 8.9 percent (UNAIDS, 2002)
Initial Sources of Drugs (# of patients)	<ul style="list-style-type: none"> FHI: 100 USAID: 200 Global Fund: 1,700 planned 	<ul style="list-style-type: none"> FHI: 120 USAID: 300 Global Fund: expected 	<ul style="list-style-type: none"> FHI: 60 USAID: 300 Global Fund: expected Clinton Foundation: expected
ARV Start Date	May 30, 2003	May 30, 2003	February 27, 2003
Existing Services (at time of start-up)	<ul style="list-style-type: none"> National pilot PMTCT program supported by UNICEF at Atua and St. Martin's hospitals Home-based care: limited HBC program through St. Martins hospital 	<ul style="list-style-type: none"> PMTCT Services: Port Reitz VCT: Port Reitz, Mkomani-Bomu and Magongo Clinics (established through IMPACT subagreement) Clinical Care: preventive therapy for TB and OIs at Mkomani-Bomu and Magongo Clinics. HIV clinic at CGPH Home-based care (Pathfinder/COPHIA) 	<ul style="list-style-type: none"> Treatment & Research AIDS Center (TRAC, formerly NACP) supports ART at 3 hospitals. Currently 500 are receiving ART. Clinical care: TB and OI preventive therapy offered at Kabgayi District Hospital. PMTCT: June 2002, Kabgayi launched PMTCT program with Kabgayi Health Center (ANC offered here). IMPACT-supported PMTCT services at Biryogo. VCT: Kabgayi District Hospital and IMPACT-supported VCT at Biryogo PLHA Groups: Duteraninkunga at Kabgayi and Ihumure at Biryogo

HANDOUT Table A4, 1.1 (cont.)

	Ghana	Kenya	Rwanda
Guidelines	<ul style="list-style-type: none"> National Guidelines on ART, 2002 National Guidelines on OIs, 2002 National Guidelines on VCT being finalized (2003) 	<ul style="list-style-type: none"> National Guidelines on ART, 2002 National Guidelines on OI, 2002 National Guidelines on VCT, 2001 	<ul style="list-style-type: none"> National Guidelines on ART, 2002 (2nd edition) National Guidelines on OIs, 2002 National Guidelines on VCT, 2002
FHI's Role	<ul style="list-style-type: none"> Provide technical assistance in developing national guidelines on HIV clinical management and ART. Collaborate with Ministry of Health, District Health Services and health facilities to develop and/or expand VCT, clinical care and PMTCT services. Leverage resources and secure additional funds to support existing program as well as expansion (USAID, DFID, Global Fund). Organize trainings for NGO staff and HCWs on VCT, PMTCT, clinical care, clinical management of OIs and TB, antiretroviral therapy and adherence. Facilitate development of a BCC strategy for care. Support refurbishment and upgrading of laboratory and expansion of clinical facilities. Fund, design and co-teach workshops on OI and ART for national audience of providers. Develop client referral systems. Strengthen data management system and analysis. 	<ul style="list-style-type: none"> Provide technical assistance on development of national guidelines on HIV clinical management and ART. Develop site assessment tools to assess accessibility, capacity and quality of the 4 sites (including laboratory) identified to provide ART and determine the needs for training, equipment and other support. Train health care providers on clinical management of OIs and TB, antiretroviral therapy and adherence. Develop client referral systems. Strengthen the capacity of the laboratory services to provide quality ART services, including training of laboratory technicians in procedures for clinical management of HIV patients, including ARV monitoring. Develop health literacy campaign on adherence, early-treatment seeking and patient education materials on ART and OI treatment. Strengthen data management system and analysis at the 4 sites, including staff training in data collection methods, analysis and reporting related to ARV management. Provide ART to eligible patients over a five-year period, and develop a client monitoring system and surveillance for drug resistance. Sensitize and strengthen communities and PLHA support groups in HIV/AIDS comprehensive care, including ART. 	<ul style="list-style-type: none"> Provide technical assistance on development of national guidelines on HIV clinical management and ART. Conduct an assessment of the two facilities to determine availability of human resources, training needs, infrastructure (including laboratory), inventory of HIV-related drugs and commodities, capacity and functionality of drug management systems, referral networks and capacity of potential local CBO partners. Organize trainings for health care providers on clinical management of OIs and TB, antiretroviral therapy and adherence. Develop counseling training program in collaboration with TRAC. Establish a mechanism for the follow up and monitoring of patients receiving ART. Implement community-based prevention programs and home-based care programs and develop BCC materials.

HANDOUT Table A4, 1.1 (cont.)

	Ghana	Kenya	Rwanda
Program Development	<ul style="list-style-type: none"> January 2002: Program Development Workshop January 2002: BCC, VCT, PMTCT, clinical care and laboratory support subagreements finalized with 6 NGOs, 2 hospitals, 2 labs February 2002: program launch Formative research and community preparedness activities July 2002: VCT services begin April–November 2002: Clinic, laboratory and pharmacy upgrading August 2002: OI Workshop November 2002: ARV Workshop February 2003: Grant to Ghana Health Services to procure ARVs for 100 patients for six months May 2003: ART begins 	<ul style="list-style-type: none"> February 2002: Task Force on ART (under NAACC) begins meetings to monitor use of ART in Kenya (FHI is secretariat and provides TA) April 2002: Stakeholders workshop organized September 2002: Clearance to proceed with implementation obtained September 2002: Health system capacity assessment April 2003: Health care provider training on HIV clinical management, including ART May 2003: ART begins 	<ul style="list-style-type: none"> November 2002: Assessment to determine existing health system capacity and needs completed November–February 2003: Capacity building process including: upgrading of services, improving drug management systems and personnel training (based on findings of assessment phase) February 2003: Health care provider training on HIV clinical management, including ART February 2003: ART began
Implementing Partners (in addition to intervention facilities)	<ul style="list-style-type: none"> Centre for Integrated Rural Environmental Development (CEFRIEND) Klo Drivers Alliance Manya Krobo Youth Club PHLAB Foundation Noguchi Memorial Institute for Medical Research Public Health Reference Laboratory Queenmothers Association Youngsters Peer Education Project 	<ul style="list-style-type: none"> Management Sciences for Health/RPM-Plus Population Council/HORIZONS COPHIA Aga Khan Local PLHA Group International Centre for Reproductive Health (ICRH) 	<ul style="list-style-type: none"> PLHA Groups: Duteraninkunga and Ihumure

Table A4, 1.2: Summary of Technical Approaches to Treatment at the Three Learning Sites

	Ghana	Kenya	Rwanda
Treatment Criteria	<p>Adults</p> <ul style="list-style-type: none"> • WHO Clinical Stage III or IV • CD4 <250. • Resident of Manyara or Yilo Krobo • Disclosure to at least one person <p>Children</p> <p>The child must meet any one of the following:</p> <ul style="list-style-type: none"> • Symptomatic children in Pediatric Stage II and III whose mothers are HIV positive • CD4 <20 percent in child less than 18 months • CD4 <15 percent in child more than 18 months 	<p>Adults</p> <ul style="list-style-type: none"> • WHO Clinical Stage III or IV • CD4 <200 <p>Children</p> <ul style="list-style-type: none"> • CD4 <15 percent in child more than 18 months <p>Social criteria:</p> <ul style="list-style-type: none"> • Resident of Mombasa District • Willingness to visit CPGH regularly and be contacted anytime at home or elsewhere • Staff of health facilities and their spouses who meet the medical criteria and is willing to start treatment • Tuberculosis patient who meets the medical criteria and has completed the intensive phase of treatment 	<p>Adults</p> <ul style="list-style-type: none"> • WHO Clinical Stage III or IV • CD4 <200 <p>Children</p> <ul style="list-style-type: none"> • CD4 <15 percent in child more than 18 months
Drug Regimen	<p>First line</p> <ul style="list-style-type: none"> • AZT 300mg + 3TC 150mg: one tablet two times a day • NVP 200mg: one tablet daily for two weeks. If there are no adverse reactions at this dosage, the dosage will be increased to one tablet two times a day. <p>Second line</p> <ul style="list-style-type: none"> • For patients who develop severe adverse side effects to AZT, d4T will be used in its place. These patients will therefore receive d4T, 3TC and NVP. • For patients who react to NVP or experience severe adverse drug reactions, EFZ will be used in its place. 	<p>First line (adults & adolescents)</p> <ul style="list-style-type: none"> • d4T + 3TC + efavirenz <p>For pregnant women or women likely to become pregnant:</p> <ul style="list-style-type: none"> • d4T + 3TC + NVP <p>Second Line</p> <ul style="list-style-type: none"> • AZT + ddl + LVP/r <p>OR</p> <ul style="list-style-type: none"> • AZT (retrovir) + ddl + NVP 	<p>First line</p> <ul style="list-style-type: none"> • d4T + 3TC + EFV or • AZT + 3TC + EFV <p>Second line</p> <ul style="list-style-type: none"> • AZT + ddl + IDV for patients who fail the first line combination of D4T + 3TC + EFV • d4T + ddl + IDV for patients who fail the first line combination of AZT + 3TC + EFV <p>*For women of reproductive age, EFV will be systematically replaced with NVP.</p>

Table A4, 1.2 (cont.)

