TRAINING MANUALS FOR PHARMACISTS ON THE USE OF ANTIRETROVIRAL DRUGS IN NIGERIA

(First Edition: 2005)

Produced by

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In Collaboration with

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With the Support of

APIN

TRAINING MANUALS FOR PHARMACISTS ON THE USE OF ANTIRETROVIRAL DRUGS IN NIGERIA

FIRST EDITION: October, 2005

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FORWARD

Infection with the Human Immunodeficiency Virus (HIV) which is the causative agent of the Acquire Immunodeficiency Syndrome (AIDS) remains the greatest public health problem of this age. The first cases of HIV infections and AIDS were diagnosed in the USA in 1981 amongst homosexual drug abusers. Essentially, the infection spread so dramatically that by 1987 cases had been diagnosed in virtually all countries of the world. The pandemic had touched virtually all aspects of the social fabrics of most nations. It has affected men and women in urban and rural areas, as well as adolescents high and low profile politicians and socialities, servicemen and women, public and private sector workers, students and sex workers.

Despite several strategies to prevent emergence of new infections, the morbidity and mortality rates of HIV increased progressively in several countries. As new cases emerged, the pool of people living with the virus continued to increase and a substantial number were dying of AIDS. The impact of the pandemic was initially on the health sector but it soon evolved to enormously affect the socio-economic and development sectors. In most countries, the pandemic has had a selective impact on young men and women who constitute the mainstay of agriculture, education, commerce, industry and health. These developments stimulated efforts to strengthen preventive efforts as well as develop strategies for care and support of those already infected.

A turning point in the global control of the pandemic was the development of the Antiretroviral Drugs (ARVs). The use of adequate combination of ARVs was documented to be effective in the clinical management of HIV infections. The ARVs reduce morbidity and mortality of those infected through sustainable suppression of viral replication and reconstitution of the depleted immune system. The beneficial aspects of ARVs encouraged countries to adopt their use in the clinical management of HIV infections. However, ARVs are a new set of drugs with different levels of potencies and side effects. Their use in proper combinations achieve the desired results. However, when there are not properly used, treatment outcome can be enormously adverse. It is therefore imperative that health care personnel implementing ARV programmes must be adequately trained on the proper use of the ARVs.

In 2002, the Federal Government of Nigeria initiated a national ARV programme. Subsequently, other ARV programmes were initiated by various stakeholders including non-governmental organizations, faith-based organizations, state and private sector health facilities. To ensure that these programmes are properly implemented, there was the need to adequately train the various health personnel implementing these programmes. A training manual was developed by the Nigerian Institute of Medical Research in 2003 to meet this challenge. With this manual, several health personnel implementing ARV programmes in the country were trained between 2004 and mid 2005. A recent exercise was carried out by a team of consultants to evaluate the impact of these previous trainings on the quality of the ARV programmes implemented. One of the major recommendations in the outcome of the evaluation exercise was the need to develop specific training manuals for the various cadres of health care personnel. This was against the rather generic manual which was used in the earlier training programmes for all cadres of personnel including Doctors, Pharmacists, Nurses, Counsellors, Laboratory Scientists and Record Officers. It was envisaged that the use of specific modules for each cadre will help enhance the knowledge base of each group on the proper use of ARVs.

This challenge of developing new manuals was further taken up by the Nigerian Institute of Medical Research with the support of the Federal Ministry of Health and other agencies. The efforts have resulted in the development of separate training manuals for Doctors, Pharmacists and Nurses on the use of ARVs in the country. This achievement came at a good time in view of the need to continuously build a critical mass of trained personnel to sustain the national ARV scale up plan which is envisaged in the country in the next five years. I therefore highly commend the efforts of NIMR, NACA, NASCP and APIN for putting these new training manuals together.

It is with pleasure that I recommend this training manual for phramarcists for wide usage by all sectors and stakeholders implementing ARV programmes in the country.

Professor Eyitayo Lambo
Honourable Minister of Health
Federal Republic of Nigeria.

PREFACE - FMOH

Despite the fact that in the past two decades several preventive strategies have been implemented in the developed and the developing countries, the HIV/AIDS pandemic is still growing globally. While the number of new cases is declining or stabilizing in the developed and a few developing countries, new infections are still emerging at a geometric rate in several developing countries. Africa and South-East Asia are bearing the greatest brunt of the pandemic as the two continents account for over 75% of the estimated 40million people living with the virus globally in 2004. Cumulatively, the pool of people infected globally is growing, and a substantial number are dying of AIDS.

Clinical management of infected individuals had essentially been palliative with focus on adequate nutrition and effective treatment of associated opportunistic infections. The development of the antiretroviral drugs in the mid 1990s was a landmark in the global control and management of those infected. Though the drugs don't offer a complete cure, their proper use has been documented to significantly reduce mortality and morbidity amongst those infected. Indeed the antiretroviral drugs, when taken in right combinations, have been reported to suppress viral replication and enhance the reconstitution of the immune system of those infected. These attributes of the ARVs have encouraged several countries to adopt their use in the clinical management of HIV infections.

A national ARV programme was initiated in Nigeria in 2002. Since then many more ARV programmes are being implemented in various centres in the country. The desire for the proper use of the ARVs to enhance the quality of the treatment underlined the need for training of the health personnel involved in the implementation of these programmes. Also with the proposed scaling up of the national programme, it has become imperative to train personnel that will implement the programmes in the new sites. The initial challenge was developing adequate manuals for the training programmes. However, with the support of APIN, the training manuals were developed by NIMR in 2003. With these manuals several training programmes were carried out between 2004 and mid 2005. However, it was observed that the training will be more effective if separate training manuals are used for the various cadre of personnel; namely, Doctors, Pharmacists, Nurses, Counsellors, Laboratory Scientists and Record Officers.

Efforts were deployed to develop these documents and by the end of third quarter of 2005, separate training manuals had been developed for the various cadre of personnel. These documents will serve as effective training companions to the health care providers for a better understanding of the fundamentals of ARV therapy. I therefore wish to recommend these manuals to the various health personnel especially those involved in the implementation of ARV programmes. I want to particularly commend the members of the Expert and Review Committees, other technical partners particularly NASCP, NIMR, NACA, APIN who contributed to the successful completion of this activity. The Federal Ministry of Health is also pleased to project this training programme as one example of the Health Sector Response Programmes of this administration.

DR. EDUGIE ABEBE mni
DIRECTOR OF PUBLIC HEALTH
FEDERAL MINISTRY OF HEALTH
ABUJA, FCT.

PREFACE - APIN

The global HIV/AIDS pandemic continues to spread with more than 40 million cases reported in 2004. Nigeria represents one of the top five nations in the world contributing to the global pandemic, largely due to its large population size. The Government of Nigeria has made significant efforts towards prevention and control of the HIV/AIDS epidemic and part of the response has included the critical attention to those already infected with the HIV virus and in need of antiretroviral therapy (ART).

It is well recognized that prevention efforts to encourage voluntary counselling and testing, prevention of mother to child transmission and behaviour change interventions are enhanced when access to ART treatment and care is provided. In this way, stigma is reduced and communities are encouraged to mobilize prevention efforts while caring for those already infected and affected by the virus. Enacted by the Federal Ministry of Health, the Nigerian ART program has already provided life-saving ART to over 15,000 Nigerians suffering from AIDS. The plans for massive scale-up of this program through the support of the Government of Nigeria and other international ART partners are ambitious but necessary to provide drugs to the 100,000s of HIV infected Nigerians still in need of ART. The early success of the program is noteworthy and provides confidence that the goals for roll-out and scale-up will be achievable.

As provision of ART has begun in many developing countries, it has become clear that a major obstacle to successful implementation is the need for training of all sectors of the health care system. In the absence of such critical training, ART provision and management would be doomed to poor quality, a lack of standardization and a low potential for sustainability. In 2003, the National Institute of Medical Research (NIMR) initiated a critical program to design and implement the training required for ART treatment and care throughout Nigeria. Spearheaded by the leadership and vision of the Director General, ***Dr. Emmanuel Idigbe***, the modules were first drafted with input of Nigerian and outside experts in ART diagnosis, clinical management, counselling, and laboratory techniques. Training modules were designed, edited and finalized with important consultation of all ART treatment partners in Nigeria.

As Nigeria embarks on scale-up of their National ART program, the contribution of all members of the health care delivery system is clearly warranted. The training of doctors and ART specialists is obviously important yet nurses and counsellors will play a major and under appreciated role in the sustained delivery and management of ART therapy, so critical to effective treatment and care. The training modules directed to these groups should be commended. The development of high quality laboratory standards required for monitoring of patients on ART is another challenge of ART provision in developing countries. Nigeria has tremendous capacity for developing this key component of the ART program and the developed laboratory worker training modules will provide the necessary foundation for development of this capacity. The Nigerian ART training modules not only represent the highest quality and state of the art training materials for ART provision, but through the coordinated development with Nigerian investigators, stakeholders and government, represent content that is appropriate and specific to the Nigerian context.

The AIDS Prevention Initiative in Nigeria (APIN) funded by the Bill & Melinda Gates Foundation has been honoured to contribute and support this important effort. Our program has not only considered training and capacity building as a critical foundation to Nigeria's prevention and control efforts, but also a requirement for a high quality and sustainable ART treatment and care program. The wide-scale implementation of these training modules will allow more and more ART centres throughout the country

to be developed and deliver high quality ART. The multidisciplinary approach will allow all sectors of the health care system to participate in this ambitious program allow for more rapid expansion and support their local sustainability. The Government of Nigeria has set high goals for the scale-up of the Nigerian ART program, the implementation of the Nigerian ART Training modules will play an important role in our efforts to achieve these goals.

The program will no doubt serve as a model to other developing countries as they look to Nigeria's example for guidance in developing their own ART national programs.
More widespread access to high quality ART treatment and care will facilitate and integrate well in Nigeria's HIV/AIDS prevention and control programs already underway. We acknowledge this important contribution and remain confident that it will aid in our efforts to impact the HIV/AIDS epidemic in Nigeria.

Prof. Phyllis Kanki
Director
AIDS Prevention Initiative in Nigeria (APIN)
Harvard School of Public Health
Boston, USA.

ACKNOWLEDGEMENT

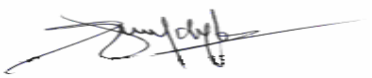
The Federal Government of Nigeria initiated a national antiretroviral treatment programme in 2002. Under this programme, 10000 adults and 5000 children living with the virus were to be treated in 25 health facilities. This was followed by other ART initiatives by NGOs, FBOs, the Organized Private Sector, the AIDS Prevention Initiative of Nigeria (APIN), the USA President's Emergency Programme for AIDS Relief (PEPFAR) and the Global Funds Programmes. The thrust of these other initiatives was to ensure that more people living with the virus have access to ART in the country.

For these programmes to be effectively implemented, it was pertinent to train the health care providers working in the various ART centres, on all issues related to national antiretroviral drug administration and monitoring. The Nigerian Institute of Medical Research was charged with the responsibility of conducting these training programmes. A training manual was subsequently developed by the Institute and in 2004/2005 several training programmes were carried out. A team of health personnel was trained from each ART centre and this comprised of a doctor, pharmacist, nurse, counsellor, laboratory scientist and record officer.

In June 2005, the impact of the training programmes was evaluated by a team of independent consultants. One of the main recommendations from the evaluation exercise clearly identified the need to develop separate training manuals for the various cadres of health personnel in place of the rather generic manual that was used in the previous training programmes. This edition of the training manual for Pharmacists was therefore developed as an outcome of the evaluation exercise. This revision came at a good time, when cummulative efforts are being directed towards a further scale up of the ARV treatment programmes in the country. It therefore became imperative to build a critical mass of health care providers with adequate expertise to sustain these various scaling up programmes.

This revised manual essentially addresses the training needs of Pharmacists to effectively provide antiretroviral therapy as well as other components of care and support of people living with the virus. To achieve this, an expert committee whose membership comprised of experienced Pharmacists from Public Sector Establishments, Pharmaceutical Industries, Schools of Pharmacy, Research Institutes, Teaching Hospitals, International Agencies and the Organised Private Sector Establishments was set up. The task of the committee was to review the earlier manual and develop the outline and content of a new manual that will be specific for Pharmacists. The draft recommendation of this expert committee was further reviewed by a sub-committee for its structure and content validity. Subsequently, this final version of the manual was developed by a consultant.

I would therefore want to acknowledge the brilliant efforts and contributions of the members of the Expert Committee as well as members of the Review Committee. They have been adequately listed in the document. I would also like to acknowledge the efforts of our consultant Dr. M. O. Ukpong, who developed the manual and those of the members of the monitoring and evaluation team and respondents who took part in the exercise. Finally, the Institute is grateful to the AIDS Prevention Initiative in Nigeria (APIN) for providing the financial support for this project.



Dr Oni Idigbe
Director General(NIMR)

MEMBERSHIP OF THE EXPERT COMMITTEE

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2.	Mrs Oluremi Olaitan	Secretary	PEPFAR, NIMR, Lagos
3.	Dr. Oby Obodozie	Member	NIPRD, Abuja
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22.	Mrs. Osaretin E. Jaiyeola	Member	GlaxoSmithkline, Lagos

MEMBERSHIP OF THE REVIEW COMMITTEE

S/N	NAME	POSITION	ORGANISATION
1.	Mrs Oluremi Olaitan	Member	PEPFAR, NIMR, Lagos
2.	Mrs E.C. Herbertson	Member	NIMR, Lagos
3.	Mrs. Edosa Ogbeide	Member	NAFDAC, Lagos.
4.	Mr. Kayode Aiyegbajeje	Member	General Hospital, Lagos
5.	Pharm. Godfrey O. Obiaga	Member	C/O NIPRD, Abuja.
6.	Prof. Elijah Sokomba	Member	UNIJOS, Jos

OVERVIEW OF THE TRAINING PROGRAMME

This training targets all Pharmacists who provide clinical care and support to patients infected with HIV in health care settings. Course participants include Pharmacists working in the public, private and government hospitals (primary, secondary and tertiary health care institutions)

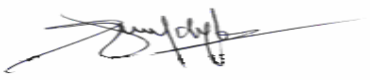
Trainers who use the various modules must be experts in their particular field. The training design uses an integrated approach to antiretroviral therapy taking cognisance of the roles of clinical pharmacy and pharmacy management in the adequate management of HIV-infected patients in health care settings. The manual consists of nine (9) training modules to be taught over a minimum of six days and maximum of twelve days. The modules are:

- Overview of HIV/AIDS
- Pharmacotherapeutics of HIV/AIDS
- HAART and Other Forms of Therapy
- Identifying the Role of Pharmacists in PLWHA Care
- Management of Opportunistic Infections
- Pharmaceutical Care in HIV/AIDS
- Adherence to Antiretroviral Therapy
- Managing Procurement and Logistics of HIV/AIDS Drugs and Related Supplies
- VCCT and Home Based Care

Specifically, this module is developed as a trainer of trainers manual. The concept is to train a critical mass of trainers that can act as facilitators at the geopolitical zones and train other health care personnel in the region. The training session entails taking an interactive lecture session in the mornings and ending the day by performing activities that would enhance their knowledge and skills through the application of the concepts learnt from the lectures. Practical sessions include visit to institutions where ARV therapy are located, demonstration of laboratory techniques and a lot of work that facilitates networking.

A complementary resource book published by NIMR should be used along with the manual to facilitate the understanding of the content of the lecture notes.