<p>Laboratory Baseline</p>	<p>Baseline</p> <ul style="list-style-type: none"> • Full blood count • Total lymphocyte count • CD4 count • Urinalysis • Stool R/E • BUN and creatinine • Liver function Tests • CXR and sputum for AFBs if indicated • Viral load • First 200 ART patients • Treatment failure <p>Baseline</p> <ul style="list-style-type: none"> • HIV serology • Complete blood count (includes TLC) • CD4 count
<p>Laboratory Monitoring</p>	<p>For patients on Nevirapine, liver function tests will be performed at:</p> <ul style="list-style-type: none"> • Baseline • One month after initiating therapy • At three 3 months <p>For patients on all regimens, including those taking Nevirapine, monitoring should be done as follows:</p> <p>At 3 months:</p> <ul style="list-style-type: none"> • Full blood count • Total lymphocyte count • Liver function tests • Other tests only as needed <p>At 6 months:</p> <ul style="list-style-type: none"> • CD4 • Full blood count • Total lymphocyte count • Liver function tests • Other tests only as needed <p>First year</p> <p>Second patient visit</p> <ul style="list-style-type: none"> • Baseline viral load • LFTs • Renal function tests • Complete urinalysis • Chest x-ray <p>Month 1</p> <ul style="list-style-type: none"> • Total lymphocyte count (TLC) • LFTs <p>Month 3 and 12</p> <ul style="list-style-type: none"> • Full blood count (includes TLC) • CD4+ count • LFTs • Other tests as needed

Table A4, 1.2 (cont.)

<p>Laboratory Monitoring</p>	<p>At 12 months:</p> <ul style="list-style-type: none"> • CD4 • Full blood count • Total lymphocyte count • Other tests only as needed <p>After the first year:</p> <ul style="list-style-type: none"> • CD4 every 6 months • Total lymphocyte count every 6 months • Full blood count every 6 months • Liver function test every 6 months • Other tests only as needed <p>Month 6</p> <ul style="list-style-type: none"> • Full blood count (includes TLC) • CD4+ count • LFTs <p>Month 9</p> <ul style="list-style-type: none"> • Total lymphocyte count • Subsequent years • Quarter • Full blood count (includes TLC) <p>Every 6 months</p> <ul style="list-style-type: none"> • CD4 count • LFTs • Other tests as needed <p>For a patient not responding to treatment, the viral load test and resistance testing will be requested.</p>
<p>Follow-up Visits</p>	<p>For the first three months, patients receiving ARVs will be seen as follows:</p> <ul style="list-style-type: none"> • A visit two weeks after initiation of ARVs • A visit once a month for the first 3 months, unless physician and patient see the need for this to be more frequent • Followed by a bimonthly schedule <p>Physicians in dialogue with the patient will determine the frequency of visits, based on patient condition, adherence needs, etc. Patients can also walk-in as needed.</p> <p>Clinical and Adherence Monitoring Visits</p> <ul style="list-style-type: none"> • First two months: every 2 weeks • Thereafter: every month • Three pre-ARV counseling sessions with ART nurse • 48-72 hours after starting ART, the patient will meet with the ART nurse for assessment of adverse drug effects and medication adherence (discuss experience, difficulties, strategies to manage difficulties, input from family member/friend, review medication and encouragement) <p>Follow-up visits every 2 weeks with a doctor.</p>
<p>Adherence Plan</p>	<ul style="list-style-type: none"> • At least one session of adherence counseling prior to starting medication • Adherence counselors must verify the location of residence during the process • If possible, a supporting relative or friend will participate in the adherence sessions and assist the patient in taking the drugs for the first two weeks. • If the patient is unable, for whatever reason, to involve a relative or friend, they will receive support to do this eventually through follow-up counseling. <ul style="list-style-type: none"> • Five adherence counseling sessions with a “buddy” prior to starting treatment • Mini-DOT for 6 weeks; patients will attend health facility in the morning to take their pill supervised by a nurse. Evening dosage will be on their own.

SESSION 2 Brief Introduction to ART**PURPOSE**

In this session, participants will learn about antiretroviral therapy (ART), including the goal and basic principles of therapy and the WHO recommendations on: what therapy to begin with, when to change therapy, the types of therapies and their modes of action, WHO-recommended first-line ARV regimens, adherence issues, monitoring ART and drug interactions. The session also covers treatment options for patients who fail therapy, including WHO-recommended second-line regimens, barriers to treatment and research treatment approaches.

OBJECTIVES:

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

1. Describe the goals and basic principles of ART.
2. List the criteria for when to start therapy, which regimen to use and when to change therapies.
3. Describe the different types of therapy, their mode of action and WHO-recommended first-line and second-line regimens.
4. Discuss adherence issues and discuss country-specific solutions.
5. Discuss the importance of and how to monitor patients on ART.
6. Describe drug interactions.
7. Discuss treatment options for patients who fail therapy, the barriers to treatment and how to address these in their local situation.
8. Discuss research treatment approaches.
9. Discuss in-country options and national guidelines for ART.

TIME:

1.5 hours

- Step 1. Explain the purpose and objectives of the session (see above).
(3 minutes)
- Step 2. Present the information on ART in its entirety: 1-6 below.
(45-60 minutes)
- Tell participants there will be time at the end of your presentation to discuss major issues concerning ART in their local situation, national guidelines and the like.

1. The goal of antiretroviral therapy (ART) is to:

- a. Prolong and improve the quality of life
- b. Reduce the viral load as much as possible, for as long as possible, 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. Provide an antiretroviral regimen that not only achieves reduced viral loads, but also preserves future therapeutic options, is relatively free of side effects and is tailored to individual needs for adherence

2. The basic principles of therapy

- a. When to start therapy
 - WHO recommends that HIV-infected adolescents and adults start ART when they have:
 - WHO stage IV disease (clinical AIDS), irrespective of CD4 cell count
 - 2003 WHO guidelines: for stage III use $<350\text{mm}^3$ in situation of rapid clinical decline
 - WHO stages I and II disease, with CD4 cell count below $200/\text{mm}^3$
 - WHO stages II or III HIV disease, with a total lymphocyte count below $1200/\text{mm}^3$
 - In cases where you cannot assess CD4 counts, use the presence of a total lymphocyte count of $1200/\text{mm}^3$ or below as a substitute indication for treatment in the presence of symptomatic HIV disease.
 - An assessment of viral load is not considered essential for starting therapy.

Table A4, 2.1:
Recommendations for Initiating Antiretroviral Therapy in Adults and Adolescents with Documented HIV Infection

If CD4 testing is available:	
<ul style="list-style-type: none"> • WHO stage IV, irrespective of CD4 cell count^a • WHO stage I, II, or IIIa with CD4 cell count less than 200/mm^{3b} 	
If CD4 testing is not available:	
<ul style="list-style-type: none"> • WHO stage IV, irrespective of TLC • WHO stage II or III^c, with less than 1200/mm^{3c} 	
<p>a Treatment is also recommended for patients with advanced WHO stage III disease, including recurrent or persistent oral thrush and recurrent bacterial infections, irrespective of the CD4 cell count or total lymphocyte count.</p> <p>b The precise CD4 level above 200/mm³ at which to start ARV treatment has not been established, but factor the presence of symptoms and the rate of CD4 cell decline (if measurement is available) into decision making. A CD4 level of 200/mm³ corresponds to a CD4 percentage of approximately 15 percent.</p>	<p>c A total lymphocyte count below 1200/mm³ can be substituted for the CD4 count when the latter is unavailable and HIV-related symptoms exist. It is less useful in the asymptomatic patient. Thus, in the absence of CD4 cell testing, do not treat asymptomatic HIV-infected patients (WHO stage I), because there is currently no other reliable marker available in severely resource-constrained settings.</p>

b. What therapy to begin with

- The only regimens potent enough to drastically reduce viral replication as well as prevent the emergence of resistance and treatment failure for a significant amount of time involve a combination of at least three antiretrovirals.
- There are currently 16 approved ART agents for the treatment of HIV-1 infection (in the U.S.), encompassing six nucleoside reverse transcriptase inhibitors (NtRTI), three nonnucleoside reverse transcriptase inhibitors (NNRTIs) and six protease inhibitors (PIs). The WHO guidelines incorporate thirteen of them.