The concept of antiretroviral therapy is ever changing and so would the content, structure and duration of this manual. The intent is that this edition would be reviewed periodically. Comments are therefore welcome on the content of this manual.



Dr Oni Idigbe
Director General
NIMR

List of acronyms

AIDS - Acquired Immune Deficiency Syndrome

ALT – Alanine Transferase

ART – Antiretroviral Therapy

ARV - Antiretroviral Drugs

AZT - Azidothymidine (Zidovudine)

BCG - Bacillus- Calmette-Guerin

CBOs - Community Based Organisations

CDC - Centres for Disease Control

CMV - Cyclomegalovirus

CTZ – Co-trimoxazole

DNA – Deoxyribonucleic Acid

EBF - Exclusive Breast Feeding

ELISA - Enzyme-linked Immunosorbent Assay

FMOH - Federal Ministry of Health

FTC - Emtricitabine

HAART - Highly Active Antiretroviral Therapy

HIV - Human Immunodeficiency Virus

IEC - Information, Education and Communication

IgG - Immunoglobulin G

INH - Isoniazid

MAC – Mycobacterium Avium Complex

MTCT - Mother-to-Child Transmission

NACA - National Action Committee on AIDS

NAFDAC - National Agency for Food and Drug Administration and Control

NASCP - National AIDS/STDs Control Programme

NGO - Non Governmental Organisation

NNRTI - Non Nucleoside Reverse Transcriptase Inhibitors

NRTI - Nucleoside Reverse Transcriptase Inhibitors

NtRTI - Non Nucleotide Reverse Transcriptase Inhibitors

NVP - Nevirapine

OIs - Opportunistic Infections

OPV - Oral Polio Vaccine

PABA - People affected by AIDS

PCP - Pneumocystis carinii pneumonia

PCR - Polymerase Chain Reaction

PI - Protease Inhibitors

PLWHA - People Living with HIV/AIDS

PMTCT - Prevention of Mother-to-child Transmission of HIV

RNA - Ribonucleic Acid

STIs - Sexually Transmitted Infections

TB - Tuberculosis

TT - Tetanus Toxoid

UNAIDS - United Nations Joint Programme on HIV/AIDS

UNFPA - United Nations Population Fund

UNICEF - United Nations Children's Fund

USAID - United states Agency for International Development

VCCT - Voluntary Counselling and Confidential Testing for HIV

WHO - World Health Organisation

Introduction to the Use of the Training Manual

Teaching the course

Familiarise yourself with some in-depth knowledge of the manual. You can get more details by reading the topics in the training manual reference document developed specifically for use along with this manual. Ensure that trainers and participants have clear and accurate expectations about the course.

Trainers play a unique role in helping their audience confront the dynamics of the HIV/AIDS epidemic. Although you might be an expert in technical content and training, your role in this course extends beyond lecturing or providing information. Trainers need to inform, support and acknowledge implementation issues within the social and cultural context of the existing training setting to ensure a successful experience for all training participants.

This section will review the principles of adult learning generally and within the specific context of training to provide HIV/AIDS treatment, care and support.

Principles of adult learning

Principles to keep in mind when working with adult learners:

- Create a supportive learning environment and establish safe training practices e.g. be sure that learners feel confident their contributions will be received respectfully.
- Build trust with learners by demonstrating that you are committed to the course and are willing to share your own experiences.
- Provide opportunities for learners to practice what they are learning and to address feelings and ideas that may arise.
- Build teamwork and a sense of group belonging by encouraging active participation.
- Be accountable. Explain how you know what you know.
- Create a culturally sensitive and respectful learning environment by becoming familiar with local customs and values.

The role of the trainer in adult learning

The trainer's role is to facilitate the learning experience of the adult learner. To this end, you should create a climate in which participants can accomplish course outcomes and explore their life experiences to help them learn.

Trainer tips

- Emphasise the immediate usefulness and applicability of material presented. Adult learners are particularly receptive to information that will make a difference in their daily practice.
- Elicit personal experiences that are culturally sensitive and appropriate. Adult learners can bring a reservoir of experience to the course, and their contributions are an important resource for training programmes.
- Encourage group interaction and participation early in each session.
- Make an effort to learn participants' names early enough and to use their names whenever possible.
- Be available after each session to answer questions and discuss concerns.

- Consult with participants throughout each presentation to gauge their comprehension and attentiveness. Generally, the more side conversation and noise in a room, the less the participants are focused on the material. Pay attention to non verbal cues to gauge learners' attentiveness.
- Be clear, concise and easily understandable
- Do not judge participants, but assist them with learning – be encouraging
- Praise or thank participants when they perform an exercise well, participate in a group discussion, ask questions or help other participants.

Strategies for educating adults

Presentations and discussions

Use didactic training methods (as directed on the following page) to present scientific and technical content. Avoid reading directly from the overhead projectors or slides. Instead, supplement them with examples, practical problems, discussions and questions. Elicit feedback from the audience at critical junctures; encourage discussions.

Small group discussions

Facilitate small group discussions to foster team coherence. Those discussions provide trainers with an opportunity to validate or modify learners' perceptions and knowledge.

- Assign a topic, issue or question that participants can address in small groups.
- Designate a leader to facilitate and summarise the group's findings.
- Consider the task objective as you determine how to constitute groups. You might divide participants according to region (clinic X or clinic Y). If you want the groups split up randomly you could ask participants to count off by threes (or any small number): the first person is in group 1, the second is in group 2, the third is in group 3, the fourth is group 1 and so on.

Story telling

Use culturally appropriate stories from learners to illustrate critical points. Weave cultural beliefs and personal experiences into stories to convey information vividly.

Case studies

Present culturally relevant, actual or hypothetical clinical situations. Ask learners to propose solutions.

Interactive exercises and games

Use interactive exercises to facilitate team building and reinforce learning.

- Invite learners to consider a specific topic.
- Pose questions, allowing time for learners to record their answers.
- Encourage participants to discuss their answers and exchange ideas.
- Record responses on the flipchart and encourage learners to respond to the group's feedback.

Panel discussions

During group work sessions, use panel discussions to help participants gain insight into the physical, emotional and financial impact of HIV/AIDS. Panels with persons infected or affected by HIV can be a powerful tool for influencing the behavioural pattern of healthcare workers. Other panels that may be considered include:

- Healthcare workers panel: to share ideas for handling the emotional challenges of caring for patients with HIV infection.
- Ministry of Health leaders and staff panel: to provide information about national policies and strategies for fighting HIV/AIDS.
- Non Governmental Organisation (NGO) employees' panel: to share information about the important role of NGOs in providing PMTCT services and support for people living with HIV/AIDS (PLWHA).

The flow of training

Flow and pacing

Pay attention to the order and flow of activities to ensure that new information is assimilated at an appropriate pace. Make sure that learners complete the course with a clear action plan for applying their knowledge.

Didactic training

Didactic training progresses from the simple to the complex. The trainer first reviews and outlines fundamental concepts to establish a shared understanding of the basics. New material is integrated gradually and illustrated with practical examples when possible. Remember that learners can absorb and integrate only five or six new pieces of information at a time.

Trainer skills

Facilitating the group

Facilitation is **not** teaching, **not** telling, **not** lecturing, **not** preaching and **not** directing nor just a technique for running workshops. It is the facilitator's role to provide resources and structures for participants to explore, learn and develop.

A facilitator helps participants learn through individual and group discussions. As a trainer, you are the facilitator.

You should be thoroughly familiar with module content. Preparation is the key to conducting a successful training course. Complete the following before starting each module:

- Read module objectives and teaching exercises.
- Prepare for each of the exercises.
- Obtain and organise the materials needed.
- Ensure that you understand national policies.

Responsibilities of the facilitator include the following:

- Introduce each module and key concept.
- Lead group discussions and training exercises.
- Answer questions.
- Explain ideas and clarify issues.
- Discuss how learners can apply the information to their own work.
- Give constructive feedback.

Familiarity with the local cultural environment is essential to effective group facilitation. Training strategies could require modification to respect various cultural standards. For example, in some areas, cultural norms dictate unacceptable eye contact or physical proximity of the trainer and learners.

Managing challenging participants

In extreme circumstances the Facilitator must also be prepared to act as a conflict manager if conflict arises. Just remember, conflict can be helpful, leading to improved communication. Do not become involved in personal conflict or arguments. Your own views are really not important. Focus on what the group thinks and feel. You may encourage participants to reflect, question and evaluate their experiences but never force participants to accept your viewpoint.

Through training, continually assess the interpersonal dynamics of the group. Occasionally, the learning environment might be disrupted by individual participants. A challenging participant might be overly talkative or dominating in discussions. He or she may be disrespectful to other participants and as a result, other participants may be hesitant to express their opinions. Depending on the situation, the trainer should address such behaviours either in public or privately.

Encourage balanced discussion

HIV/AIDS is a controversial subject in many communities likely to stimulate discussions. To tackle key underlying issues and foster discussion, the trainer should actively engage participants who express disparate viewpoints. In some settings, the group might accept the position or approach presented in the curriculum, in others, the group could need additional time to reach consensus on complex issues.

Managing time

Times allocated for each section in the curriculum serve as guide only. All of the training content is important however; the trainer should acknowledge the particular needs, knowledge and experience level of the group and make adjustments accordingly. It is very important for facilitators to be disciplined with time allocation. However, do not try to run through all the activities at lightening speed to keep to a schedule. The Facilitator needs to run at a pace that suits the group. Remember, sometimes less will mean more. Keep an eye on time and learn to interrupt a discussion gently.

Each trainer may re-allocate time provided that the key concepts of each module are addressed and the programme presented as a comprehensive ART package within the overall time frame.

Course schedule

The course schedule is outlined in the manual. It is recommended that each module begins with an introduction of its overall goal and objectives as well as a brief introduction to the content of the module. This can be done in approximately 10 minutes.

Endnote

As a trainer, you are a facilitator of learning, not merely an instructor. Encourage participants to identify their aims and objectives for the course. As a trainer, you will help them accomplish these aims and objectives. Remember that all members of the group respect and learn from each other's unique skills, perspectives, and life experiences.

Trainer's preparation checklist

Daily preparation

Each day arrive with enough time to set up the materials and equipment and arrange the furniture and audiovisual equipment in a way that fosters learning and teamwork.

Climate setting

Ensure that the physical environment is comfortable, well lit, and adequately equipped. Create a psychological environment where learners feel accepted, respected, and supported.

Room setup

Because this course uses a combination of didactic, interactive, and experiential techniques, the classroom should have tables and chairs that can be rearranged easily. For didactic presentations, the room should be set up so that all participants can see the slides or overhead projections. For interactive activities, more informal arrangements work best. In either case, you may need to arrive early to organise the room.

Goals and objectives

Review each module's goal and objectives.

Course content

Review existing resources to ensure you have all background materials related to the course content. Although you will not be able to answer every question, try to master the curriculum content, related support materials and relevant examples.

Course materials and teaching aids

Be sure that all educational materials (overheads, flipcharts, and markers) are available and that equipment is in good working order.

Module 1
Overview of HIV/AIDS

Objectives

1. Update knowledge about HIV/AIDS and discuss any misconceptions and myths.
2. Understand the biology and structure of HIV, as well as its molecular variability and epidemiology globally, in Africa and particularly in Nigeria.
3. Describe the pathogenesis and natural progression of HIV infection

Content:

- The nature of HIV/AIDS
- The biology and structure of HIV
- The molecular variability and epidemiology of HIV
- Myths and misconceptions
- Impact of HIV in sub-Saharan Africa
- Staging of HIV infection
- Laboratory investigations

Materials required

- Overhead projector
- Data/Multimedia projector
- Transparencies
- Flipcharts and flipchart stand
- Markers
- Masking tape
- Laptop
- Diskettes/Other media storage devices

Time: 280 minutes

Pre-test *Time: 15 minutes*

Activity 1: Background history of HIV

Participants would have a good understanding of how HIV infection became a diagnostic entity and how the HIV virus was identified and characterized.

Time: 25 minutes

Activity 2: Impact of HIV/AIDS in sub-Saharan Africa

The session would discuss the impact of the HIV/AIDS at the macro and micro economic levels

Time: 15 minutes

Activity 3: Myths and misconceptions about HIV/AIDS

The session would highlight the various myths and misconceptions there are about HIV/AIDS, the implications for HIV control and how the health workers can help to address this

Time: 10 minutes

Activity 4: Biology and structure of HIV

The session would describe the specific biologic and structural components of the virus which contributes to its infectivity and makes it difficult to eradicate.

Time: 20 minutes

Activity 5: Molecular variability and epidemiology of HIV

The various strains, subtypes and recombinant forms of HIV and its global distribution will be shared with participants. The implications for vaccine and drug research will be highlighted. Also, the current status of the global epidemic will be discussed. The epidemic as it affects sub-Saharan Africa and Nigeria will be highlighted

Time: 25 minutes

Activity 6: Modes of transmission

Participants will update their knowledge on the various modes of transmission of HIV, the routes of infection most common in Nigeria and the risks associated with the different modes of transmission.

Time: 20 minutes

Activity 7: Mechanism of HIV Infection

The process of actual infection of CD4-bearing cells will be described. Participants will be instructed on the basic processes in HIV infection and replication.

Time: 20 minutes

Activity 8: Pathogenesis of HIV Infection

Participants should understand the progression of HIV infection from seroconversion until AIDS. The implications of this for laboratory investigations will also be discussed.

Time: 20 minutes

Activity 9: Staging of HIV infection

The staging of HIV-1 clinical signs and symptoms helps as prognostic indicators. Participants would learn about the various staging of HIV infection, its import for diagnosis and management of patients. Finally, the Nigerian case definition would be discussed

Time: 20 minutes

Activity 10: Laboratory investigations

Once a diagnosis is made, laboratory investigations are needed to help confirm the diagnosis. The session takes participants through the necessary investigations a patient would need to undertake to confirm a diagnosis of HIV-1 and those which would also form baseline investigation for possible antiretroviral (ARV) therapy

Time: 20 minutes

Activity 11: Group activities/discussions

Lecture/Facilitator's notes

Introduction

The facilitator shall introduce the goal and objectives of the module. The goal of the module is to update the knowledge of participants on the epidemiology, biology and pathogenesis of HIV. Together with participants, the risk factors and impact of the epidemic in Nigeria would be identified and possible intervention strategies identified. The objectives of the module should be highlighted: She (he) would then introduce the lecturer who would take participants through the content of the module.

Time: 5 minutes

Activity 1: Background history of HIV

- HIV infection was first identified among homosexual men in the United States of America in 1981.
- This observation resulted in an early hypothesis (and misconception) that AIDS resulted from behaviour specific to gay men because at that time in the 1980s' gay men sometimes inhaled amyl and butyl nitrate as 'poppers' to enhance sexual performance.
- This was largely dismissed when the syndrome was later observed in other demographic groups in Europe, America and Central Africa. HIV/AIDS did not originate from gay men and neither is its origin known.
- The observations of symptoms among heterosexual, bisexuals, homosexuals, haemophiliacs, intravenous drug users and in babies of infected mothers led to the inference that HIV was an infectious process and that transmission of infection was through body fluid, blood and blood products.
- This led scientists to begin investigating a host of other infectious agents for any seroepidemiological association with AIDS.
- Among the chief suspects were cytomegalovirus because of its association with immunosuppressant, Epstein Barr virus because of its known property for populating lymphoid tissue and hepatitis B virus because it was also transmitted by sexual exposure and blood. It was thought that perhaps one or more of these viruses may have mutated to cause a new clinical syndrome, AIDS.
- Comparative seroprevalence studies showed no convincing association between AIDS and any of these viruses or a score of other agents.