Table A4, 2.2: Approved Antiretroviral Agents Included in WHO's ARV Guidelines^a

Nucleoside reverse transcriptase inhibitors (NRTIs)	Nucleotide reverse transcriptase inhibitor (NtRTI)	Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	Protease inhibitors (PIs)
zidovudine (ZDV, AZT) ^b didanosine (ddI) ^b stavudine (d4T) ^b lamiduvine (3TC) ^b abacavir (ABC) ^b	tenofovir disoproxil fumarate (TDF)	nevirapine (NVP) ^b efavirenz (EFV) ^b	saquinavir (SQV) ^b ritonavir (RTV) (as pharmacoenhancer) ^b indinavir (IDV) ^b nelfinavir (NFV) ^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.	

- WHO recommends that ARV treatment programs in resource-constrained settings choose one potent first-line ART regimen with which to start treatment in the majority of patients.

Table A4, 2.3:
WHO-Recommended First-Line Antiretroviral Regimens in Adults and Adolescents and Characteristics that Can Influence Choice

ARV Regimen	Major potential toxicities	Usage in women (of childbearing age of pregnant)
d4T/3TC/NVP	d4T-related neuropathy, pancreatitis and lipoatrophy; NVP-related hepatotoxicity and severe rash	Yes
ZDV/3TC/NVP	ZDV-related GI intolerance, anaemia and neutropenia; NVP-related hepatotoxicity and severe rash	Yes
d4T/3TC/EFV	d4T-related neuropathy, pancreatitis and lipoatrophy; EFV-related CNS toxicity and potential for teratogenicity	No
ZDV/3TC/NVP	ZDV-related GI intolerance, anaemia and neutropenia; EFV-related CNS toxicity and potential for teratogenicity	No

c. When to change therapy

- Because of failure, defined in terms of:

Clinical failure:	Clinical disease progression with development of an OI or malignancy after when the drugs have been given sufficient time to induce a protective degree of immune restoration
Immunologic failure:	A fall in the CD4 counts higher than 50 percent from the peak value or a return to a level at or below the pretherapy baseline
Virologic failure:	Refers to an incomplete virologic response, that is, not achieving HIV RNA <400 copies/mL by 24 weeks or <50 copies/mL by 48 weeks, in a treatment-naïve patient
- Because of toxicity:
 - 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 EFZ when EFZ-related central nervous system symptoms are unremitting.
 - When you cannot identify the drug causing the toxicity and/or low-grade, intolerable side effects compromise adherence, we recommend a complete regimen switch.
 - If an interruption in therapy is indicated to permit resolution of toxicity, suspend the entire regimen temporarily to prevent the emergence of drug resistance.

3. Antiretroviral therapies

- a. Medication groups: (See Tables A4, 2.2 and A4, 2.3 above for a listing of drugs.)
 - Mode of action: antiretroviral drugs (ARVs) act on the HIV by interfering with its reproductive cycle. They act to inhibit replication of the virus at these main stages of the cycle:
 - 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.* Protease enzymes are required during this stage and protease inhibitors act here.
 - Nucleoside reverse transcriptase inhibitors (NRTIs):
 - Lead to premature termination of the production of the HIV DNA chain
 - Are active against both HIV-1 and HIV-2
 - Resistance develops rapidly if given as single drugs alone (monotherapy)
 - Side effects include:
 - Nausea and vomiting
 - Anemia (AZT), neutropenia
 - Peripheral neuropathy (d4T, ddl, ddC)
 - Pancreatitis (ddl, ddC, d4T, 3TC)
 - AZT and d4T are structurally similar; do not use them together.
 - Nonnucleoside reverse transcriptase inhibitors (NNRTIs):
 - Are active only against HIV-1
 - Delavirdine and nevirapine are antagonistic in action on the HIV reverse transcriptase activity; therefore, do not use them together.
 - Interaction with some drugs occurs because of induction and/or inhibition of cytochrome P450 enzymes.
 - Adverse effects include diffuse maculopapular rash, hepatitis, headache and nausea.
 - Protease inhibitors (PIs):
 - HIV protease enzyme is responsible for cleaving various polypeptides in the process of producing mature infectious virions. Interference with this enzyme by PIs leads to significant reduction of the virus in the body to undetectable levels.

Rapid resistance will develop if PIs are used as single agents.

PIs are associated with multiple drug interactions because they inhibit cytochrome P450 enzymes.

For example: PIs increase the metabolism of rifampicin and decrease its effectiveness in treating TB

Side effects include GI problems, that is, nausea and vomiting.

Indinavir should be taken with plenty of water to prevent kidney stones.

b. Adherence

- Drug adherence is one of the key determinants of therapy success.
- Poor adherence can lead to virologic failure, evolution of drug resistance and subsequent immunologic and clinical failure.
- Adherence is promoted by simplified, well-tolerated regimens involving as few pills as possible and administered no more than two times per day.
- Counseling patients carefully before initiating therapy and involving physicians, nurses and other health care providers in the process are important.
- Do *not* start ART at the first clinic visit—a period of education and preparation to try to maximize future adherence is important.
- Once treatment has begun, continued monitoring of adherence is essential.
- Physician assessment has repeatedly been shown to be the least reliable approach; pill counts are subject to error and manipulation.
- Validated patient questionnaires have been shown to be one of the more reliable and easy-to-institute tools for monitoring adherence in the outpatient setting.
- Each country and/or health center should develop its own brief, culturally appropriate questionnaire since one standardized tool may not be applicable to all regions and cultures.

c. Monitoring of ART

- Baseline clinical assessment and preparation of the patient
 - Baseline medical and psychosocial history:
 - Essential demographic characteristics
 - Past medical history, including major illnesses (for example, tuberculosis), hospitalizations and surgeries
 - Length of time since diagnosis of HIV infection, current medications and symptoms
 - For women, current or planned pregnancy and access to contraceptive services
 - Family economic status
 - Family coping
 - Review of systems (respiratory, cardiac, neurological, genitourinary, etc.)
 - Baseline physical exam:
 - Vital signs, weight, and detailing of any abnormalities (including fundi, if possible), oropharynx, lymph nodes, lungs, heart, abdomen, extremities, nervous system and genital tract
 - Preparation of the patient:
 - Review expected benefits and potential side effects of the regimen chosen, possible drug interactions, concept of partnership between patient and caregiver, probable lifelong commitment to treatment, critical need to maintain safe sexual practices to prevent HIV transmission, the importance of drug adherence and the need to report perceived side effects.
- Establish a reasonable schedule for clinical monitoring.
 - First follow-up visit one month (preferably one or two weeks) after initiation to ensure tolerance
 - A minimum of one visit every 3-4 months thereafter (preferably monthly at first, to assess drug reaction, response and encourage adherence)
 - Monthly visits, combined with drug dispensing, are ideal to reinforce adherence.
 - At each visit, ask about any new symptoms that may be related to drug side effects, HIV progression or intercurrent processes.

- Clinical monitoring of toxicities and effectiveness of antiretroviral drugs and regimens
 - Whether CD4 cell monitoring is available or not, clinical effectiveness of ART is important and can be monitored by:
 - Patient’s perception of how he or she is doing on treatment—sense of well-being
 - Changes in body weight over the course of therapy
 - Changes in frequency and/or severity of HIV-associated symptoms (fevers, diarrhea, skin rashes and the like) and findings (oropharyngeal or vulvovaginal candidiasis)
 - Signs of immune reconstitution syndromes or HIV-related disease progression
 - Tell the patient about symptoms of ARV toxicities and the need to seek care
 - See Table A4, 2.4, below.

Table A4, 2.4 Clinical Signs and Symptoms and the Monitoring and Management of Symptoms of Serious Adverse Effects of Antiretroviral Drugs That Require Drug Discontinuation

Adverse effect	Possible offending drug(s)	Clinical signs/symptoms	Management
Acute hepatitis	Nevirapine (NVP); efavirenz (EFZ) less common; more uncommon with zidovudine (ZDV), didanosine (ddl), stavudine (d4T) (<1 percent); and protease inhibitors, most frequently with ritonavir (RTV)	Jaundice, liver enlargement, gastrointestinal symptoms, fatigue, anorexia NVP-associated hepatitis may have hypersensitivity component (drug rash, systemic symptoms, eosinophilia).	If possible, monitor serum transaminases and bilirubin. All ART should be stopped until symptoms resolve. NVP should be permanently discontinued.
Acute pancreatitis	ddl, d4T; lamivudine (3TC) (infrequent)	Nausea, vomiting and abdominal pain	If possible, monitor serum pancreatic amylase and lipase. All ART should be stopped until symptoms resolve. Restart ART with change to different NsRTI, preferably one without pancreatic toxicity (e.g. ZDV or ABC).
Lactic acidosis	All nucleoside analogue reverse transcriptase inhibitors (NsRTIs)	Initial symptoms are variable. A clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain, hepatomegaly, anorexia and/or sudden unexplained weight loss), respiratory symptoms (tachypnea and dyspnea) or neurological symptoms (including motor weakness).	Discontinue all ART; symptoms may continue or worsen after discontinuation of ART. Supportive therapy. Regimens that can be considered for restarting ART include a PI combined with an NNRTI and possibly either ABC or TDF.