- The human T-lymphotropic virus Type 1 (HTLV-1) was recognised 2 years before the discovery of HIV and therefore only a few researchers were aware of its existence. Also, retroviruses were well known in animals and were associated with leukaemia and lymphoma rather than frank immunosuppressant. The virus HTLV-1 was found at highest rates in regions of the world where AIDS had not yet been diagnosed.
- Studies on the HTLVs showed that they preferentially infected and alter T lymphocytes, the cells most often affected by AIDS and that they could cause immunosuppression. Evaluation of persons with AIDS showed the presence of HTLV-related antibodies and reverse transcriptase enzymes.
- In 1983, the HIV virus was isolated by scientists working in the laboratory of Robert Gallo and at the same time by other scientists in France. It was initially named HTLV-III or the lymphadenopathy associated virus (LAV). This was later called human immunodeficiency virus or HIV, later termed HIV-1 after the discovery of HIV-2.
- In 1986, another retrovirus that resulted in immunodeficiency in humans was identified in West Africa. This virus was named HIV-2.
- HIV–2 is found predominantly in West Africa, Angola, and Mozambique where it represents less than 2% of all HIV infections

History of HIV/AIDS in Nigeria

- Since the first reported case in 1986, prevalence has increased over the years from 1.8% in 1991 to 5.0% in 2003.
- 3.8 million Nigerians 15–49yrs are estimated to be infected, the highest in the world
- 350,000 to 700,000 PLWHA require antiretroviral therapy.
- It is estimated that 100,000 HIV positive children are born annually and 1.2 million children have been orphaned since the beginning of the epidemic; the highest number for any country globally.

Activity 2: Impact of HIV/AIDS in Sub Saharan Africa

The impact of HIV infection on the individual

- Increases medical expenditure
- Hospital stay increases
- Self stigma may result with individual feeling guilty about infection

- May need to change job to be able to take up less stressful jobs
- Associated stigma may mean loss of employment, housing and insurance policies

The impacts of HIV infection on the family

- Increased spending on medical bills
- More time may need to be spent with the sick
- Children may have to drop out of school because of financial constraints
- Loss of a bread-winner may lead to poverty

The impacts of HIV infection on the community

- The community gets depleted of resourceful individuals
- Elderly ones are left to cope with children

The impacts of HIV infection on the nation

- The microeconomics of the nation is affected
- More resources would have to be diverted to health care needs
- The productivity of the nation decreases
- The nation may be stigmatized

Activity 3: Myths and misconceptions about HIV/AIDS

Myths:

- HIV/AIDS is not real
- It is an American invention to discourage sex
- HIV has a cure
- Sex with virgins cure HIV infection
- People infected by HIV are promiscuous

Misconceptions

- HIV infection does not occur through a single sexual contact
- HIV infection is prevented by not ejaculating into the vagina
- Simple contact with a person infected with HIV can cause infection

- Mosquito bites can transmit HIV infection

Cultural issues that fuel the HIV epidemic

- Polygamy
- Widow inheritance
- Wife hospitality
- Traditional circumcision and rites

Role of health care providers in correcting myths and misconceptions

- Dissemination of factual information
- Eliminate stigma in the health care setting

Activity 4: Biology and structure of HIV

(Mount the picture of the virus on the transparency and teach with the aid of the transparency. This would enhance participant's understanding)

- The virus is made up of two parts – the outer envelope and an inner core. The outer envelope has glycosylated protein spikes that extend outward (gp120) and are the first viral proteins to be exposed to the immune system.
- The core is enclosed in a coat made of protein known as p24. Within the core protein are two identical strands of RNA.
- The RNA is the genome or repository of the genetic information of the virus.
- In addition to the RNA, the core contains three enzymes called reverse transcriptase, integrase, and protease.
- The RNA genome is made up of three major genes, *gag* (group-specific antigen), *pol* (polymerase) and *env* (envelope) which code for different products that become structural and non-structural parts of the virus.
- In addition, HIV-1 has a number of regulatory and accessory genes including *vif*, *vpr*, *tat*, *rev*, *vpu* and *nef* that encode proteins that are essential to the viral life cycle.
- There are two main types of the virus – the HIV-1 and HIV 2 viruses. They demonstrate similar virologic properties and common life cycle. They very similar features and structures under the electron microscope. There is little difference in their effect on cells. However,

HIV-2 has an additional regulatory and accessory gene – the *vpx* gene. It also utilizes more co-receptors than the HIV-1 virus to bind to cell surfaces.

Activity 5: Molecular variability and epidemiology of HIV

Molecular variability

(Mount the picture of this global distribution of the various HIV subtypes and teach with the aid of the transparency. This would enhance participant's understanding)

- The analysis of the sequences of the HIV genome led to the classification of the HIV-1 strain into three groups – M (major), N (non-major) and O (outlier).
- The latter two are limited to West and Central Africa.
- Group M, the most common globally, is further divided into nine subtypes namely, A, B, C, D, F, G, H, J and K
- A number of other forms arise from a recombination of the subtypes. These are known as recombinant forms. Recombination occur when an individual is superinfected with two or more subtypes or groups of HIV-I.
- Co-infection of HIV-1 and HIV-2 can occur but recombinants of the two types have not been reported.
- Subtype C is the most predominant subtype globally and is most often seen in Southern Africa and the Horn of Africa. It is also observed in India and China.
- Subtype A is commonly seen in Central, West and East Africa.
- The predominant subtype in Nigeria is the A/G recombinant, also called Circulating Recombinant Form_02/A/G or CRF_02/A/G.
- The subtype in Western Europe and North America is the subtype B. Most of what we know about HIV-1 comes from studies of HIV-1 subtype B.
- Most of the diverse groups of known HIV-1subtypes have been found in Africa. All HIV-1 subtypes have been reported in Central Africa.

Epidemiology

(Mount the transparencies on epidemiology of HIV. this would enhance participant's understanding)

- In the first decade of the AIDS pandemic, cases were reported largely from North America, Europe, Australia and part of Latin America.

- In the second decade of the global pandemic, studies showed rapid increase in HIV-1 infection in Asia, Africa and further increase in the number of people infected in Latin America.
- Although the prevalence of HIV-1 infection is decreasing in North America and Europe, success in containing the infection globally is being overwhelmed by failure to prevent millions of new infections in Africa and Asia.
- Globally, 47 million people have been infected with HIV infection. As of December 2004, 39.4 million people are estimated to be living with the virus. Of these, 37.2 million are adults, of which 17.6 million are women and 2.2 million are children under the age of 15 years. Approximately 20 million adults and children have died from HIV/AIDS and an estimated 14 million children have been orphaned by HIV/AIDS.
- According to UNAIDS, about 14,000 new infections occurred *each day* in 2004. Of these new infections:
    - About 6,000 of these were persons 15 to 24 years old.
    - Almost 2,000 each day were in children younger than 15 years old.
    - Most of the infections in children younger than 15 years old occurred through mother-to-child transmission (MTCT) of HIV.
- Sub-Saharan Africa is the worst affected by the epidemic with 28 million of the global 40 million infected persons living on the continent. In 2003, 3.4 million Africans became infected with HIV-1 of which 700,000 were children under 15 years. In the same year, 2.4 million people died of AIDS in sub-Saharan Africa.
- In Nigeria, the picture is the same. The national prevalence in 2003 for HIV-1 is 5.0% with some states having as high as 12%. 3.5 million Adults are infected with HIV-1 with Nigeria being the third worst affected nation in the world after South Africa and India.
- Since the first reported case in 1986, prevalence has increased over the years from 1.8% in 1991 to 5.0% in 2003.
- 3.8 million Nigerians 15–49yrs are estimated to be infected, the highest in the world
- 350,000 to 700,000 PLWHA require Anti-retroviral therapy (ART).
- It is estimated that 100,000 HIV positive children are born annually and 1.2 million children have been orphaned since the beginning of the epidemic; the highest number for any country globally.

Activity 6: Modes of Transmission

Sexual exposure:

- Heterosexual exposure is the main mode of transmission of HIV in Nigeria and other parts of sub-Saharan Africa.
- This risk of infection from sexual intercourse depends on a number of factors including:
  - The type of sexual practice (most infections occur through vaginal intercourse though evidence exists as to the increased risk of infection from receptive anal sex)
  - Susceptibility of the exposed individual (the lower the immune status, the higher the risk of infection)
  - Gender (women are more susceptible to infection than men because of prolonged contact of the virus with the vaginal and cervical mucosa compared with the male penis and urethral orifice)
  - The presence of concurrent genital infections (usually arising from sexually transmitted infections).

Perinatal transmission:

- This term is used for mother-to-child transmission.
- It takes cognizance of all the various routes a child can get infected with the virus from the mother.
- An infected mother can infect her child during her pregnancy, at the time of delivery or through breast feeding.
- The sperm of the father and the ovum of the mother do not appear to play a role in the infective process.
- Rather, during pregnancy, the virus could:
  - cross the placenta barrier
  - there could be contact between the mother and child's blood during passage through the birth canal and exposure to virus infected tissues and fluids
  - the virus could be transmitted to the child through the breast milk
- The proportion of HIV-infected women who pass on the infection to their infants in sub-Saharan Africa range from 30%-40%.
- Transmission through breast milk is estimated at 14-29%.
- Currently, about 1 million children under the age of 5 years are infected with HIV.

Blood and blood products:

- HIV infection can be spread through the use of contaminated needles or equipment.
- Through the sharing of needles by intravenous drug users.
- The risk of infection from blood transfusion has been significantly reduced around the world because of antibody screening of donor blood for HIV and the widespread use of disposable and/or sterilisable needles and medical equipment.

Occupational exposure:

- HIV transmission by occupational exposure has been intensively studied and monitored.
- Percutaneous, mucous membrane and cutaneous exposures to contaminated body fluids would be ready sources of viral exposure in many health care settings.
- Studies indicate an average risk of HIV-1 seroconversion after needle stick injury as approximately 0.3%.
- Post-exposure prophylaxis with antiretroviral drugs significantly diminishes the risk of transmission of HIV by this route

Activity 7: mechanism of HIV infection

(Mount the picture of this process on the transparency and teach with the aid of the transparency. This would enhance participant's understanding)

- HIV targets the CD4 receptor bearing cells such as T lymphocytes, glial cells, macrophages, Langahan cells. The sperm and ovum do not contain CD4 receptors. .
- HIV virus has affinity for these cells because it bears a molecule that allows for attachment to cells
- Other cells in the body that can be infected by HIV are the macrophages and glial cells of the brain.
- When the virus binds to the CD4 containing cells, in association with the co-receptor, the HIV envelope penetrates the cell wall, through a mechanism not well understood, allowing viral entry.
- As soon as this happens, the envelope of the virus is shed and the viral contents are released into the cytoplasm of the host cell.

- Within the host cell, the virus deposits its RNA to reprogram the cell's machinery to produce more viruses.
- First, the viral RNA must be translated into DNA since DNA is the language of all human cells.
- To do this, the HIV uses its own enzyme reverse transcriptase, which is carried within the virus particle.
- Once the reverse transcriptase has made a DNA transcript of the viral RNA, the DNA is integrated into the host cell DNA and the viral DNA is ready to make new HIV.
- To do so, long chains of viral transcripts may be transcribed and then translated into polypeptides, using host cell machinery.
- Using the protease enzyme provided by the virus, these chains are cut or cleaved into smaller pieces so that they can be assembled into new viruses.

➢ As the packaging step is completed, HIV-1 moves to the host cell membrane and interacts with the membrane to allow viral release. The viral envelope incorporated around the assembled virion structure, incorporate portions of the host cellular material as the virion is released from the cell. This process is known as viral budding.
➢ HIV use part of the cell's membrane to complete its final structure.
➢ On completion of the cycle, the host cell may be destroyed in a process that is incompletely understood.

Activity 8: Pathogenesis of HIV infection

(Mount the transparencies on the pathogenesis of HIV. This would enhance participants' understanding)

➢ Only 30-70% of primary HIV-1 infection is associated with acute clinical symptoms ranging from a mild viral syndrome to a severe systemic illness.
➢ The incubation period from initial infection to onset of symptoms is an average of 21.4 days.
➢ The initial symptoms are self-limiting and resolve within 1-2 weeks.
➢ HIV-1 viral load in the blood peaks in the first 15-30 days concurrently with a drop in CD4 cell count and an increase in CD8+ T lymphocytes
    - The CD8 cells are killer cells which are produced to kill foreign bodies through the production toxins. These killer cells are produced as a response to the presence of the HIV.

- The CD4 cells are known as helper cells. They stimulate B lymphocytes to produce antibodies against the virus. Unfortunately, most of these antibodies are not effective against the virus. The antibodies they produce against the virus, forms the basis of a number of laboratory diagnostic tests.

- Following primary infection, there is widespread dissemination of the virus. An immune response is established with a rebound increase in the level of CD4 lymphocyte count. The count however, does not return to pre-infection level.
- Seroconversion occurs between 2 – 12 weeks after the onset of initial symptoms.
- Together with the symptomatic period, this time frame is in the order of 3 – 12 weeks. During this period, an antibody test for the virus will be negative. This is known as the *window period*.
- After the acute retroviral syndrome, clinical symptoms subside and patients enter a clinically latent period of the disease. This period of *clinical latency* varies with the median time being estimated as 7-10 years. During this period, the amount of HIV (the viral load) in the peripheral blood is relatively low compared to that in lymphoid tissues; the viral load increases as the diseases advances. Also, the CD4 cell count gradually decreases in number because they are destroyed by the virus.
- Eventually, the immune system is overwhelmed.
- The hallmark of HIV-1 infection is the depression of immunity caused by destruction of the CD4 cells. The normal signals from the helper T-cells to monocytes, cytotoxic T lymphocytes, delayed typed hypersensitivity T cells, T suppressor cells and natural killers cells are lost or reduced. The patients are therefore at increased risk of developing infection which the body could otherwise have coped with. These are referred to as *opportunistic infections.*
- In most cases, HIV-1 progresses from primary infection, to asymptomatic period and then to symptomatic period and finally to AIDS.