Table A4, 2.4 (cont.)

Adverse effect	Possible offending drug(s)	Clinical signs/symptoms	Management
Hyper-sensitivity reaction	Abacavir (ABC), nevirapine (NVP)	ABC: Constellation of acute onset of symptoms including: fever, fatigue, myalgia, nausea/vomiting, diarrhea, abdominal pain, pharyngitis, cough and dyspnea (with or without rash). While these symptoms overlap those of common infectious illnesses, the combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC is more typical of a hyper-sensitivity reaction. NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, eosinophilia with or without rash.	Discontinue all ART until symptoms resolve. The reaction progressively worsens with drug administration and can be fatal. Administer supportive therapy. Do not rechallenge with ABC (or NVP), as anaphylactic reactions and death have been reported. Once symptoms resolve, restart ARVs with a change to different NsRTI if ABC-associated or to PI- or NsRTI-based regimen if NVP-associated.
Severe rash / Stevens-Johnson syndrome	Non nucleoside reverse transcriptase inhibitors (NNRTIs): nevirapine (NVP), efavirenz (EFV)	Rash usually occurs during the first two to four weeks of treatment. The rash is usually erythematous, maculopapular, confluent, most prominent on the body and arms, may be pruritic and can occur with or without fever. Life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis has been reported in ~0.3 percent of infected individuals receiving NVP.	Discontinue all ARVs until symptoms resolve. Permanently discontinue NVP for rash with systemic symptoms such as fever, severe rash with mucosal lesions or urticaria, or Stevens-Johnson syndrome or toxic epidermal necrolysis; once resolves, switch ART regimen to different ARV class (e.g. three NsRTIs or two NsRTIs and PI). If rash is moderate (not severe) and without mucosal or systemic symptoms, change in NNRTI (e.g. NVP to EFV) could be considered after rash resolves.
Severe peripheral neuropathy	ddl, d4T, 3TC	Pain, tingling, numbness of hands or feet; distal sensory loss, mild muscle weakness and areflexia can occur.	Stop suspect NsRTI and switch to different NsRTI that does not have neurotoxicity (e.g. ZDV, ABC). Symptoms usually resolve in two to three weeks.

- Laboratory monitoring
 - Basic laboratory monitoring for toxicity and effectiveness of ART
 - Baseline tests before the initiation of ART:
 - HIV antibody test
 - Hemoglobin or hematocrit level
 - Additional basic testing should include:
 - White blood cell count and differential (to assess neutropenic side effects and total lymphocyte cell count)
 - Serum alanine or aspartate aminotransferase level (to assess the possibility of hepatitis coinfection and to monitor for hepatotoxicity)
 - Serum creatinine and/or blood urea nitrogen (to assess baseline renal function)
 - Serum glucose (given the propensity of PIs to induce insulin resistance)
 - Pregnancy test for women
 - Resources permitting, serum bilirubin, amylase and lipids (triglycerides and cholesterol)
 - CD4 lymphocyte counts
 - Useful in deciding whether a patient should start ART
 - Important for assessing effectiveness of ART with rises of >100 CD4 cells/mm³ in the first 6-12 months of therapy or immunologic failure
 - Plasma HIV-RNA levels (viral load)
 - A useful indicator of the activity of the ARV regimen in individual patients, but not currently recommended because of its high cost and unavailability in resource-constrained settings. Treatment failure will need to be assessed immunologically and clinically rather than virologically until inexpensive methods for viral quantitation are established.
- d. Drug interactions (For details, see appendices below)
- Drugs of NNRTI and PI classes interact with the cytochrome P450 enzyme system, resulting in either inhibition or induction of these enzymes.
 - When coadministered with other drugs metabolized by the cytochrome P450 enzyme system, increases or decreases in the given NNRTI or PI and/or concomitant medication may occur
 - This can result in increased toxicity because of elevated drug concentrations (or increased efficacy, such as in RTV-boosted PI regimens) or drug failure due to subtherapeutic drug concentrations
 - The only recommended PI-containing combination for patients receiving rifampin is SQV/r/ZDV (or d4T) 3TC. Use of other PIs (NFV, IDV/r, LDV/r) is contraindicated because rifampin induces hepatic enzymes that reduce exposure to protease inhibitors to subtherapeutic levels.
 - Review handout of concomitant medications and requirements for dose modification.

See Table A4, 2.5.

Table A4, 2.5: Relevant Drug Interactions for Non-Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors for Resource-Poor Countries

	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	EFZ decreased 25-33 percent Recommendation: Consider EFZ 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	EFZ unchanged Rifabutin decreased 35 percent Recommendation: Increase rifabutin dose to 450-600 mg daily (or 600 mg two or three times weekly); EFZ 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	EFZ 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

Table A4, 2.5 (cont.)

Anticonvulsant	Nevirapine (NVP)	Efavirenz (EFZ)	Indinavir (IDV)	Lopinavir (LPV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
Additional drugs that should NOT be coadministered	Herbs: St. John's wort, garlic supplements	Antihistamine: astemizole, terfenadine Gastrointestinal: cisapride Psychotropic: midazolam, triazolam Ergot alkaloids: dihydroergotamine, ergotamine Herbs: St. John's wort, garlic supplements	Antihistamine: astemizole, terfenadine Gastrointestinal: cisapride Psychotropic: midazolam, triazolam Ergot alkaloids: dihydroergotamine, ergotamine Herbs: St. John's wort, garlic supplements When IDV is used with low-dose RTV: Cardiac: flecainide, propafenone Neuroleptic: pimozide	Antihistamine: astemizole, terfenadine Gastrointestinal: cisapride Psychotropic: midazolam, triazolam Ergot alkaloids: dihydroergotamine, ergotamine Herbs: St. John's wort, garlic supplements Cardiac: flecainide, propafenone Neuroleptic: pimozide	Antihistamine: Astemizole, terfenadine Gastrointestinal: cisapride Psychotropic: midazolam, triazolam Ergot alkaloids: dihydroergotamine, ergotamine Herbs: St. John's wort, garlic supplements	Antihistamine: astemizole, terfenadine Gastrointestinal: cisapride Psychotropic: midazolam, triazolam Ergot alkaloids: dihydroergotamine, ergotamine Herbs: St. John's wort, garlic supplements When SQV is used with low-dose RTV: Cardiac: flecainide, propafenone Neuroleptic: pimozide
Miscellaneous	Can induce glucocorticoid metabolism, resulting in lower serum steroid levels	Monitor warfarin if used concomitantly.	Grapefruit juice decreases IDV by 26 percent			Grapefruit juice increases SQV levels. Dexamethasone decreases SQV levels.

Source: *Scaling Up Antiretroviral Therapy in Resource Limited Settings: Guidelines for a Public Health Approach*. Geneva: WHO, 2002, pp. 114-119.

4. Treatment options for patients who fail therapy

- a. As previously stated, reasons for altering an initial ART regimen include:
- intolerance, leading to poor adherence
 - drug toxicity
 - the occurrence of active tuberculosis or pregnancy
 - treatment failure
- b. The Table A4, 2.6 below outlines alternative treatment regimens.

Table A4, 2.6: 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 viral load and resistance monitoring are not defining treatment failure, virological failure will probably have been present for an extended period by the time treatment failure is detected. Viral replication over time leads to the evolution of more drug resistance mutations; without drug resistance testing, it will be hard to know which drugs have been compromised.

5. Barriers to treatment

Barriers to treatment need to be assessed according to each country's resources and limitations.

a. Cost: How much does ART cost in-country?

b. Drug-specific issues

- Availability:
 - Which drugs are available in-country?
 - Where (at what locations) are they available?
 - Is refrigeration needed? Available?
 - Are there any issues around toxicity? resistance?

c. Laboratory: which tests can be done in-country and where?

d. Culture-specific issues affecting adherence?

6. Research treatment approaches

a. Structured treatment interruption (STI)

All forms of STI are considered experimental because there are no data providing guidance and indications of when to stop, when to restart and what agents to use.

- Virologic failure

Discontinuation of ART usually results in rapid CD4 decline beginning at 2-4 weeks and is attributed to the return to wild type HIV, which is more "fit" than resistant strains. The wild type HIV strain is usually sensitive to those drugs to which there was previous resistance and responds to reintroduction of ART. However, resistant strains presumably remain as minority species and will eventually return with selective pressure.

- Structured intermittent therapy (SIT)

This is an experimental protocol in which patients who have achieved good virologic control with ART receive the successful ART regimen every other week in an attempt to decrease toxicity and cost. The experience to date shows preservation of CD4 level and viral suppression.

- Pulse therapy

The goal of this therapy is to keep the CD4 cell count above a predetermined threshold using cycles of therapy followed by prolonged interruptions. A subset of patients—presumably those with relatively low viral load set points and good CD4 cell count responses to HAART—may be able to discontinue therapy safely for prolonged periods of time. Randomized, controlled clinical trials are in progress to evaluate this approach, although results may not be available for several years. If the CD4 cell count is truly the most important predictor of time-off therapy, and the most important indicator of the need to resume therapy, this raises the question of whether we might combine a pulse-therapy strategy with immune-based therapies, such as interleukin-2, to increase the CD4 cell count and prolong the treatment interruption. (Medscape General Medicine 4(3), 2002)

b. Directly observed therapy (DOT): WHO recommendations

- There is a need to try and evaluate innovative models such as DOT for an initial training period for patients.
- Try introducing DOT with the assistance of caregivers or family members, to assist in adherence.
- Sites with tuberculosis treatment programs may consider DOT (although the open-ended nature of ART, as opposed to the limited course of treatment for TB, raises questions about sustainability of such an approach).

Step 3. Lead a discussion with participants on using ART in their local situation. Use the following questions as a guide. Ask a participant to record the discussion points on a flip chart, which can be referred to in the discussion.

Are any ART national guidelines available?

How do they compare to the WHO guidelines discussed today?

Do you have any concerns around these guidelines and/or the use of ART in your local situation?

What recommendations would you make?

(30 minutes)

Table A4, 2.7: 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.

Table A4, 2.7 (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	EFZ decreased 25-33 percent Recommendation: Consider EFZ 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	EFZ unchanged Rifabutin decreased 35 percent Recommendation: Increase rifabutin dose to 450-600 mg daily (or 600 mg two or three times weekly); EFZ 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	EFZ 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

Table A4, 2.7 (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 is 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

Prophylactic Treatment as Recommended in the U. S.

Prevention and the use of chemoprophylaxis are an important part of clinical management of individuals infected with HIV.

The following guidelines and recommendations are for the use of prophylaxis; they are grouped into measures that are strongly recommended, generally recommended and not recommended.

1. Strongly recommended as standard of care

a. *Pneumocystis carinii* or *p. jiroveci* pneumonia (PCP)

- Risk: CD4 count < 200/mm³, prior PCP, or HIV-associated thrush or FUO x 2 weeks
- Preferred: TMP-SMX (co-trimoxazole) 1DS/day or 1 SS/day
- Alternatives: dapsone 100 mg qd or 50 mg po bid
 - Dapsone 50 mg qd plus pyrimethamine 50 mg/wk plus leucovorin 25 mg/wk
 - Dapsone 200 mg/wk plus pyrimethamine 75 mg/wk plus leucovorin 25 mg/wk
 - Atovaquone 750 mg po bid with meals
- Comments: test patients given dapsone for G6PD deficiency
CP is the major AIDS-defining diagnosis and the major identifiable cause of death in patients with AIDS.
Risk of PCP for patients with prior PCP is 60-70 percent; with CD4 < 100/ mm³ is 40-50 percent/year.
Risk increases with progressive declines of CD4 count.

b. *M. Tuberculosis*

- Risk: positive PPD (≥5mm induration) with prior treatment, recent TB contact or history of inadequately treated TB that healed
- Preferred: INH 300mg/day + pyridoxine 50 mg/day ≥270 doses, 9 months or up to 12 months with interruptions
INH 900 mg + pyridoxine 100 mg twice weekly with directly observed therapy, ≥76 doses, 9 months or up to 12 months with interruptions
- Alternatives: rifampin 600 mg qd x 4 months
- Contact with INH resistant strain: rifampin plus pyrazinamide x 2 months (above doses)
- Contact with strain resistant to INH and rifampin: use 2 agents with anticipated activity—ethambutol + pyrazinamide or levofloxacin + pyrazinamide
- Pregnancy: INH regimens

c. *Toxoplasmosis gondii*

- Risk: CD4 count < 100/mm³ plus positive IgG serology for *T. gondii*
- Preferred: TMP-SMX 1 DS/day
- Alternatives: TMP-SMX 1 SS/day
 - Dapsone 50 mg qd plus pyrimethamine 50 mg/wk plus leucovorin 25 mg/wk
 - Dapsone 200 mg/wk plus pyrimethamine 75 mg/wk plus leucovorin 25 mg/wk

d. *M. avium* complex

- Risk: CD4 count < 50 mm³ Preferred measure: Clarithromycin 500 mg po bid or azithromycin 1200 mg po weekly
- Alternatives: rifabutin 300 mg po qd or azithromycin 1200 mg/wk plus rifabutin 300 mg po qd
- Immune reconstitution: It appears safe to discontinue primary MAC prophylaxis when CD4 count has increased to >100mm³ for 3-6 months. Continue preventive therapy for patients with prior MAC bacteremia.

e. *Varicella*

- Risk: significant exposure to chicken pox or shingles and no history of either, or negative serology
- Preferred: VZIG 5 vials IM within 96 hours of exposure, preferably within 48 hours
- Alternatives: acyclovir 800 mg po 5x/day x 3 weeks

f. *S. pneumoniae*

- Risk: All patients (standard of care for patients with CD4 count >200/mm³)
- Preferred: pneumovax 0.5 ml IM x 1
- Revaccinate: when CD4 count increases to >200 mm³ if initial immunization was done with CD4 count <200 mm³

2. Generally recommended

a. Hepatitis B

- Risk: negative anti-HBc screening test
- Preferred: recombivax HB 10 ug IM x 3 or energix-B 20 ug IM x 3

b. Influenza

- Risk: all patients annually
- Preferred: influenza vaccine 0.5 ml IM each year preferably October-November
- Alternative: amantadine 100 mg po bid or rimantadine 100 mg po bid

c. Hepatitis A

- Risk: gay men, hepatitis C infection, injection drug users, community outbreak and travel to endemic area
- Preferred: Havrix 0.5 ml IM x 2 separated by 6 months

3. Not recommended for most patients—consider for selected patients

a. Cryptococcosis

- Risk: CD4 count <50/mm³
- Preferred: fluconazole 100-200 mg po qd
- Alternatives: itraconazole 200 mg po qd

b. Histoplasmosis

- Risk: CD4 count <100/mm³ plus residence in endemic area
- Preferred: itraconazole 200 mg po qd

c. CMV

- Risk: CD4 count <50/mm³ plus positive CMV serology
- Preferred: oral ganciclovir 1 gm po tid

d. Bacterial infection

- Risk: neutropenia
- Preferred: G-CSF 5-10 µg/kg sc qd x 2-4 wks

SESSION 3 Management of Drug Side Effects**PURPOSE**

In this session, participants will review the major side effects of antiretroviral drugs and of some of the drugs given to prevent and treat OIs. They will learn how to advise patients in managing these symptoms.

OBJECTIVES:

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

1. List the common side effects of these drugs and the rough percentage of people reporting each side effect for each drug.
2. Advise the patient on how to manage some of the major side effects, such as fatigue, anemia, headaches, nausea and vomiting, diarrhea, weight loss, dry mouth, rash, peripheral neuropathy, menstrual problems and hair loss.

TIME:

45 minutes

- Step 1. Explain the purpose and objectives of this session (see above).
- Step 2. Introduce the session and go over the information in the chart on drug side effects, giving particular attention to the drugs most commonly used in the local situation.
(12 minutes)

1. Introduction

- a. All antiretroviral drugs, as well as drugs used to treat and prevent OIs, have some side effects. These side effects may vary from person to person. Some may experience few or no side effects, while others have mild to severe side effects.
- b. Side effects often occur after starting a new drug or therapy; they may decrease or disappear entirely after several weeks or may persist throughout the therapy.
- c. Some of the more common side effects include: fatigue, anemia, headaches, nausea and vomiting, diarrhea, weight loss, dry mouth, rash, peripheral neuropathy, menstrual problems and hair loss. There is information in Part B, Module 1, Session 4 on the drugs most commonly used in HIV disease and the side effects most commonly reported with these drugs.

- Step 3. Review the common side effects 2. a-j below, one by one. After presenting each side effect and the advice to patients, ask the participants:
- Will this advice work in your local situation?
 - What other advice would you give, based on local resources and cultural beliefs/practices?
 - What are local equivalents/substitutions for foods recommended?
- List participant responses on a flip chart.
(30 minutes)

2. Advice a caregiver can give to the patient on some of the more common side effects associated with antiretroviral drugs and drugs used for prevention and treatment of OIs. Local practices and remedies should be assessed and integrated as appropriate.