Activity 9: Staging of HIV infection

- CDC staging system
  - This is used for adults and adolescents above 13 years of age.
  - It is a two tier system: one tier looks at the amount of immune suppression patient is experiencing through the determination of the CD4 count while the second is a clinical staging
  - WHO Clinical Conditions by Clinical Stage
  - It can be used for surveillance case definition of AIDS
  - One drawback of this classification system is that it is not reversible. Once classified, a person may not be reclassified even if improvement of clinical and immunological status occur
  - Any person classified as A3, B3 or C1-3 would be considered to have AIDS

- WHO clinical staging system
  - This classification takes cognizance of the fact that CD4+ counting facilities are not available in many parts of the world
  - Patients are classified based on major and minor symptoms .Two or more major plus two or more minor symptoms define symptomatic HIV-1 infection.
  - The WHO system has also developed a system to categorise immunosuppression of adults based on total lymphocyte count

    (*Present and discuss the revised CDC classification and the WHO classification on transparencies*)

- The Nigerian AIDS Case Definition
  - The current Case Definition that FMOH is using for Adults in 12 sites piloting an AIDS Case Reporting System is based on the presence of one or more of the under listed conditions plus an HIV positive test defines AIDS in an adult
  - •10% body weight loss or cachexia with diarrhoea or fever or both, intermittent or constant, for at least one month
  - • Pulmonary or extrapulmonary tuberculosis
  - • Cryptococcal meningitis
  - • Kaposi's sarcoma
  - • Neurological impairment sufficient to prevent independent daily activities

- • Candidiasis of the oesophagus (may be presumptive based on the presence of oral candidiasis accompanied by dysphagia)
- • Clinically diagnosed life-threatening pneumonia or recurrent episodes of pneumonia
- • Invasive cervical cancer

B. The Case Definition for children remains unchanged.

Activity 10: Laboratory investigations

The Nigerian algorithm recommends that two rapid tests, using different testing formats be used; one for diagnosis and another for confirmation

The ELISA test is the screening test used for the diagnosis of HIV infection in patients above 18 months. It detects HIV antibodies. It is highly sensitive but rarely can also be positive for other diseases such as autoimmune diseases, syphilis, haematological malignancies and pregnancy. This does not make it highly specific since false positive HIV results can be obtained, thus a confirmatory test is required.

A confirmatory test is often recommended for an initial diagnosis of HIV infection in view of false positive results with an ELISA or rapid test. The Western blot test is such a confirmatory test.

- The western blot has viral proteins that were previously electorphoresed and transferred to the western blot membrane. These viral proteins are the envelope (gp41, gp120, gp160; core proteins (p17, p24, p55) and polymerase (p31, p51, p66). When reacted with patient sera that are specific to the viral proteins, a series of enzyme detection steps reveal the presence of the viral proteins recognized by the patients' antibodies. If no bands are seen, the Western blot is negative. Control HIV antibody positive and negative sera are usually run with patient sera to insure that the test is working properly.
- The Western blot could be inconclusive or indeterminate when only few bands are seen during the test.

- For indeterminate results, the test is repeated again two weeks later and periodically for the next six months. If the pattern persists after six months, the individual is not likely to be infected with HIV

Several rapid tests have been developed. These tests detect anti-HIV antibodies much like the ELISA assay. The advantage is that results are available within minutes increasing the effectiveness of post test counselling

No patient should be allowed to take an HIV test without pre-test counselling.

Following pre-test counselling, a patient should go voluntarily for an HIV-1 test only when the patient is ready for it. Allow the participants to react to this information; clarify information and answer questions before going ahead with a test session

(Present the flow chart. this would help increase participants' understanding of diagnosis in the clinical setting)

Other required laboratory tests

The diagnosis of HIV infection cannot be made during the window period through the use of ELISA test. The window period refers to the time for adequate antibody development to the viral proteins, such that standard antibody tests can detect them as positive. Therefore, an ELISA may only be able to detect HIV antibodies 3-12 weeks after initial infection when the HIV antibodies would be present in sufficient quantity for possible detection. The patient can however transmit the virus during this period. A PCR would however detect HIV during this period since this detects viral infected cells present at very low quantities immediately after infection.

Detuned ELISA can be used to detect recent HIV seroconversion.

There are other rapid HIV test kits including those that use oral mucosa transudates, urine or vagina secretions but they are presently expensive.

The CD4 cell count may also be required to help with the clinical staging of HIV infection and in making a recommendation for ARV therapy. The CD4 cell count indicates the health of the person's immune system. The normal range is 800 to 1,200 CD4 cells per millilitre. Someone with a measurement of 500 or less is said to be "immune compromised". Anyone with less than 200 CD4 cells and with some sort of opportunistic infection in tow is said to have AIDS

Where this is not available, a total lymphocyte count can also be used. Clinical staging of the disease could be made based on CD4 cell count or through the use of lymphocyte count in combination with clinical symptoms.

WHO clinical staging, which does not depend on laboratory parameters, could also is used.

The viral load measures the number of viruses per millilitre of blood. It is needed as a base line investigation and a monitoring tool. A person who is HIV infected will start to show a viral load that increases from the time that the virus infects the body until the person eventually succumbs to opportunistic infections. People who have viral loads of less than 50,000 are usually not treated with HAART therapy unless their T-cells are extremely low.

The other tests listed below would be needed for baseline investigations because ARV therapy may affect organ functions. This is because HIV-1 infected individuals may have multi-system disease prior to ARV therapy and may therefore require multiple drug therapies. These must be evaluated.

Tuberculosis diagnostic tests

- Sputum microscopy
- Tuberculin skin testing
- Chest radiography

Liver function tests: (These are used in determining the appropriate ARV therapies and monitoring of patients on ARV for hepatotoxicity)

- Total and direct bilirubin
- Total protein
- Glutamic pyruvic transaminase (GPT)/ALT
- Glutamic oxaloacetate transaminase (GOT)/AST
- Alkaline phosphatase (ALP)

- Hepatitis B antibodies and antigen and hepatitis C antibody assays
- Pancreatic function tests (pancreatitis is associated with certain ARV drugs)
  - serum amylase
- Lipid profile (certain ARV drugs will lead to abnormal lipid profile)
  - Cholesterol (total, High density lipids and low density lipids)
  - Triglycerides

- Full blood count to help determine the impact of the infection and associated conditions on haematological parameters.
    - ARV drugs like AZT may result in anaemia - many guidelines suggest that patients not be put on AZT if haemoglobin levels are below 8.5 mg/mL.
- Blood film for malaria parasites
- Electrolytes, urea and creatinine to assess renal function
- Serum chemistry tests should be repeated annually in HIV infected patients and more frequently in patients with abnormal results and in those who are taking antiretroviral drugs with proven haematologic, hepatotoxic or nephrotoxic side effects.

Activity 11: Group Activities/Discussions

- Discuss the National Guidelines for the use of ARV drugs with reference to Drug Selection, Combination, Monitoring and Referrals.
- Discuss the national prevalence studies: What is the difference between prevalence and incidence? How is prevalence determined during the sentinel surveys?
- Identify the limitations of the various survey methods
- Let participants discuss some of the myths and misconceptions about HIV/AIDS they are aware of.
- Identify the various ways for preventing HIV transmission

Module 2

Pharmacotherapeutics of HIV/AIDS

Objectives

1. 1. Update Participants knowledge of the basic chemistry and pharmacology of antiretrovirals
2. Understand the various adverse drug reactions, toxicity and drug interactions associated with ARV use
3. Apply the knowledge of Pharmacotherapeutics to improve the care and management of HIV/AIDS.

Content

- Mechanism of action of ARV drugs
- Drug classes and Pharmacology of ARVS
- Drug-drug interactions
- Drug regimens
- Pharmacokinetics of ARVS

Materials required

- Overhead projector
- Data/Multimedia projector
- Transparencies
- Flipcharts and flipchart stand
- Markers
- Masking tape
- Laptop
- Diskettes/Other media storage devices

Time: 170 minutes

Activity 1: Drug classes and mechanisms of action

The lecturer will help participants understand the different classes of ARV available, their mechanism of action, criteria for starting ARV and the side effects.

Time: 20 minutes

Activity 2: Chemistry of Antiretroviral Drugs

This session would discuss the structure of selected ARVS. It would also focus on quality control and pharmaceutico-technical properties of ARVS, its bioavailability and ensuring stability in the tropics.

Time: 20 minutes

Activity 3: Drug-Drug Interactions

The various indications and contra-indications for the use of ARVS would be highlighted during this session. In addition, features and management of drug interactions would be highlighted

Time: 20 minutes

Activity 4: Dosage Forms and Regimen

Participants would learn about the available dosage forms in which ARVS exist for use in adults and children. The session would also highlight the need for therapeutic drug monitoring with respect to ARVS. Presenter to include a slide of Photographs / samples of drugs

Time: 20 minutes

Activity 5: Pharmacokinetic profiles of Antiretrovirals

This session would discuss the absorption, distribution, metabolism and excretion routes of the commonly used ARVS in Nigeria. It would also highlight some of the side effects of the drugs.

Time: 20 minutes

Activity 6: HIV-Related Drugs with Overlapping Toxicities

The session would discuss about interactions between ARVS when used in combinations, interactions between ARVS and other drugs as well as possible overlapping toxicities with the use of these drugs

Time: 20 minutes

Activity 7: Group Activities/Discussions

Trainers should give values for determination of BA and BE so as to appreciate their importance in switchability of ARVS and therapeutic response; use the chemistry of ARVS to emphasize the need for stability and storage requirements in high humidity and in the tropics. Case studies to recognize toxicity of ARVS and possible interventions would be discussed.

Time: 40 minutes

Lecture/Facilitator's notes

Introduction

Facilitator would introduce the objectives of the module. She (he) would highlight the history of ARV therapy and the focus of future research. The lectures for the session would then be introduced

Time: 5 minutes

Activity 1: Drug classes and mechanisms of action

(Use the picture prepared on the data projector to help with the teaching of this session)

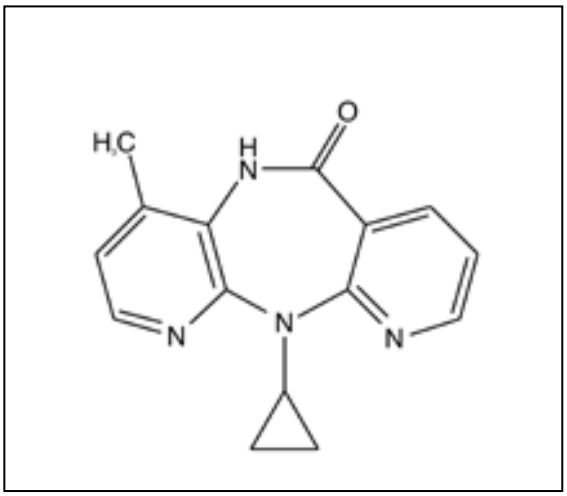
- HIV has three viral enzymes: reverse transcriptase (RT), protease and integrase.
- The currently available anti-HIV drugs have targeted the RT and protease enzymes. However, integrase inhibitors, entry inhibitors and co-receptor antagonists are under development.
- A sub-class of entry inhibitors that target the fusion process have shown some early promise in human trials.
- The first class of anti-HIV drugs developed were nucleoside reverse transcriptase inhibitors (NRTIs) - each drug functions as an analog of one of the cellular nucleosides. The NRTIs require intracellular kinase phosphorylations to become active and once phosphorylated, they become incorporated into proviral DNA by RT, which results in chain termination.
- NRTIs can also inhibit cellular DNA polymerases, particularly mitochondrial polymerase.
- It is felt that mitochondrial toxicity may explain some of the long-term side effects caused by drugs in this class.
- In contrast to NRTIs, the non nucleoside reverse transcriptase inhibitors (NNRTIs) noncompetitively inhibit the RT enzyme. It is believed that they inactivate the RT by inducing conformational changes in the binding pocket of the enzyme.
- Because of their high selectivity for the HIV-1 RT, NNRTI's are not active against the HIV-2 RT, eliminating this class of drugs for treatment of HIV-2.
- NNRTIs are all metabolized by the cytochrome P-450 enzyme system. They have different potential drug interactions as P-450 inducer (nevirapine), inhibitor (delavirdine), or both (efavirenz).
- The newest type of reverse transcriptase inhibitors are the nucleotide analogs (NtRTI). The only approved nucleotide for clinical use is tenofovir. Tenofovir is a nucleoside monophosphonate (nucleotide) analog of adenosine.

- HIV requires the viral protease to cleave the translated precursor polyproteins to individual proteins in order to form mature, infectious viral particles. Protease inhibitors (PI) act by blocking the viral protease, resulting in non-infectious viral particles. They work at the last stage of the virus reproduction cycle. They prevent HIV from being successfully assembled and released from the infected CD4 cell.
- Examples of PIs include Saquinavir (SQV), Ritonavir (RTV) {as pharmacoenhancer}, Indinavir (IDV), Nelfinavir (NFV), Amprenavir (APV), Lopinavir-ritonavir, (LPV/r), Atazanavir (AZV) and Tipranavir

Activity 2: Chemistry of Antiretroviral Drugs

Nevirapine

- Nevirapine binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent DNA polymerase activities causing a disruption of the enzyme's catalytic sites.
- The activity of Nevirapine does not compete with the template or nucleoside triphosphates.
- These actions are only reported in HIV-1. HIV-2 reverse transcriptase and eukaryotic DNA polymerases are not inhibited by Nevirapine.
- It is structurally a member of the dipyridodiazepinone chemical class of compounds
- Its molecular formula is $C_{15}H_{14}N_4O$
- Its molecular weight is 266.3



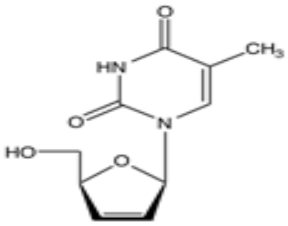
Nevirapine Chemical Structure

Stavudine

- Stavudine is a synthetic nucleoside analogue of thymidine
- It inhibits the replication of HIV in vitro
- It is phosphorylated by cellular kinases to stavudine triphosphate which exerts antiviral activities
- It inhibits HIV replication by 2 mechanisms:

- It inhibits HIV reverse transcriptase by competing with the natural substrate deoxythymidine triphosphate
- It inhibits viral DNA synthesis by causing DNA chain termination because stavudine lacks the 3 hydroxyl group necessary for DNA elongation

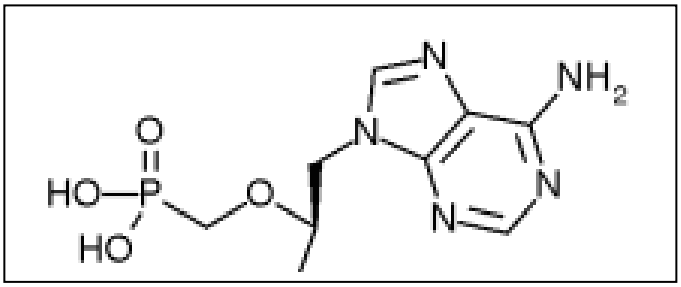
- In addition to the inhibitory effect on HIV reverse transcriptase, stavudine triphosphate inhibits cellular DNA polymerase beta and gamma, and markedly reduces the synthesis of mitochondrial DNA.
- Its molecular formula is $C_{10}H_{12}N_2O_4$
- Its molecular weight is 224.2



Stavudine Chemical Structure

Tenofovir

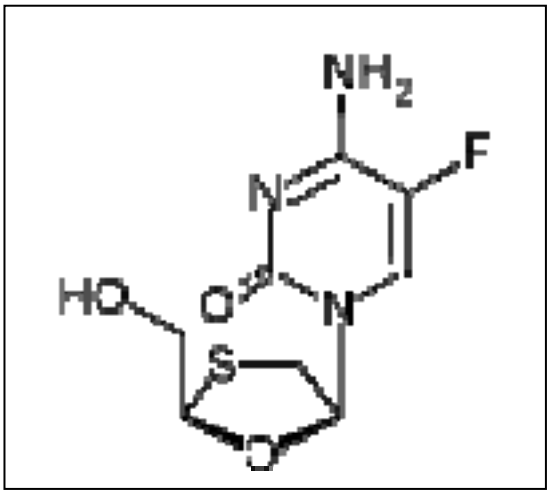
- Tenofovir disoproxil fumarate is an acrylic nucleoside phosphonate diester analog of adenosine monophosphate.
- It is a fumaric acid salt of the di-iso-propoxycarbonyloxymethyl ester derivative of tenofovir
- Its molecular formula is $C_{19}H_{30}N_5O_{10}P.C_4H_4O_4$
- Its molecular weight is 635.52
- Its solubility is 13.4mg/ml in water at 25°C
- Its pKa is 3.5 while its partition coefficient is 1.25
- Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate.
- Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5-triphosphate and, after incorporation into DNA, by DNA chain termination.
- Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, b and mitochondria DNA polymerase gamma.