- a. Fatigue
 - Symptoms of fatigue can be physical (it may be hard to get out of bed or to walk upstairs) or psychological (patient may find it hard to concentrate; suffer depression, anxiety, and/or stress).
 - Fatigue may result from sleep problems (having trouble falling asleep, staying asleep, suffering sleep disturbances).
 - Fatigue can also be a symptom of anemia.
 - Advise the patient to:
 - Try going to sleep at night and waking in the morning at the same time every day; changes in sleep patterns can make a person feel more tired.
 - Avoid caffeine, alcohol, or nicotine for 4-6 hours before going to bed. A light snack, chamomile tea, warm milk and relaxation techniques before bedtime are often helpful.
 - Try to get a little exercise. Exercise eases stress and makes a person feel stronger and more alive.
 - Have someone help with day-to-day chores such as cooking. Keep easy-to-prepare foods on hand for times when cooking is too tiring.
 - Eat snack foods throughout the day and fresh fruits that don't require preparation.
 - Drink high-energy, high-protein liquids.

b. Anemia

- Anemia may be caused by HIV itself or be a side effect of drugs.
- Give intramuscular injections of vitamin B12 every 1-2 weeks, if necessary or feasible.
- Advise the patient to:
 - Return to the clinic to check hemoglobin count regularly
 - Eat a diet of locally available foods that are high in folic acid, including spinach and other green leafy vegetables, and high in iron and vitamin B12, such as fish, meat and poultry, if available
 - Take multivitamins and/or supplements of folic acid or iron
- If the patient develops pale palms or other signs of anemia when on ZDV, advise the patient to go to the health center to have his or her hemoglobin checked. If there is a drop of more than 25 percent from the baseline value, consider switching the drug.

c. Headache

- Headaches are generally treatable with nonprescription drugs and by stress reduction.
- Advise the patient:
 - For on-the-spot relief, try resting in a quiet, dark room with your eyes closed; place cold washcloths over your eyes; massage the base of your skull with your thumbs and massage both temples gently; take hot baths or showers.
 - To prevent headaches from recurring, try to anticipate when the pain will strike. Avoid or limit those foods known to trigger headaches, especially caffeine (in coffee, tea, soft drinks), chocolate, alcohol, citrus fruit (if more than half a cup a day), food additives (monosodium glutamate), nuts, onions, hard cheese and vinegar.
- The patient should be advised to go to the health center if he or she has a headache that is severe or persists beyond the first two or three weeks of therapy. The headache could be a sign that an opportunistic infection is still present.

d. Nausea and vomiting

- Persistent vomiting can lead to serious medical problems, such as dehydration, chemical imbalances or even tearing of the esophagus. Advise the patient to come to the clinic if nausea or vomiting persists and/or interferes with his/her taking the medications.
- Give anti-nausea medications, as needed.
- Nausea often improves if antiretrovirals are taken with food, and most ART drugs can be taken with a meal or snack. Ritonavir or saquinavir should be taken with foods that are high in fat. Indinavir can be taken with a light, fat-free, low-protein meal or snack. Only ddI must absolutely be taken on an empty stomach.
- Advise the patient to:
 - Eat a diet of bananas, rice, applesauce, toast and tea, if possible (known as the BRAT diet).
 - Eat small amounts of bland, odorless foods such as toast, crackers, clear soup or broth, which are easier to keep down. Eat simple boiled foods such as porridge, potatoes and beans.
 - Avoid hot, spicy, strong-smelling and greasy food.
 - Keep some dry crackers at your bedside. Before getting out of bed in the morning, eat a few dry crackers and sit in bed for a few moments.
 - Eat small snacks throughout the day, and avoid large meals.
 - Try peppermint, chamomile or ginger tea (or the equivalent in the local situation).
 - Sip cold carbonated drinks like 7-Up.

e. Diarrhea

- Watch for signs of dehydration and weight loss. If patient is dehydrated, teach him or her how to make an oral rehydration solution.
- A small study found that taking 500 mg of calcium twice a day greatly reduced nelfinavir-related diarrhea.
- Advise the patient to:
 - Eat a diet high in soluble fiber (which slows the diarrhea by absorbing liquid). These include the BRAT diet (see

d. above) and soft white rice, oatmeal (or oat bran), cream of wheat or other locally available porridge and soft bread (not whole grain). Psyllium husk fiber is another source of soluble fiber, if available locally.

Avoid foods high in insoluble fiber, such as corn, popcorn, fruits (dried and raw), vegetables, nuts, seeds and most grains. These can make diarrhea worse.

Decrease high fat foods.

Avoid milk products and greasy, high fiber or very sweet foods. These tend to aggravate diarrhea.

Prevent dehydration by drinking lots of fluids. If dehydrated, drink rehydration solution.

Drink rice or barley water made by boiling a half cup of rice or barley in one liter of water. Once the rice or barley is cooked, pour off the water and drink it in small sips.

- The patient should seek care at the health center if the diarrhea is persistent, if there is blood in the stool, if the diarrhea presents with a fever, or if it persists after a few weeks on ART.

f. Weight loss

- Weight loss is a serious problem and may result from some of the other drug side effects such as vomiting, diarrhea, dry mouth, anemia or fatigue. Monitor the patient's weight regularly and determine the cause of weight loss: is it stress related? accompanied by nausea and vomiting? has it occurred after starting a new medication? and so on.
- Advise the patient to:
 - Take a diet high in protein (and low in sugar), and/or take high protein supplement drinks, if available
 - Take multivitamins

g. Dry mouth

- Dry mouth can make chewing, swallowing and talking difficult; it can affect one's sense of taste and can promote mouth problems, like tooth decay and oral yeast infections (thrush).
 - * If necessary, prescribe a synthetic saliva or anti-dry mouth medication, such as pilocarpine.
- Advise the patient to:
 - Drink plenty of liquids during or between meals.
 - Rinse the mouth throughout the day with salted warm water.
 - Avoid sugary or sticky foods or caffeinated drinks; these can make the mouth even drier.
 - Chew sugarless gum; it can stimulate saliva flow. Suck on sugarless candies, lozenges, or crushed ice (if available), to cool the mouth and give it moisture.
 - Try slippery elm or licorice tea (or the local equivalent). This will lubricate the mouth.

h. Rash

- Many people get a rash when starting antiretrovirals, but most of the time it is mild and goes away after a couple of weeks.
- Rash seems to be a slightly more common side effect among women taking certain antiretroviral medications than among men. Nevirapine appears to be the main culprit, along with abacavir, efavirenz and amprenavir, as well as cotrimoxazole, isoniazid and many antibiotics. Women also seem more prone to severe rash.
- Sometimes the rash can be a sign of hypersensitivity that can include fever and flu-like symptoms, such as aches, pains, fatigue, headache, difficulty breathing, sore throat and cough. If a rash develops, the patient should seek a consultation.
- Be sure to monitor a patient's skin for discoloration and changes in its surface, as well as for signs of hypersensitivity, especially after starting a new medication; teach the patient to monitor for such signs.
- Advise the patient to:
 - Use creams, moisturizers or a topical ointment such as Benadryl to soothe and comfort the skin, if a rash should develop.
 - Use unscented, nonsoap cleansers or oatmeal soaps.
 - Avoid taking very hot showers or baths; they tend to irritate the skin.
 - If a rash should develop, protect skin from sun exposure; the ultraviolet (UV) rays of the sun may exacerbate a rash.

i. Peripheral neuropathy

- Peripheral neuropathy results from damage to the nerves, which may be caused by HIV itself or be a side effect of certain drugs. Signs of peripheral neuropathy include a sensation of burning, stinging, stiffness, tickling or numbness in the feet, toes or hands.
- Look for these signs during a patient's follow-up visits and advise the patient to watch out for these signs and report them to his or her caregiver.
- Treatment of peripheral neuropathy includes stopping or decreasing the offending drug. Once there is damage to the nerves, it cannot be reversed, therefore be sure to monitor for signs of peripheral neuropathy from the start of therapy.
- Because vitamin B deficiency can contribute to peripheral neuropathy, prescribe a B-complex supplement containing thiamine (B1), riboflavin (B2), niacin, pyridoxine (B6) and cobalamin (B12). Consider giving the patient a weekly B12 injection.
- Patients taking both INH and d4T have an additional risk of developing neuropathy. Pyridoxine must be given with the INH.
- Amitriptyline might be useful in relieving the symptoms of neuropathy, especially at night when sleep might be difficult.
- Advise the patient to:
 - Wear loose-fitting shoes, roomy cotton socks and padded slippers around the house. Good air circulation around the feet helps.
 - Keep feet uncovered in bed. Bedding that presses down on the toes can add to the problem.
 - Walk around, but not too much. Walking helps blood to circulate in the feet, but too much walking or standing can make the problem worse.
 - Soak feet in ice water (or the coldest water available) to reduce foot pain.
 - Massage the feet; this reduces foot pain temporarily.
 - Try ibuprofen (or the equivalent) to reduce pain and swelling.
 - Take vitamin B complex supplements.
 - If available, use L-acetyl carnitine to prevent the peripheral neuropathy related to ddI, d4T and/or hydroxyurea.