Tenofovir Chemical Structure

Emtricitabine

- It is a synthetic analogue of cytidine.
- It is the enantiomer of a thio analogue of cytidine which differs from other cytidine analogs in that it has a fluorine in the 5-position.
- It is phosphorylated by cellular enzymes to form emtricitabine 5-triphosphate which inhibits the activity of HIV-1 reverse transcriptase
- It does this by competing with the natural substrate deoxycytidine 5-triphosphate and by being incorporated into the nascent viral DNA which results in chain termination
- Emtricitabine 5-triphosphate is a weak inhibitor of mammalian DNA polymerase α, b and mitochondria DNA polymerase gamma.
- Its molecular formula is $C_8H_{10}FN_3O_3S$
- Its molecular weight is 247.24
- Its pKa is 2.65 while its partition coefficient is -0.43



Emtricitabine Chemical Structure

Activity 3: Drug-Drug Interactions

- Potential for drug-drug interactions is significant in the HIV infected patient this may be an important cause of treatment failure
- Overlapping toxicities may increase the risk of adverse events
- Beneficial drug-drug interactions are increasingly being used to enhance efficacy and reduce toxicity
- Drugs may interact with each other through:
  - Pharmacokinetic mechanisms i.e. body's effect on the drug
  - Alterations of drug pharmacodynamics i.e. drug's effect on the drug
- Pharmacokinetics: Hepatic Metabolism
  - Hepatic metabolism of drugs takes place most often through the more than 25 cytochrome P450 isoenzymes that either oxidise or reduce drugs.
  - The cytochrome enzymes are located in hepatocytes, as well as enterocytes in the GI tract
  - The P450 3A4 subset is the major enzymatic route of metabolism of the PIs and NNRTIs, and hence a major point of drug interactions
  - Drugs may either inhibit (block the activity of) or induce (upregulate the production of) cytochrome P450 enzymes. P450 inhibitors have the potential to increase plasma levels of the other drugs that are metabolized by this pathway
  - This may result in the drug's increased effect.
  - The protease inhibitors and ketoconazole are all P450 inhibitors: 3A4>2D6
  - Co-administration of another drug that is metabolized by the 3A4 subsystem is relatively contraindicated:
  - The protease inhibitor may inhibit the cytochrome resulting in elevated levels of the second drug. This is a potentially life-threatening reaction.
  - The NNRTIs (nevirapine and efaverenz) have some inducing properties
  - A P450 inducer increases the amount of the P450 enzyme
  - The increased enzyme results in a more rapid rate of metabolism of drug substrates
  - For many drugs, the metabolite formed is less active; hence the result will be a decreased pharmacological effect.
  - Drugs such as rifampicin or nevirapine activate the P450 system and thereby increase the liver metabolism of drugs that use the P450 system and thus decrease their plasma level very rapidly.

Management of Drug-Drug Interactions

- Knowledge of drug-drug interactions continues to evolve
- Large number of interactions can be overwhelming to the clinician
- Consideration of drug-drug interactions when initiating therapy + dose adjustments and careful monitoring are important
- A thorough drug history including non-prescription drugs and alternative therapies must be taken at each follow-up visit
- A high index of suspicion regarding drug interactions is needed in the patient with treatment failure, especially if factors such as adherence can be ruled out
- Interactions may be suspected also if patients have serious toxic effects

Please refer to the National Guidelines on use of ARV for more detailed information

Activity 4: Dosage Forms and Regimen

- NRTIs
  - Zidovudine present as capsules, tablets, oral liquid, IV formulation
  - Lamivudine present as tablets, oral liquid
  - Stavudine present as capsules, oral solution
  - Didanosine present as chewable tablets, capsules, oral suspension
  - Combivir present as tablets
- NNRTI
  - Nevirapine present as tablets, oral solution
  - Efavirenz present as capsules/tablets

- Protease inhibitors
  - Nelfinavir present as capsules, white powder
  - Ritonavir present as soft gelatin capsules, oral solution
  - Saquinavir present as soft gel capsules/Hard gel capsules

- Dosing schedules in adults as defined in the national guidelines
  - Preferred first line regimens
    - Stavudine (d4T) or Zidovudine (AZT) + Lamuvidine (3TC) or FTC + Nevirapine (NVP) or Efavirenz (EFV)
  - Alternative first line regimens
    - Tenofovir (TDF) + Lamuvidine (3TC) or FTC + NVP or EFV
    - Abacavir (ABC) or Didanosine (ddI) + 3TC + NVP or EFV
  - Second line regimen for adults and adolescents
    - Tenofovir (TDF) + Lamuvidine (3TC) or FTC + Indinavir/ritonavir (IDV/r) or Saquinavir/ritonavir (SQV/r) or Lopinavir/ritonavir (LPV/r)
    - AZT + Lamuvidine (3TC) or FTC + Indinavir/ritonavir (IDV/r) or Saquinavir/ritonavir (SQV/r) or Lopinavir/ritonavir (LPV/r)
  - Second line regimen for children
    - Stavudine (d4T) or AZT + Abacavir (ABC) + Lamuvidine (3TC) + Lopinavir/ritonavir (LPV/r) or Nelfinavir (NVF)
  - Third line regimen
    - Saquinavir (invirase) + Ritonavir (norvir)
- Refrigeration recommended for IDV/r, LPV/r and SQV/r
- In the face of treatment failure with second line drugs, consider referral to a tertiary centre and performance of resistance testing if feasible.
- The choice of salvage therapy is more difficult if resistance testing is not readily available.
- In the event of treatment failure, a comprehensive evaluation of why a patient failed must be performed. For instance, if a patient was non-adherent because the regimen was too complex, it is unlikely that such a patient would respond to an even more complex salvage regimen. This type of patient may require significant in-depth counselling prior to starting a new therapeutic regimen.
- Salvage therapy include:
  - 3 or 4 reverse transcriptase inhibitors including 3TC or FTC + SQV + LPV/r (may substitute Tipranivir/r for the SQV, LPV/r combination when available)
  - Enfuvirtide in addition to the above
- Dosing schedule in children

- Zidovudine: In neonates 4mg/kg bid; in paediatrics 90-180mg/m^2 bid
- Lamuvidine: In neonates 2mg/kg bid; in paediatrics 4mg/kg bid (max 150mg bid)
- Nevirapine: In paediatrics >3months to 8yr 7mg/kg bid; > 8yr 4mg/kg bid (max 200mg bid)
- Efavirenz: Not for use in children < 3yrs; Children > 3 yr 200-600mg od. May sprinkle capsule contents on food. Avoid high fat meal
- Stavudine: In paediatric 1mg/kg bid (max 40mg bid). Keep refrigerated. May sprinkle capsule contents on food
- Didanosine: In neonates (<90 days) 50mg/m^2; in paediatric 90-150mg/m2 bid. Give on empty stomach. Keep refrigerated. Do not give at the same time as indinavir or ritonavir
- Nelfinavir: In paediatrics 30-40mg/kg tid. Give with a meal or light snack. Do not give with citrus juice. Powder may be put on food or in liquids
- Ritonavir: In paediatrics 400-50mg/m^2 bid (max 600mg bid). Keep refrigerated. Taste can be improved by mixing with food. Keep capsules moisture free
- Saquinavir: In paediatrics 50mg/kg tid. Give within 2 hrs after a full meal. Protect patient from direct sunlight

Please refer to the National Guideline on use of ARV for more detailed information

Therapeutic Drug Monitoring (TDM)

- The large number of potential drug-drug interactions may affect the achievement of the optimal antiretroviral drug concentrations
- There is therefore an interest in therapeutic drug monitoring (TDM) to individualize antiretroviral drug therapy.
- The goal of therapeutic drug monitoring is to maintain plasma concentrations of the drug within a therapeutic range for each patient.

Activity 5: Pharmacokinetics profiles of Antiretrovirals

Antiretroviral agent	Metabolism	Effect on cytochrome P450
Zidovudine	Hepatic glucuronidation, Renal excretion	-
Other NRTIs	Renal excretion	-
Nevirapine	Cytochrome P450	Modest Induction
Delavirdine	Cytochrome P450	Modest Inhibition
Efavirenz	Cytochrome P450	Modest Induction and Inhibition
Ritonavir	Cytochrome P450	Potent Inhibition
Amprenavir,)	Cytochrome P450	Modest Inhibition
Indinavir,)	"	"
Nelfinavir)	"	"
Saquinavir	Cytochrome P450	Weak Inhibition

Pharmacodynamic Interactions

Drug's effect on the body:

- Interactions alter either drug efficacy or toxicity
- Interaction occurs at the site of drug action either at target cell receptors or post-receptor sites
- Interactions may be additive, synergistic or antagonistic.
- May be desirable or undesirable depending on their effect on efficacy or toxicity: For example, due to overlapping toxicity profiles, enhanced bone marrow suppression may occur with concurrent administration of zidovudine and ganciclovir.
- Alternatively, enhanced clinical efficacy occurs with the use of agents with complementary mechanisms of action, such as Zidovudine and Lamivudine.

Activity 6: HIV-Related Drugs with Overlapping Toxicities

- Combining NRTIs
  - Interactions between NRTIs occur due to competition for the same intracellular phosphorylating enzymes, or due to overlapping toxicities. Nucleoside analogues that are activated by the same intracellular enzymes include zidovudine and stavudine, or zalcitabine and lamivudine – Competition has been demonstrated *in vitro* studies. Zidovudine + stavudine causes a decline in CD4+ T cell counts
  - It is recommended that these combinations are avoided.
  - Other combinations have no demonstrated interaction *in vitro* and clinical studies Combinations of didanosine + zalcitabine, and stavudine + zalcitabine, are not recommended due to overlapping potential for the development of peripheral neuropathy.
  - Strongly recommended are Stavudine and Didanosine, Stavudine and Lamivudine, Zidovudine and Didanosine, Zidovudine and Lamivudine
  - Alternative combinations are Didanosine and Lamivudine, Zidovudine and Zalcitabine

Interactions between NRTIs and PIs

- Protease inhibitors cause modest alterations to the area under the concentration-time curve for NRTIs.
  - These alterations in the AUC have not been found to be clinically relevant because activity of NRTIs mainly depends on the extent of intracellular phosphorylation.
  - One important interaction involves didanosine and indinavir, or didanosine and nelfinavir. The neutralising agents in the oral formulations of didanosine result in increased gastric pH.
  - Optimal absorption of indinavir and nelfinavir requires an acidic pH
  - It is recommended that these drugs are given at least one hour apart from didanosine.
  - Interactions between NRTIs and NNRTIs are not significant
  - NNRTIs would not be expected to interact with NRTIs, because NNRTIs undergo extensive hepatic metabolism, and NRTIs are predominantly eliminated by renal excretion.
  - In addition, they do not compete for nucleoside triphosphates.

Combining Protease Inhibitors

- Since protease inhibitors are extensively metabolised by the same cytochrome P450 enzymes in the liver, and inhibit these enzymes, administering two PIs can prolong the life of one or both drugs
- They also inhibits gastrointestinal cytochrome P450 during absorption and inhibits P-glycoprotein (a cellular efflux transporter) reducing intracellular drug elimination and prolonging intracellular t ½
- The interactions between protease inhibitors are increasingly being utilized to increase anti-viral effect, while creating more tolerable and convenient drug regimens.
- Main use at present is in salvage regimens. Role in first line treatment is not well yet established.
- The advantages of dual PI regimens may include:
  - Improving adherence by decreasing the number of daily doses, reducing pill burden and eliminating meal requirements
  - Compensation for the induction of cytochrome P450 during the concurrent use of NNRTIs (nevirapine and efavirenz)
  - Overcoming resistant viral variants
  - Lower pill burdens and lower dosing requirements may also result in reduced costs.
- Saquinavir – Ritonavir are used in trials and practice since 1996, mainly in salvage regimens. Studies have found that when saquinavir was combined with ritonavir, the AUC of saquinavir was increased by 30 to 50-fold. The combination reduces the pill burden (from 1200 mg tid to 400mg/400 mg bd). Hence, may also improve adherence and reduce costs of therapy. The use of this combination may be limited by the 400mg dose of ritonavir which can be poorly tolerated. Hence studies are underway to determine whether the same effects can be achieved with lower ritonavir doses (100mg).
- PI "Boosting" Using Ritonavir is froth with uncertainties though prospective roles include:
  - The resistance profile of patients in whom dual-PI therapy fails
  - The efficacy in prospective randomized clinical trials
- To date only ritonavir-saquinavir and ritonavir-lopinavir have been evaluated in such trials. No data from head-to-head comparisons of dual PI enhanced regimens with NNRTI based regimens or of the different PI combinations

Interactions between PIs and NNRTIs

- No significant alterations of NNRTIs
- NNRTIs and PIs undergo extensive hepatic metabolism via cytochrome P450, therefore drug interactions are expected when NNRTIs are combined with PIs.
- Studies have suggested some modest but no significant alterations in the pharmacokinetics of NNRTIs when saquinavir, ritonavir, indinavir or nelfinavir are administered with niverapine, delavirdine or efavirenz.
- NNRTIs alter the kinetics of PIs: Delavirdine inhibits the metabolism of PIs, increasing the AUC of indinavir, ritonavir and nelfinavir by 50-80% and saquinavir by over 400%
- PI doses may therefore be reduced when given in combination.
- Nevirapine induces hepatic enzymes, reducing the plasma concentrations of some protease inhibitors
- The dose of indinavir or nelfinavir may be increased to accommodate for decreased AUCs when administered with Niverapine for example, Indinavir may be increased from 800 mg tds to 1000mg tds, and nelfinavir may be increased from 750 mg to 1000 mg tds.

- Efavirenz not as predictable as Nevirapine. It reduces the AUC of indinavir; increases AUC of ritonavir; increases AUC of nelfinavir, but reduces the active metabolite, the net result being an inhibitory effect; Decreases the AUC of amprenavir
- These effects require further evaluation to determine clinical significance and dosage modifications that may be required.

Interactions between Antiretroviral Agents and Other Drugs

- Macrolide antibiotics, azole antifungals and H-2 blockers are P450 inhibitors and hence interact with PIs and NNRTIs.
- Rifamycin derivatives, alcohol and anticonvulsants are P450 inducers and hence also interact with PIs and NNRTIs.
- Simvastatin and lovastatin are potent inducers, and other agents such as atorvastatin and pravastatin are less likely to interact and are recommended for use.
- Drugs that undergo hepatic metabolism but have narrow therapeutic indices include non-sedating antihistamines, long acting opiate analgesics, promotility agents, antiarrhythmics, long-acting benzodiazepines, ergotamines, coumarin anticoagulants and oral contraceptives. These must therefore be used with caution and careful monitoring when used with antiretroviral agents.
- Ergotamines is contraindicated for use with nevirapine and efavirenz
- Renally cleared drugs with narrow therapeutic indices include ganciclovir, foscarnet and aminoglycosides (gentamycin, tobramycin, amikacin).
- Ketoconazole, itraconazole, and fluoroquinolones have specific requirements for absorption and may be affected by the concomitant administration of other drugs.
- AZT should not be combined with aspirin, codeine, interferon, morphine, methadone, indometacin, lorazepam, dapsone, paracetamol and probenecid as they inhibit the metabolism of AZT
- Antacids and cimetidine might increase the absorption of DDI.
- Tuberculosis is a major cause of morbidity and mortality in the HIV-infected patients. The current recommendation for the treatment of tuberculosis includes isoniazid and rifampicin for 6 months, and pyrazinamide and either ethambutol and/or streptomycin for the first two months. INH + rifamycin derivatives or INH + ethambutolare then used for the next 4 months. The rifamycin derivatives that are used for the treatment or prophylaxis of tuberculosis are cytochrome P450 inducers. They induce the metabolism of PIs and NNRTIs, and cause sub-therapeutic levels of these agents. PIs and NNRTIs retard the metabolism of rifamycins, resulting in increased serum levels of rifamycins and increased potential for drug toxicity.

- **Rifampicin** is the most potent P450 inducer, and results in significant reductions in PI (by 90%) and NNRTI (by 30-37%) plasma concentrations. Recent studies suggest that rifampicin can be used with certain combinations of antiretroviral agents. It could cause a decrease in concentrations of efavirenz. An increased dose of efavirenz to 800 mg/day is suggested to maintain therapeutic levels.

- **Rifambutin** is a less potent inducer, and current guidelines suggest that it may be used with agents such as indinavir or nelfinavir with appropriate dosage adjustments.
- Both rifampicin plus efavirenz containing HAART, and rifabutin plus indinavir containing HAART were found to be effective in treating TB and suppressing viral load.
- Limited but favourable clinical experience include:

- Rifambutin (reduced or usual dose) + Indinavir or Nelfinavir
- Rifampicin + two NRTIs and Efavirenz (increased dose about 800mg)/nevirapine (200mg bd)

➢ Other possible combinations (limited or no clinical experience) are Rifambutin at reduced doses (150 mg 2-3 times a week) when given with ritonavir (+/- Saquinavir); Rifambutin at increased doses (600 mg 2 –3 times a week or 450-600 mg daily) when given with Efavirenz; Rifampicin + two NRTIs and ritonavir; Rifampicin + two PIs (Ritonavir and Saquinavir)

Overlapping Toxicities

➢ Drugs used in the HIV-infected individual may have overlapping adverse effects
➢ Important toxicities include the potential for bone marrow suppression induced by antiretroviral agents (such as zidovudine), and antimalarial agents such as primaquine and pyrimethamine or ganciclovir
➢ Other overlapping toxicities include the potential for hepatotoxicity, pancreatitis and peripheral neuropathy induced by excess alcohol in combination with antiretroviral drugs
➢ Pancreatitis could be induced by the use of DDI/3TC/D4T/ RTN with sulphonamides, high quantities of cotrimoxazole, corticosteroids, and high levels of alcohol
➢ Eye toxicity occur with the use of DDI with ethambutol or rifabutin

Tips about Combivir

➢ Avoid using in patients requiring dose reduction including:
➢ Children under 12 years
➢ Patients with renal impairment
➢ Patient with low body weight

Activity 7: Group Activities/Discussions

Module 3
HAART and Other Forms of Therapy

Objectives

1. Rationale for HAART, the various combinations available and the basis for modification and switching.
2. The various approaches to ARV therapy and complications associated with the use of ARVS in pregnancy, paediatrics and in various disease conditions.
3. The role of nutrition in the management of HIV/AIDS (including paediatrics)

Content

- Goals of HAART therapy
- Strategies of HAART therapy
- Adverse drug reactions and reporting systems
- Drug combinations and drug availability
- ART in pregnancy, for PMTCT and for use in children
- Alternative therapies to HAART

Materials required

- Overhead projector
- Data/Multimedia projector
- Transparencies
- Flipcharts and flipchart stand
- Markers
- Masking tape
- Laptop
- Diskettes/Other media storage devices

Time: 210 minutes

Activity 1: Strategies of ARV therapy and their limitations

This session would discuss the history of HAART as well as the limitation in using HAART. The impact of HAART on HIV related complications would also be highlighted

Time: 15 minutes

Activity 2: Definitions and Goals of HAART

The goals of therapy for HIV/AIDS would be discussed

Time: 10 minutes

Activity 3: Various combinations of drugs available for HAART

The various drug combinations in HAART and the basis for such combinations would be discussed and the basis, including advantages and disadvantages of these drug use.

Time: 20 minutes

Activity 4: Adverse Drug Reactions

This lecture session would highlight the various adverse drug reactions that occur with the use of HAART and its implication for patient management. The session would also discuss on how to report these observed drug reactions and the importance of this reporting system

Time: 20 minutes

Activity 5: Specific Side Effects of ARVs

Participants would learn about the specific side effects of each available ARV drug. The reporting of these observed side effects would also be discussed.

Time: 10 minutes

Activity 6: New developments in Antiretroviral Therapy

The session would discuss research findings on new ARV drugs such as fusion inhibitors and integrase inhibitors.

Time: 15 minutes

Activity 7: Antiretroviral therapy in pregnancy and PMTCT

The session would discuss the place for ARV therapy during pregnancy, perinatally and post partum. It also focuses on management options and implications of ARV management

Time: 20 minutes

Activity 8: Antiretroviral therapy for Children

The session would discuss the place for ARV therapy in managing HIV infection in children. It also discusses the limitations there are with ARV management in children

Time: 20 minutes

Activity 9: Drugs used for prophylaxis

Participants would learn about the drugs used in the prophylactic management of opportunistic infections.

Time: 20 minutes

Activity 10: Gene therapy

The session would discuss on efforts of scientists at re-engineering cells in management of HIV infection. It would discuss the successes so far and the prospect for the future

Time: 15 minutes

Activity 11: Herbal products and other used in HIV/AIDS Management

Participants would learn about immune boosters and nutraceuticals being developed for the management of HIV/AIDS. a number of promising researches are still on going

Time: 15 minutes

Activity 12: National Guideline on the Use of ARV Drugs

Participants would be taken through a summary guide on the National directives with respect to antiretroviral therapy for PLWHA in Nigeria

Time: 15 minutes

Activity 13: Group Activities/Discussions

These should bring out life cases and experiences, e.g., Prospects/Constraints encountered in the use of HAART in Resource-limited economy; largely illiterate society; polypharmacy. Nutrition and HAART, Prepare drug regimens (different HAART) based on relevant chemistry/pharmacokinetics, bring up problems on drug combinations and determining when to switch.

Time: 30 minutes

Facilitator's/lecturer's notes

Introduction

Introduce the objectives of the module and give general background information on the ARV programme in Nigeria. Explain that the Nigerian Government presently offers subsidized ARV drugs for persons infected with HIV-1 at the cost of N1, 000:00 in 25 centres. The list should be presented on a flip chart for participants to be able to refer to it at the end of the session. For the south of Nigeria, these centres are the Nigerian Institute of Medical Research (NIMR), Creek Military Hospital, Ikoyi, Lagos University Teaching Hospital, University College Hospital, Ibadan, University of Benin Teaching Hospital, University of Ilorin Teaching Hospital, Nnamdi Azikwe Teaching Hospital, University of Nigeria Teaching Hospital University of Port-Harcourt Teaching Hospital, Federal Medical Centre Uyo, and Federal Medical Centre Owerri.

For the North the centres are: NIPRD Abuja, National Hospital Abuja, Directorate of State Service Clinic Annex 1 Abuja, National Intelligence Agency Clinic Annex 2, Gwagwalada Specialist Hospital, Central Bank Clinic, Jos University Teaching Hospital, Ahmadu Bello University Teaching Hospital, University of Maiduguri Teaching Hospital, Usman Dan Fodio University Teaching Hospital, Federal Medical Centre Gombe, Aminu Kano Teaching Hospital and Federal Medical Centre Makurdi. There are also some private initiatives on ARV therapy in the country.

These include the provision of ARV at subsidized prices through some NGOs like Centre for the Right to Health, Lagos, AIDS Alliance Lagos, StopAIDS Lagos, and NELA Ibadan. There is also a starfish project run by the Olabisi Onabanjo University Teaching Hospital, Sagamu in conjunction with Obafemi Awolowo University Teaching Hospital Ile-Ife. The APIN initiative of controlling mother-to-child infection in 8 centres in Nigeria also entails the use of ARV. The PEPFAR supported programmes also run in 12 sites in 6 states of Nigeria. There are some state initiatives also. Taking ARV has its implications. The lecture would help participants understand when to start ARV, what are the complications associated with ARV use and what to do when complications set in. The facilitator should then introduce the lecturer.

Time: 10 minutes

Activity 1: Strategies of ARV therapy and their limitations

History of ARV therapy

- The first therapy became available in 1987 with the approval of zidovudine (AZT)
  - A reverse transcriptase inhibitor
  - A nucleoside analogue.
  - Beneficial effects were short-lived - within months the disease would again progress.
- Combination therapy
  - Use of two nucleoside analogues
  - Offered some improvement
  - The benefits were again time limited regardless of the specific combination.
- New classes of antiretroviral agents brought about sustained and clinically phenomenal results. These include:
  - The non-nucleoside reverse transcriptase inhibitors (NNRTI)
  - Protease inhibitors (PI)
- These new classes were used in combination with two nucleoside RT inhibitors (NRTIs).

- Combination options are 2 NRTI + 1 NNRTI; 2 NRTI + 1PI; 2 PI or 3 NRTI
- The use of three antiretroviral agents from two drug classes has been termed "highly active antiretroviral therapy" or HAART.
- The different drugs target different sites in the viral lifecycle
- Simultaneous combination of effective ARV therapy reduces the chance of resistance. It is the most effective means to accomplish durable suppression of HIV replication.
- HAART
  - HAART is associated with sustained suppression of plasma HIV-1 RNA (viral load) as measured by PCR, and significant improvement in immune status as measured by absolute and percentage CD4 cell counts.
  - These results have translated into a proven increase in survival, reduced morbidity, decreased vertical and sexual transmission and prevention of infection following inadvertent exposure. International guidelines for drug combinations are:
  - First line regimens
    - Zidovudine (AZT)/D4T + Lamuvidine (3TC) + Nevirapine (viramune)
    - Zidovudine (AZT)/D4T + Lamuvidine (3TC) + Efavirenz (sustiva)
  - Second line regimen
    - Stavudine (d4T) + Didanosine (ddI) + Nelfinavir (viracept)
  - Third line regimen
    - Saquinavir (invirase) + Ritonavir (norvir)
- Impact of HAART on HIV-related complications
  - There is usually a decline in some opportunistic infections (PCP, toxoplasmosis) within three months of initiation of HAART, while decline in other OIs (MAC and CMV) occurs between six to nine months, assuming CD4 count response.
  - Also no OIs seen in patients with CD4 counts recovered to >200 cells/mm3
  - These increased CD4 counts represent reconstitution of some (but not all) parts of the immune system.
  - Effective combinations can result in better control of chronic infections and malignancies like Cryptococcal meningitis, MAC and Kaposi's sarcoma. The effect on PML is still been investigated
  - Limitations of HAART
  - Not all three drugs in HAART regimens are equally effective. Those with inferior potency include triple nucleoside combinations, hard-gel saquinavir and nelfinavir-based regimens.
  - Not every HAART regimen has been tested and thoroughly compared.
  - The best overall results have been demonstrated with regimens based on the non-nucleoside reverse transcriptase inhibitors efavirenz and nevirapine or with pharmacologically enhanced protease inhibitors, such as lopinavir, atazanavir, indinavir and saquinavir.
  - Limited impact on lymphoma and cervical disease reported to date, but work is ongoing
  - Disadvantages of early initiation ARV therapy in asymptomatic HIV infection include:
  - Resistance may develop, reducing treatment options in the future.
  - Long-term, strict adherence to ARV therapy may be difficult to maintain (leading to resistance)
  - In asymptomatic patients, ARV therapy may decrease quality of life because side effects are very common and taking large numbers of pills at regular intervals may interfere with employment and daily activities, and can be stressful.

- Long-term ARV therapy is very expensive
- Asymptomatic patients may be less willing to adhere to difficult ARV therapy regimens than symptomatic patients, because ARV therapy does not obviously improve their lives, and has significant side effects
- Adverse consequences of some ARV therapy such as lactic acidosis and pancreatitis may be life threatening.
- The long term side effects of ARV therapy drug regimens remain unknown.

Activity 2: Definitions and Goals of HIV/AIDS therapy

The goals of therapy for HIV/AIDS are to provide the optimal and individualized treatment for individuals infected with HIV at all stages of disease. Specifically:
Therapeutic goals of HIV/AIDS therapy are:

- Reduction of HIV related morbidity and mortality
- Improve the quality of life
- Restore and preserve immune functions
- Maximal and durable suppression of viral replication
- Reduce need for medical intervention and support
- Prevention/reduction of drug resistance strains of HIV and OIs

Clinical goals are:

- Improved overall health status
- Viral load reduction to <20c/ml and CD4 within normal range
- Reduction and control of drug side effects
- Support for adherence
  - Provide the most convenient HAART regimen by choosing one with a low pill burden, few food effects, and infrequent dosing schedule.
  - Select a regimen with the least acute and chronic adverse effects.
  - Choose the most "forgiving" regimen, one that has favourable pharmacokinetic properties and a high threshold for the development of resistance

Activity 3: Various combinations of drugs available for HAART

Drug combination

Nucleoside Combinations Used in HAART

NRTI Combination	Advantages	Disadvantages
Stavudine +Lamivudine (a recommended combination)	Acutely well tolerated; inexpensive; readily available	Peripheral neuropathy; pancreatitis; lactic acidosis (rare); lipoatrophy; hypertriglyceridemia.
Zidovudine +Lamivudine (a recommended combination)	Inexpensive; readily available.	Gastrointestinal effects; anemia;neutropenia; lipoatrophy (less so than stavudine-based).
Tenofovir +Lamivudine or Emtricitabine (an alternative	Acutely well tolerated.	Fewer long term complications; expensive; limited availability; drug interactions more likely with

recommendation)		tenofovir (i.e. atazanavir); tenofovir must be taken with food.
Stavudine + Didanosine (an alternative, not recommended initially)	Effective; inexpensive	Peripheral neuropathy; pancreatitis; lactic acidosis; lipoatrophy; hypertriglyceridemia; Didanosine, must be taken without food.
Zidovudine +Didanosine (an alternative, not recommended initially)	Effective; inexpensive.	Side effect profile not optimal: gastrointestinal effects; anaemia; neutropenia; peripheral neuropathy; pancreatitis; lactic acidosis; lipoatrophy.
Zidovudine +Stavudine (contraindicated)	None should ever be used.	Antagonistic interaction. Should never be used together.
Zalcitabine +Zidovudine or any other NRTI (contraindicated)	None should ever be used.	Low potency and peripheral neuropathy associated with zalcitabine-containing combinations.

* Dual NRTI combinations must always be used with a third agent, preferably from another class (i.e. protease inhibitor or non-nucleoside reverse transcriptase inhibitor).