j. Menstrual problems

- Women with weakened immune systems tend to have more problems with their periods, including irregular, heavier, lighter and/or painful periods, or no menstrual bleeding at all. These problems can also be a side effect of some medications: recently, excessive bleeding has been noted with the use of ritonavir.
- Monitor for these symptoms and advise the woman to note any changes in her periods, especially when starting a new antiretroviral drug.
- Oral contraceptives may be used to regulate abnormal periods, but before prescribing them to the patient, check to see if there are any drug interactions with the antiretroviral drugs she may be taking.
- Advise the patient to:
 - Consider what else is happening in her life. For example, weight loss or stress may affect the periods as well, and addressing these issues may alleviate the menstrual problem.
 - For menstrual cramps, hold a hot water bottle or heating pad over the lower stomach or back, or take a hot bath. This will also reduce stress.
 - Do mild exercise, like walking or stretching. Exercise may increase blood flow and decrease period pain.

k. Hair loss

- Sudden or abnormal hair loss may result from taking certain medications.
- Advise the patient to:
 - Protect the hair from further damage or loss: avoid or decrease damaging hair practices or use them infrequently. These include dyeing, perming, straightening, braiding, using hair dryers and so on.
 - Stress can make hair loss worse, so taking steps to reduce stress and anxiety often helps.

SESSION 4 Case Studies: Managing Patients with Multiple Issues

PURPOSE

In this session, participants will receive two case studies of patients with multiple issues in order to apply what they have learned in Module 2 about managing patients with HIV-related diseases.

OBJECTIVES:

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

1. Identify the needs of the patient and give the probable cause of the patient's symptom.
2. Discuss the management and treatment for the presumptive diagnosis and any follow-up that may be indicated.
3. Discuss whether ART is appropriate for this patient, which ART regimen would be best and how the medicines can be managed to ensure adherence.
4. Discuss other clinical interventions that may be indicated.
5. Discuss the psychosocial and economic needs of the patient and any other issues that may need attention.

TIME:

2 hours

PREPARATION:

Make copies of the participant handouts for each case study.

- Step 1. Explain the purpose and objectives of the session (see above). (2 minutes)
- Step 2. Distribute copies of the case studies; ask participants to break up into small groups and discuss the following case studies using the questions as a guide.
Select one participant to facilitate each group. That person's role is to read the case studies to his or her group and facilitate the discussion. Explain that this facilitator should stop at each set of questions to allow the group to discuss the questions before moving on to the next part of the case study.
- Ask one participant in each group to record the main points from the discussion on a flip chart paper. (60 minutes)
- Then bring the participants together again and ask each recorder to report on the group's discussion. Add any information or comments from the suggested responses to the cases in the trainer's guide, below.
Discuss any questions participants may have. (1 hour)

Note: You may do this exercise in several different ways. You could do it with the entire group if you have a small number of participants or you could have the participants break into two smaller groups, have each group discuss a different case study and then have the recorder from each small group report on the discussion to the entire group.

PARTICIPANT HANDOUT: CASE STUDY 1

CASE STUDY 1: MULTIPLE ISSUES

Mrs. N is a 45-year-old widow who is a known HIV-positive patient (diagnosed in 1999). She has been coming to your health center for many years. She has three adult daughters, one of whom accompanies her today. Mrs. N complains of a chronic dry cough and intermittent headaches that are not severe. Today, Mrs. N's daughter tells us that the family wants her mother to start ART.

Medical history:

Herpes zoster in 1999

Diagnosed with TB in 2000, recurrence of active TB in December, 2002

Positive HIV test: 1999

Physical exam:

Weight: 54 kg; 12/02 59 kg

General: Fatigued

Orientation: Alert, oriented X 3

Eyes: Pale conjunctivae

Throat: White clusters on pharynx, light white coat on tongue (patient denies difficulty swallowing or pain on swallowing)

Lungs: Clear

Abdomen: Soft, no tenderness, without hepatosplenomegaly

Current medications:

Rifampicin, INH, pyrazinamide, ethambutol, cotrimoxazole. Laboratory tests ordered

Adherence: Good

Plan:

Laboratory: Complete blood count, LFTs, renal function tests, CD4

Return appointment in one week for the lab results

Question:

What other needs does this patient have that might require referral or immediate attention?

1. Is the prescribed treatment appropriate for the presumptive diagnosis?

Why?

Why not?

Continuing Case Situation

It is four days later.

Mrs. N returns to the health center with her three children, unable to talk or walk. Her daughter reports that the patient complained of worsening headaches. During the past two days, her speech and ability to ambulate have progressively decreased. She also had two episodes of vomiting. There has been no seizure activity.

Physical exam:

Clouded mentation

Aphasia

Afebrile

Left hemiparesis

Normal babinski

Laboratory findings:

RBC 3.090/mm³, Hg 9.1 gr/dl, Hct 28.6%, WBC 2.600/mm³

Liver function tests normal

Renal function tests normal

CD4 24/mm³; CD8 360/mm³.

2. What is the probable cause of the patient's symptoms?

3. What course of treatment do you recommend?

4. Is the prescribed treatment appropriate for the presumptive diagnosis?

Why?

Why not?

Continuing Case Situation

After three weeks, the patient and her children return for follow-up.

The patient is alert and oriented X 3, her speech is normal, the paresis has diminished, but she is unable to walk without assistance.

Her weight is 52 kg; Hg 9.7 gr/dl.

Her daughter reported that it was difficult to find the medications prescribed at the last visit. Folic acid was available at a nearby pharmacy, but the family had to go to a neighboring country to purchase the two other drugs. Covering the cost for a six-week supply of the three drugs (\$367.04) was also difficult, and they purchased a four-week supply with assistance from a family friend.

5. What steps can be taken to assure that the patient will obtain the needed supply of drugs and complete the initial treatment?

What about drugs for maintenance treatment?

6. Are the psychosocial and economic needs of this patient being addressed?

The patient wishes to start ART. To monitor medication adherence of patients starting on ARVs, the health center has a modified DOTS policy: during the first six weeks of treatment, the patient must take the morning dose in the presence of the facility's ART nurse. This patient, however, does not want to come to the health center each day.

7. Is starting ART appropriate for this patient at this time? Why? Why not?

8. When ARTs are started, what ARV regime would you prescribe?

9. What should be done to assure adherence?

10. What other clinical interventions are indicated for this patient at this time?

TRAINER'S GUIDE: CASE STUDY 1

Suggested Responses to Case Study 1

1. Identify any needs of this patient – initial visit

- Weight loss: referral for nutritional consult
- Symptoms of oral candidiasis: initiate treatment with nystatin

2. What is the probable cause of the patient's symptoms?

- The likely diagnosis is toxoplasmosis. The patient exhibits several common symptoms, including headache, altered mentation, lethargy, vomiting, hemiparesis, ataxia and aphasia. Although fever is often associated with this infection, it does not occur in all patients.

3. What course of treatment would you offer?

- In cases of acute toxoplasmosis, it is recommended that a patient be hospitalized. In this case, the family refused.
- You should start pharmacologic treatment immediately. Supportive treatment to manage her nutritional status, hydration, pain and safety is also indicated.

4. Is the prescribed treatment appropriate for the presumptive diagnosis?

- Pyrimethamine: a loading dose of 200mg is preferred, then 50 mg qd
- Sulfadiazine 4-8 g qd
- Folinic acid 10 mg qd

This combination is prescribed for six weeks. Rapid clinical improvement is expected (usually within one week). Treatment is followed by a lifelong maintenance regime.

- Pyrimethamine 25-50 mg qd
- Sulfadiazine 0.5-1 g qid
- Folinic acid 10 mg qd

The role of immune reconstitution is under study; discontinuation of maintenance therapy is currently recommended when $CD4 > 200/mm^3$ for > 3 months.

5. What steps can you take to assure that the patient will obtain the needed supply of drugs and complete the initial treatment? What about drugs for maintenance treatment?

- First and second line drug regimens to treat an opportunistic infection, such as toxoplasmosis, must be available to manage the infection effectively. In this case, the family attempted to obtain the prescribed drugs without informing the health center of the difficulties they were having.
- Instruct patients and their household members to report difficulties such as these to the health center to immediately.
- Establish referrals to pharmacies to secure drugs, as needed.
- Discuss drug stock issues with appropriate authorities in your country, including the Ministry of Health, the national AIDS organization and the pharmaceutical regulatory agency.