Triple drug regimen

The third drug of HAART is a critical choice and should be based on potency, good pharmacokinetic profile, good safety margin and availability

Antiretroviral Drugs Added to Dual Nucleoside Combinations in HAART

3rd HAART Drug	Advantages	Disadvantages
Nevirapine (a recommended choice)	Can be used in pregnant women; inexpensive; available.	Rash (can be severe but rarely fatal); hepatotoxicity (rarely fatal); unfavourable interaction with rifampicin.
Efavirenz (a recommended choice)	Inexpensive; available; dosed once daily; can be used with rifampicin at higher dose (800 mg daily).	Central nervous system effects common (usually self-limiting); rash (usually mild-moderate); potential foetal abnormalities- can't be used in pregnancy.
Lopinavir/ritonavir (Kaletra®) (an alternative choice)	Potent; relatively well tolerated.	Gastrointestinal effects; hyperlipidemia; abdominal and truncal fat accumulation; expensive.
Indinavir with or without ritonavir (an alternative choice)	Inexpensive relative to other protease inhibitors.	Without ritonavir, IDV must be taken without food three times daily; nephrolithiasis; skin disorders; abdominal and truncal fat accumulation; glucose

		intolerance.
Atazanavir with or without ritonavir (an alternative choice)	Once daily administration; low pill burden (2); no effect on serum lipids; unique resistance profile.	Indirect hyperbilirubinemia; must be dosed with ritonavir (100 mg daily) if tenofovir co-administered.
Nelfinavir (an alternative choice, not recommended for first line therapy)	Relatively expensive, favourable safety data in pregnant women.	Gastrointestinal effects common; less effective than other protease inhibitors that are given with ritonavir; should not be given with ritonavir; hyperlipidemia; abdominal and truncal fat accumulation.
Saquinavir (an alternative choice, not recommended for first line therapy)	Less effect on lipids than other protease inhibitors.	Gastrointestinal effects (especially the soft gel formulation); poor pharmacokinetics; should be used with ritonavir and not alone; abdominal and truncal fat accumulation.

Activity 4: Adverse Drug Reactions

- The adverse effects of antiretroviral drugs occur commonly. They are a significant barrier to successful therapy and may lead to a reduction in the quality of life. They may be an important cause of non-adherence to therapy.
- An important consideration in decisions regarding initiation of therapy in early versus late disease.

- **Hyperglycaemia:** New onsets of diabetes mellitus, exacerbation of pre-existing diabetes and diabetic ketoacidosis have been reported in those on HAART.
  - Increases in insulin levels and insulin resistance occur in patients on PIs. Abnormal insulin sensitivity is reported in 63% of patients on protease inhibitors. Glucose intolerance has also been strongly but not exclusively, associated with the use of protease inhibitors.
  - Data are conflicting on whether abnormalities of glucose metabolism reverse with discontinuation of protease inhibitors
  - The exact aetiology is still unknown but features that are important to this include pancreatic beta cell dysfunction, peripheral insulin resistance and hepatic gluconeogenesis
  - It is important to advise the patient about, and monitor the patient for signs of hyperglycaemia. This is particularly so if the patient has pre-existing diabetes or risk factors for diabetes (obesity, family history).
- The underlying deficits (hyperinsulinemia and peripheral insulin resistance) are similar to type II diabetes mellitus. Therefore, therapy should start with diet modification and weight loss and exercise

Oral hypoglycaemic agents include: (most are sulpha drugs)

- Metformin: Decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity.
- Thiazolidinediones: pyoglitazone, etc: Increase peripheral insulin sensitivity particularly in adipose tissues.
- Insulin
- Limited data on changing the HAART regimen

- Since the advent of HAART, **lipid abnormalities** have become a more pronounced problem in those on therapy especially hypertriglyceridemia and hypercholesterolemia.
- Lipid abnormalities are independent of other aspects of the lipodystrophy syndrome and independent of diet.
- Hyperlipidemia has been most strongly but not exclusively associated with protease inhibitor therapy.
- Improvements in lipid profiles are more prominent with neviripine and abacavir than with efavirenz.
- The choice of the nucleoside analogue is not significantly associated with increase in lipid levels.
- Although the long-term consequences of hyperlipidaemia are not known, there is concern for possibility of pancreatitis, cholelithiasis, acceleration of cerebrovascular disease and acceleration of cardiovascular disease
- Impairment of adipocyte differentiation by PIs may play a role in the fat redistribution syndrome. Although Nucleoside RT Inhibitors alone have no effects on adipocyte functions, they may have synergistic effect on functions along with PIs. NRTIs may decrease the mitochondrial DNA content in adipose tissues.
- Management of hyperlipidaemia includes lifestyle modifications such as dietary changes, exercise, smoking cessation, lipid lowering drugs.
- HMG-CoA reductase inhibitors ("statins") lower the morbidity and mortality from atherosclerotic heart disease. The statins lower total and LDL cholesterol with only a modest effect on triglycerides.
- Concurrent use of Protease Inhibitors and statins must be done carefully:
  - Avoid toxicity due to PI-induced inhibition of cytochrome P450-3A4 (rhabdomyolysis, hepatitis)
  - Avoid lowering the levels of Protease Inhibitors due to P450 induction by the statin drugs.
- Fibrates are Drugs that increase the oxidation of fatty acids in the liver and muscle tissues by increasing the activity of lipoprotein lipase. Principal effects are lowering triglycerides and increasing the HDL cholesterol, with a modest effect on lowering LDL cholesterol.
- **Fat Redistribution Syndrome (Lipodystrophy)** is also another complication associated with HAART use.
- Fat accumulation associated with dorsocervical fat pad, breast enlargement (gynecomastia in men), visceral adiposity and lipomas
- Fat loss (atrophy) include facial fat loss, subcutaneous fat loss in the extremities and fat loss in buttocks
- Protease inhibitor use for 2 years or more increases the odds ratio for lipodystrophy by 2:1. NRTI use for over 2 years increases the odds ratio for lipodystrophy by 3:0, *if other risk factors are also present* but are not an independent risk factor alone. Non Nucleoside RT inhibitors do not increase the risk.
- Other adverse effects are Adverse effects of ARVs include lactic acidosis, hepatic steatosis, osteoporosis and aseptic Necrosis.

Activity 5: Specific side effects of ARVs

- Efavirenz: Dizziness, impaired concentration, somnolence, abnormal dreams, insomnia, ataxia, emotional liability. May occur in up to 50% of those on the drug, usually beginning within the first few days of therapy and resolving in most patients within 2-4 weeks.
- Indinavir: May crystallize in the renal tubules and collection system resulting in crystalluria. This may progress to nephrolithiasis in 9-22% of patients. The calculi are radiolucent usually occurs 5-7 months after initiating therapy with indinavir. Risk factors include low urine output, urine pH > 6.0.
- Non-Nucleoside RT Inhibitors: Rash. Although rashes may occur with any drug, they are more common with neviripine and efavirenz. An erythematous and maculopapular rash that may progress to Stevens-Johnson syndrome or toxic epidermal necrolysis. Rash with neviripine is more common and more severe in women than men (12% vs. 8%). Usually occurs within the first four weeks of therapy.
- Abacavir: Hypersensitivity Reaction. Manifests as fever in 80%, drug rash in 70%, GI symptoms in 50%; elevated hepatic liver enzymes and CPK may occur. On average, the onset is within the first 11 days of therapy but may occur weeks after starting abacavir. May occur in those who previously tolerated abacavir if they are put on the drug a second time. Re-challenge may be fatal.
- Zidovudine: Bone marrow suppression related to drug dose and stage of HIV infection.
- Indinavir causes hair and nail changes: but also causes dry skin, hair loss, dry mucous membranes, and ingrown nails.
- Protease inhibitors: generally cause circumoral parasethsias especially with indinavir and amprenavir. Increase in bleeding in haemophiliacs also noted.

Reporting system (Pharmacovigilance)

Monitoring and reporting of adverse drug events should follow the National Food and Drug Agency and Control (NAFDAC) guidelines, which have special forms for the purpose of recording of Adverse Drug reactions observed. These forms will be distributed to facilities as they become certified to deliver ART.

Summary

Adverse effects of antiretroviral agents are common and an important cause of treatment discontinuation and non-adherence to therapy.

- Mild to moderate side effects and those that resolved with time, may be managed with symptomatic therapy.
- Serious or disabling effects may necessitate discontinuation of the offending drug.
- It is important to educate patients about the potential adverse effects of these medications.
- It is important to be vigilant to these adverse effects when initiating therapy and also during follow up.

Activity 6: New developments in Antiretroviral therapy

- The use of antiretroviral drugs in Nigeria has significantly reduced the morbidity and mortality from HIV and AIDS. Those that have this privilege are however limited due to the fact that:

- People living with the virus in the Nigeria presently have very limited access to the antiretroviral drugs.
- The present level of infrastructural facilities in Nigeria is equally a limiting factor in the safe and effective delivery of antiretroviral drugs including inadequate health care funds and the lack of laboratory monitoring tests.
- Presently, health care personnel in Nigeria are professionally over-taxed and under-trained. With the present level of work burden the additional responsibility of caring for patients on long term antiretroviral treatment will significantly stretch the responsibilities of the health care providers.

- In response to several demands to make antiretroviral drugs available, the costs of triple combination drugs regimens have been reduced.
- However, the costs and logistics of drug procurement and distribution are also key factors to operational barriers in the effective implementation of ARVs in these countries.
- Ensuring adherence to treatment is crucial for clinical effectiveness and prevention of viral resistance, especially in the face of treatment toxicities, stigma and other barriers to care.
- In Nigeria there is the need to prioritize the specific training of the clinicians, other care providers and the patients to address these requirements. This is an important precondition for the appropriate use of antiretrovirals.
- Palliative care, including symptom control, psychosocial support and terminal care is important in all stages of HIV-related illnesses especially with advancing disease. Access to basic palliative care services is indeed limited to a large proportion of the population. The main factors responsible for this situation include the lack of access to essential drugs in health facilities and the scarcity of trained human resources for patient care.
- In 1984, the World Health Organization (WHO) launched its essential Drugs Programme to regulate drugs in the private sector and provide safe, effective and low-cost drugs through the public sector. Nigeria subsequently developed national drug policies and adopted lists of essential drugs that would meet principle country needs. In an attempt to improve health services and drug availability, especially in the rural areas, programmes that promote cost recovery through community financing, such as the Bamako Initiative has been recommended and implemented in several sub-Saharan countries. However, management of components of this scheme has been inadequate in most of these countries. As a result, it has been estimated by WHO that less than 50% of the sub-Saharan African Population have access to essential drugs including basic palliative drugs.
- In Nigeria, the shortage of drugs is not only due to a lack of financial resources, but also to inefficient drug supply and distribution systems in the public sector, unregulated procurement and dispensation in the private sector, and waste due to overuse by some providers. The shortage results in poor health facilities and high prices for drugs in the private sector, affecting access to essential drugs especially for the poor. Drug supply and distribution therefore remains an important area for improving access to even basic levels of HIV and AIDS care in many countries.

Fusion inhibitors

- Fusion inhibitors prevent HIV from entering target cells.
- Drugs of this class bind to the HIV envelope protein gp41, which is involved in viral entry.
- By blocking the interactions between regions of the gp41 molecule, fusion inhibitors interfere with the conformational change (folding) of the envelope molecule required for fusion with the target cell membrane.

- Enfuvirtide, a fusion inhibitor, was approved by the FDA in March 2003 for use in adults, and in children ages six and older, with advanced HIV infection.
- The first agent to be approved in the class of fusion inhibitors, enfuvirtide functions by binding a region of the HIV envelope glycoprotein gp41 and preventing viral fusion with the target cell membrane.
- FDA approval was based on two randomized, open-label Phase III studies of enfuvirtide used in patients with viral loads >5000 copies/mL and prior experience with (or documented resistance to) each of the NRTI, NNRTI, and PI drug classes. In these highly pre-treated patients, the combination of enfuvirtide with individualized background regimens of antiviral agents, compared with individualized background regimens alone, resulted in significantly greater decreases in viral load at 24 weeks (a difference of 0.846 $\log_{10}$ copies/mL in pooled analyses, $p<0.0001$) and better rates of viral suppression. Significantly greater CD4 cell increase were seen in the enfuvirtide groups than in the control groups (a difference of 36.6 cells/μL in pooled analyses, $p<0.0001$).

- Formulation and Dosing
  - Enfuvirtide is administered by subcutaneous injection.
  - It is available in powder form and must be reconstituted with sterile water.
  - Single-dose vials contain 108 mg of enfuvirtide for the delivery of approximately 90 mg/mL when reconstituted. Standard dosing is twice daily.

PA-457: Maturation Inhibitor

- PA-457, being developed by biotech Panacos pharmaceuticals, is a derivative of the natural product betulinic acid whose anti-HIV activity was first announced at the 10th Retrovirus Conference in 2003.
- HIV particles produced in the presence of this drug are non-infectious and have distorted capsids (the 'core' of HIV containing the RNA genome).
- Further investigation found that PA-457 is unique in its mechanism of action. It inhibits neither a viral enzyme like current classes of ARVs nor a host factor like CCR5, but a protein produced by HIV-infected cells which would normally become a component of new HIV particles.
- During the viral life cycle the protein components making up new viruses are synthesized as one long protein chain. HIV protease then snips these into individual viral components; protease inhibitors block this action.
- What PA-457 does is to create a chemical bridge between two protein components so that HIV protease cannot separate them. Metaphorically speaking, while protease inhibitors blunt HIV's scissors, PA-457 makes its cloth impossible to cut.
- The most interesting finding was that the viral reduction appeared to be sustained for many days. PA-457 has a half-life of 2-3 days and a viral load reduction of more than 0.35 logs was maintained for eight to nine days after treatment in the 150mg and 220mg doses.

L-870810 – Integrase Inhibitor

- In contrast to PA-457, which is a recent and serendipitous discovery, drugs to inhibits the third HIV enzyme integrase, which splices the HIV genome into the human one, have been hypothesised ever since HIV's life cycle was first understood.
- Research on L-870810 has now been stopped after unacceptable liver and kidney cell toxicity was found in dogs.

- One of the reasons for the slow progress on integrase inhibition is that many candidates have turned out to be toxic and inhibit other vital cellular functions.
- However current research notes that there was no evidence of human toxicity in the current study and that studies in rats had shown none.
- Research on the related drug candidate L-870812 is proceeding.