6. Are the psychosocial and economic needs of this patient being addressed?

- Because HIV affects not only the physical, but all dimensions of the person, support in such areas as mental health, finances, spirituality and socialization are essential components of care.

Does your health facility have a referral network for psychosocial and economic assistance for PLHA and their households?

If it does not, what are the steps to develop a functioning network?

- You should inform the patient and household members about the possibility of referrals for community social and economic services, and how to access this network.
- Has your facility established a costing policy for HIV care? What measures can be taken to cover the cost of drugs so that the patient can continue her treatment and maintenance therapy?

This is open-ended, as no definitive answers currently exist. Encourage participants to brainstorm and develop creative, but viable, strategies.

7. Is starting ART appropriate for this patient at this time?

- Treating an opportunistic infection first, before starting ARVs, is a general principle of ART management.
- For toxoplasmosis, treatment lasts a minimum of six weeks. By the last visit, the patient had completed three weeks of treatment and was exhibiting signs of favorable response to treatment.
- With a CD4 of 24, she is extremely vulnerable to infection in general. Anemia is also pronounced.
- In addition to the toxo treatment, the patient takes an anti-TB regime of four drugs.
- The prudent approach is to defer ARVs for three additional weeks and continue to monitor the patient's functional status and resolution of CNS symptoms. If she exhibits continued clinical improvement, start ART.

8. What ARV regime would you prescribe?

- The recommended regime is:
 - d4T 30 mg (lower dose because her weight is < 60 kg)
 - 3TC
 - Efavirenz (increase dose to 800 mg qd)
- Avoid AZT because of patient's anemia.
- Advise patients of and monitor for the possible CNS effects of Efavirenz.

9. When ART is appropriate, how can the medications be managed to assure adherence?

- Patient's daily pill burden is high (without ARVs), but she has history of good adherence.
- She has a supportive family whose role in medication adherence you can encourage.
- Schedule the patient to visit the ART nurse at the health center twice weekly for the initial six weeks of ART. You can dispense enough pills for the doses between visits.
- Instruct patient and family members about each medication, dose, schedule and possible adverse effects. Instruct them to report any adverse effect to the ART nurse immediately. Instruct about whom to contact and where to go during the hours that the health center is not open.

10. Are there other clinical interventions indicated for this patient at this time?

- Are the patient's headaches totally resolved? Treat pain as indicated.
- Instruct on hygienic measures. Good hand washing is key. Patient's immune status is severely compromised, and good hygiene is essential.
- The patient has lost additional weight. Nutritional interventions are indicated. Schedule visit with nutritionist; high iron foods should be encouraged (for example, lentils, beans, peanuts, groundnuts, dried fruits and, if possible, red meat, poultry, shellfish and eggs).
- Discuss the patient's safety. Until she is stronger and her gait is steady, allowing her to ambulate safely without assistance, explore measures to assure safety. Is an adult or adolescent at home with her at all times to help with walking and to be certain that her needs (food, hygiene) are being met?
- As the patient is able, encourage her to do light exercise (in the beginning, lifting arms and legs) to work muscles.

11. What other aspects of this patient's care require attention?

- Assess the patient's mental status: is she depressed? If yes, arrange referral for mental health services.
- How is the cost of the patient's current medications (toxco meds and anti-TB meds) being covered? Refer to Social Services for guidance and assistance.
- Assess caregivers' needs: How are they coping? Are they overwhelmed by the patient's health needs? If home care is available, would the patient and her family be interested in a referral? Would they accept visits or assistance from a local PLHA group?
- Do the patient and her family have other needs, for example, legal issues? Refer to Social Services, as needed.

CASE STUDY 2: MULTIPLE ISSUES

A 32-year-old woman is hospitalized in a district hospital with diffuse lesions on her face, all extremities and her back. This is her second hospitalization in the past three months.

Family members, including her mother, several sisters and brothers, visit regularly. They report that the patient's husband left home two years ago and that her three-year old son died six months ago from a respiratory infection. The patient currently lives with a sister and the sister's family. The sister indicates that the patient has been getting weaker and spending more time in bed. Her appetite is poor.

Medical history:

Latent TB (1997) followed by a course of INH (adherence unknown)

Oral candidiasis (1997)

Herpes zoster (1998)

Chronic diarrhea

Lymphadenopathy

Physical exam and symptoms:

Weight: 41 kg

Previous hospitalization: 44 kg

Dysphagia

Pale conjunctivae and nail beds

Dry skin and oral mucosa

Dry cough

Diminished lung sound bilaterally

Mild hepatomegaly, no pain on palpation

Current medications:

ART (started last hospitalization): combivir and nevirapine

Cotrimoxazole

Laboratory findings:

Red blood cell count: $2.802/\text{mm}^3$; hemoglobin: 8.7 gr/dl ; hematocrit: 26.1 percent

White blood cells: $2.300/\text{mm}^3$

Liver function tests: mildly elevated

Renal function tests: normal

CD4 (3 months ago): $21/\text{mm}^3$; current: $22/\text{mm}^3$

1. How would you manage this patient?

2. What referrals can you make to assist the patient and her family when she is discharged home?

Continuing Case Situation

One month after the patient's discharge home, she returns to the hospital with additional lesions, including two lesions in her mouth: one on the upper rear palate and the second on the posterior wall of the oropharynx. She reports dysphagia and odynophagia. The patient also complains of intermittent pain in the right upper abdominal area. She has lost an additional 2 kg.

She continues to take combivir, nevirapine and cotrimoxazole, but says that even when the pills are crushed, it is hard for her to swallow these drugs.

On examination, you note increased hepatomegaly, with pain on palpation of the liver. There is bilateral lower extremity 3+ pedal to midcalf edema. Laboratory test results are comparable to those of the previous hospitalization, with the exception of increased elevation of liver function tests.

You initiate chemotherapy, including: vinblastine 3.7 mg/m² IV single dose, with plans to increase weekly by 1.8 mg/m² to maximum of 5.5 mg/m² weekly.

3. Discuss the current management of this patient. What else would you offer?

Continuing Case Situation

One month has passed, and the patient remains in the district hospital. She is very weak, is unable to get out of bed and needs assistance to walk. Her family members no longer visit. They say they cannot care for her at home and that it is too difficult to see her in this condition.

The patient responds to questions appropriately but is minimally interactive. She continues to have difficulty swallowing and often refuses to eat. The nurses crush her medications and mix them with soft foods, but the patient frequently gags and is unable to swallow the mixture. The patient's abdomen is now grossly distended. She complains of increased pain in the upper right quadrant, radiating to her back.

The attending staff is considering additional diagnostic workup of the distended abdomen. Discontinuation of the ARVs and the chemotherapy is also being considered. Treatment options have not been discussed with the patient.

4. Identify the needs of this patient.

5. How would you manage this patient at this point?

6. Discuss the proposed discontinuation of ARVs and chemotherapy. What issues are involved?

TRAINER'S GUIDE: CASE STUDY 2

SUGGESTED RESPONSES TO CASE STUDY 1

1. How would you manage this patient? (1st hospitalization)

- Check sputum for TB.
- Rehydrate with IV fluids.
- Refer for nutrition consult and counseling.

2. What referrals can be made to assist the patient and her family when she is discharged home?

- Home care to assist patient with ADLs; monitor and use strategies to promote medication adherence; monitor nutritional status and food security.
- Determine how the cost of the patient's medications is covered. Refer to Social Services if needed.
- Discuss other needs with the patient and her family before discharge, and make referrals, as appropriate.

3. Discuss the current management of this patient. What would you offer?

- Is chemotherapy appropriate for this patient?
This is open-ended, to encourage discussion and rationales (pro or con).
- Chemotherapy for KS is palliative, not curative.
- Monotherapy for treatment of disseminated KS is suboptimal (except for liposomal daunorubicin). Is the patient able to tolerate the addition of vincristine or adriamycin + bleomycin? Is this treatment available locally?
- Nutritional consult is a high priority.
- Pain management is a high priority.

4. Identify the needs of this patient.

- The patient is assessed to be lucid. She is capable of discussing her needs and wishes regarding her health.
- The patient-provider relationship is essential to effective, ethical health care
- What does the patient wish at this time? Discuss all treatment options; the patient has the right to know what these options are.

5. How would you manage this patient at this point?

Open-ended discussion

- Suggested probing questions:
- Is further diagnostic workup indicated? If yes, what specifically?
- Is a change in ARV regimen appropriate?

6. Discuss the proposed discontinuation of ARVs and chemotherapy. What issues are involved?

- Are there ethical issues involved?
- Does your facility have guidelines for discontinuing treatment?
- Do the patient's wishes need to be in writing?
- Should the patient's family be involved in the discussion?

References

PART A: MODULE A4

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