Activity 7: Antiretroviral therapy in pregnancy and PMTCT

- All HIV infected pregnant women should be on ARV either as a result of their disease or for infant post exposure prophylaxis and HAART is the preferred choice. Avoid EFV if possible. However this is contraindicated in first trimester.
- For pregnant mother not eligible for HAART, initiate HAART after the *first trimeste*r. Follow guidelines for HAART-eligible mothers. Avoid nevirapine if CD4 count is >250 cells/mm^3. If used, educate patient and monitor closely for hypersensitivity reaction and other toxicities.
- If mother chooses to breastfeed, continue HAART for the period of breastfeeding, which should not exceed 6 months.
- If mother chooses to use breast milk substitute, and nevirapine or efavirenz are part of the HAART regimen, stop these drugs immediately, and continue the 2NRTIs for 1 week
- Give infant single dose NVP as soon as possible after birth, plus AZT for 6 weeks. A less effective alternatively is to give the infant single dose NVP as soon as possible after birth, plus AZT for 1 week.
- Specific Scenario in pregnancy
  - Pregnant woman who is HAART eligible, but not currently on ART: Delay the initiation of ART until after the first trimester, unless benefits outweigh risks. Include AZT in the regimen whenever possible
  - CD4 cell count is < 250 cells/mm^3
    - Nevirapine + 2 NRTIs
    - PI plus 2 NRTIs
    - EFV + 2 NRTIs in the **third trimester only,** if patient has nevirapine toxicity and there is no available PI
  - CD4 cell count > 250 cells/mm^3
    - Avoid nevirapine if possible. If used (NVP + 2 NRTIs), closely monitor for hepatotoxicity and systemic toxicity
    - P I + 2 NRTIs
    - EFV + 2 NRTIs in the **third trimester only,** if there is no available PI*
  - Previous clinical or virologic failure on NNRTI-containing regimen
    - PI + 2 NRTIs
    - Zidovudine + lamivudine + abacavir
    - Zidovudine + lamivudine + tenofovir
  - Previous single-dose nevirapine
    - PI + 2 NRTIs
    - NVP + 2NRTIs (follow CD4 guideline above, and monitor closely for virologic failure)
    - EFV + 2 NRTIs (third trimester only and monitor closely for virologic failure)
    - Zidovudine + lamivudine + abacavir
    - Zidovudine + lamivudine + tenofovir

- Mother receiving HAART at the time of current pregnancy: HIV-1 infected women receiving HAART in whom pregnancy is identified should continue therapy. Zidovudine should be a component of the regimen whenever possible .Replace EFV with NVP if she is on EFV containing regimen.
- Pregnant woman with active tuberculosis: Delay treatment until third trimester, if possible. If treatment is initiated in second trimester
  - Zidovudine + lamivudine + abacavir
  - Ritonavir boosted PI + 2 NRTIs (change rifampin to rifabutin)
  - Zidovudine + lamivudine + tenofovir
- If treatment is initiated in third trimester
  - EFV (800 mg) + 2NRTIs (in view of EFV CNS effect, this drug should ONLY be used if there is no alternative)
  - Zidovudine + lamivudine + abacavir
  - Ritonavir boosted PI + 2 NRTIs (change rifampin to rifabutin)
  - Zidovudine + lamivudine + tenofovir
- HIV-infected patient who presents in labour: Single dose NVP followed by (zidovudine + lamivudine) for 4 days. Mother should be seen within 5 days of delivery. If mother chooses to breastfeed, recommend HAART (follow guidelines for HAART eligible mothers). If mother chooses to formula feed, determine if mother is eligible for HAART for her own disease, and follow appropriate guidelines.

- HIV-infected mother who presents within a few days after delivery: If mother chooses to breastfeed, recommend HAART (follow guidelines for HAART eligible mothers). If mother chooses to formula feed, determine if mother is eligible for HAART and follow appropriate guidelines.

HIV-infected women on ART who become pregnant

- Options are:
  - Suspend therapy temporarily during first trimester
  - Continue same therapy
  - Change to a different regimen if initial regime is not same or has an intolerable side effect.
- Issues to consider:
  - Gestation of the pregnancy
  - Severity of maternal disease
  - Tolerance of regimen in pregnancy
  - Potential for adverse foetal effects
- Foetus most susceptible to potential teratogenic effects of drugs during the first 10 weeks of gestation. Risks of ARV to fetes during this period are generally unknown.
- As more women with HIV are considering pregnancy because of the therapeutic advances in HIV care as well as dramatic reductions in perinatal transmission, it is important to give appropriate preconception care and counselling to HIV-infected women of childbearing age
- Recommended components of preconception counselling include:
  - Selection of effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy.
  - Counselling about perinatal transmission risks and prevention, and potential effects of HIV or treatment on pregnancy course and outcomes.

- Initiation or modification of antiretroviral therapy prior to conception in order to: avoid agents with potential foetal toxicity; choose agents effective in reducing risk of perinatal transmission; attain a stable and maximally suppressed maternal viral load; and evaluate and manage therapy associated side-effects which can adversely affect maternal-foetal health outcomes.
- Give indicated immunizations and/or OI prophylaxis.
- Optimize maternal nutritional status.
- Screen for psychological and substance abuse disorders.
- Implement other standard components of preconception evaluation and management.

Short-course perinatal ARV prophylaxis to prevent mother to child transmission of HIV

- Short-course perinatal ARV prophylaxis is to be distinguished from long-term ARV therapy for treating HIV-infected people. They are regimens prescribed to prevent mother-to-child transmission of HIV and not to treat the HIV-infected mother.
- The three most common courses are listed below.
  - Administration of Zidovudine (AZT) to women from 36 weeks gestation through labour and delivery, with additional prophylactic AZT to the mother after birth in some regimens.
  - Administration of AZT and Lamivudine (3TC) to mother and baby during the antenatal, intrapartum, and post-partum periods.
  - Administration of Nevirapine (NVP) during labour and to infant within 72 hours of birth.
- Short-course ARV regimens, that do not fully suppress viral replication, may be associated with development of ARV drug resistance
- The women who had the highest risk of developing resistance with the single dose of NVP are those who should have gotten HAART (3 drugs)
- Nevirapine and infants
  - Because infants (particularly those infected BEFORE labour and delivery) may have a high viral load, there is a high risk of resistance
  - However, more children were born HIV-negative than if no nevirapine was used

Activity 8: Antiretroviral therapy for Children

- Data on the efficacy and tolerability of antiretrovirals in children are limited.
- However, antiretroviral options are often limited in young children as only some of the antiretrovirals are available as paediatric formulations.
- All antiretrovirals have been associated with toxicities in children but in general, they are relatively well tolerated.
- The gastrointestinal system including hepatic system is most prone to being affected by these drugs.
- Skin rashes and hypersensitivity reactions are also associated with antiretroviral use, particularly with the non-nucleoside reverse transcriptase inhibitors.
- Mitochondrial toxicities that lead to impairment of liver function, pancreatic function and lactic acidosis are associated with most of the nucleoside analogues.
- Haematological toxicity is often a dose limiting adverse effect especially of the nucleoside analogues, in particular zidovudine.

- The protease inhibitors are associated with gastrointestinal intolerance (diarrhoea) and metabolic derangements that can lead to hypercholesterolemia and hypertriglyceridaemia, which in turn can lead to changes in body habitus.
- The renal system is also affected by several drugs, the most important of which is indinavir, which has been associated with renal stones and damage to the renal tubules.
- Fortunately, with lower incidence of major toxicity and with the range of drugs now available for paediatric use, toxicities are usually not a barrier to effective antiretroviral therapy in children.
- The same principles of antiretroviral therapy apply to HIV-infected children and adolescents. The treatment of HIV-infected children however, involves unique pharmacologic, virologic, and immunologic considerations
- The goals of therapy in children are:
    - Promote or restore normal growth and development
    - Prevent complicating infections and cancers
    - Improve quality of life
    - Prolong survival
- Paediatric antiretroviral formulas come in form of suspensions, tablets, capsules, and powder or intravenous formulations. The liquid may be flavoured.
- The ideal combination of antiretroviral therapy consists of 3 drugs minimum of which 2 NRTIs form the backbone. The 3rd drug may either be a protease inhibitor or an NNRTI.
- Adherence to treatment is also a major issue in children. Children depend on caregivers for administration or supervision of administration. Medications are not always available in palatable liquids or mixable formulations for infants/young children. Adherence is affected by a number of factors. These include;
    - Parental factors e.g. misunderstanding/misinformation to parents, cultural beliefs, secrecy, stigma, shame
    - Children factors such as taste, child refusal
- There is a need to facilitate adherence to ART. These include:
    - Family-Focused Adherence Support
    - Provider-Focused Support
    - Child-Focused Strategies
    - Teaching the child pill swallowing techniques

Activity 9: Drugs used for prophylaxis

- MAC prophylaxis is recommended in patients with CD4 cell count < 50 cells/mm^3. This is in form of Azithromycin 30 mg/kg weekly or Clarithromycin 7.5 mg/kg twice a day. Can stop prophylaxis if CD4 count > 100 cells/mm^3 for 3-6 months.

Isoniazid prevention therapy (IPT)

- IPT is used in HIV positive individuals who do not have active TB infection in order to prevent the development of active TB disease. Dose of Isoniazid is 5mg/kg/day to a maximum of 300mg/day for 6 months. Ensure that patient does not have active tuberculosis before commencement of IPT
- It is important to ensure adherence with drug use in these patients
- If patient however develop active TB during the course of prophylaxis, discontinue with prophylaxis and refer for TB management

Cotrimoxazole prevention therapy (CPT)

- CPT should be offered to HIV positive adults (over age 13): all persons with symptomatic HIV stage (stage II, III or IV); asymptomatic persons with CD4 count of 200/mm^3 or less or total lymphocyte equivalent or less than 1,200; pregnant women after 1st trimester.
- CPT can also be given to children born to HIV infected mothers from 6 weeks of age until confirmed that the child is not infected.
- Patients to commence CPT should not have allergies to sulphur containing drugs: They should be able to adhere to drug use and should be counselled about the possible side effects of the drug.
- CPT can be discontinued once the total lymphocyte count is above 4,000/mm3 or CD4 > 500 cells/mm^3, in patients on ART, when there is a reaction to cotrimoxazole and when the child is found to test negative to HIV after 18 months
- If patient unable to tolerate cotrimoxazole, another option is Dapsone 50 mg BD or 100 mg OD
- CPT provides protection against:
  - Pneumocystic jiroveci (carinii)
  - CNS toxoplasmosis
  - Various bacteria pathogens
  - Diarrhoeal pathogens
- Cotrimoxazole potential toxicities include:
  - GI upset
  - Hepatic toxicity
  - Rash including Steven Johnson's syndrome
  - Cytopenias
  - Elevated potassium
  - Other (rhabdomyolysis / pancreatitis. Both very rare)
- Prophylaxis against thrush is not recommended because:
  - Acute treatment very effective
  - Increased potential for resistance
  - Possibility of drug-drug interactions

Activity 10: Gene therapy

- Scientists in the United States have used gene therapy techniques to try to boost immune systems.
- Initial results from the trial have been promising.
- The technique involves taking T cells from patients and re-engineering them so that they can destroy HIV.
- These cells are treated with a "gutted" form of HIV in the laboratory, which has been genetically engineered to stop HIV in the body from replicating and spreading.
- After the cells have been treated in this way, they are re-introduced into the body where they lie in wait until HIV attacks.
- The idea is that the re-engineered cells will paralyse HIV and prevent it from spreading to other cells.
- It does this by cutting up the virus and inserting its own genetic material, which is designed not to spread.

- The three patients who have received the treatment so far have all been resistant to some of the drugs normally used to treat the virus.
- Reports from Germany reported of progress in constructing a vehicle for an artificial gene called C36 that produces a peptide with the same fusion-blocking sequence of T-20 (Fuzeon). The idea is to inject the gene, deliver it to blood cells, and let the cells manufacture a new protective weapon against HIV to place on their outer envelopes.
- The group has engineered an elegant bit of genetic trickery that not only blocks HIV before it can get its foot in the door, but is carefully designed to minimize unwanted side effects.

Activity 11: Herbal and other products used in HIV/AIDS Management

Immune boosters

- Treatment with HAART (highly active antiretroviral therapy) usually results in decreased CD4 cell counts.
- Although HAART can reduce the risk of certain complications of AIDS, strangely, it does not usually restore the immune system's ability to fight HIV. Unless researchers find some way to do what so far elude them, people with HIV/AIDS will depend on drug therapy for the rest of their lives.
- Since prolonged use of HAART is a difficult option, other strategies need to be developed.
- Various researchers all over the world have been testing immune boosters on PLWHA
- There is also ongoing research in NIPRD, Abuja, Nigeria on the development of immune boosters from herbs.

Nutraceuticals

- The function of the intestinal tract is to absorb nutrients and calories and to protect our bodies from foreign substances that enter the G.I. tract. Preserving one's intestinal integrity and function is critical to maintaining or gaining weight and protecting against infection.
- Glutamine has been shown to play an important role in the nutritional management of patients with HIV and AIDS.
- HIV is known to grow in the cells that line the small intestine especially in the lower part (the ileum). Functional loss of the ileum results in poor absorption of many nutrients. Tests among people with AIDS demonstrate lower levels of vitamins, bile acids and essential lipids in their bodies.
- When absorption of essential nutrients is poor, immunity is lowered, allowing bacteria and pathogens to invade the intestinal cells and cause irritation, malabsorption and diarrhoea.
- The thin layers of cells that line the intestinal tract are the only defence against the millions of microbes and bacteria that are found in the G.I. tract.
- The fuel that these cells live on and use for growth is Glutamine. Supplemental glutamine is known to keep these cells healthy and in good repair, and thus, block the movement of bacteria and germs through the intestinal lining.
- When these cells are weak and damaged, microbes and bacteria will cross the lining of the G.I. tract and "leak" into other parts of the body's immune system. Hence the term "leaky gut." When this happens, people experience fevers and night sweats.
- Another example of unhealthy or damaged intestinal cells is diarrhoea.
- Research has shown that supplementing the diet with glutamine may help manage diarrhoea.

- Results of a two-year study, double-blinded, randomized, placebo-controlled trial on patients with AIDS and weight loss proves the product to be an Immune System Booster, which is a significant factor in increasing body weight and body cell mass.
- People who should not use glutamine are those with end stage liver or kidney disease where protein is restricted.
- Glutamine is derived from corn.
  There are a number of immune boosters and nutraceuticals being developed by NIPRD, Nigeria

IL-2 (interleukin-2)

- These are GM-CSF (granulocyte-macrophage colony-stimulating factor)
- Preliminary results suggest that combined use of these chemical messengers, or cytokines, seems to help the immune system and stimulates it in fighting HIV.
- Central to this fight is the production of another cytokine called interferon-gamma. People with HIV infection appear to produce less of this cytokine as their immune system degrades. Combination therapy with IL-2 and GM-CSF appears to invigorate the immune system and allows it to resume production of interferon-gamma.
- Study details show that three HIV-positive subjects who each had fewer than 100 CD4+ cells despite their use of HAART for at least 12 months and with viral loads below the 200-copy mark for at least one year, received IL-2 in addition to HAART. IL-2 was injected under the skin at a dose of five million units daily for five consecutive days every six weeks. Researchers called each of these periods a "cycle." One of the subject who had MAC also received GM-CSF during the third cycle
- Results show that the T-cells of subjects before they received IL-2 suggested that the cells were either unable to respond to viruses and fungi or could produce only a weak response. Moreover, the type of response produced by these cells was not likely to provide protection from these pests.
- Despite the use of IL-2, there were no significant increases in CD4+ cell counts in the three subjects. However, there was a rise in the number of other types of immune system cells, called natural killers. The ability of these cells to destroy infected cells doubled after subjects received IL-2.
- Blood samples from the subject who received IL-2 and GM-CSF contained immune system cells that were able to mount a strong response against HIV as well as the yeast candida.

Side effects

- All subjects experienced the following temporary side effects during and just after exposure to the immune boosters:
  - Mild fever
  - Night sweat
- After three cycles of IL-2 and one of GM-CSF, the subject with MAC began to recover from that infection and experienced the following improvements:
  Increased weight
  Reduced fever
  Disappearance of belly pain
- CAT scans and other tests revealed smaller lymph nodes in his belly and fewer numbers of MAC.
- During the period subjects received immune boosters, viral load did not increase.

- The results of this very small study suggest that, even in a subject with AIDS, it is possible that the use of IL-2 and GM-CSF may help restore some of the immune system's defences.
- Specifically, some researchers think that these two immune boosters when used together may enhance the function of CD8 cells. These cells may be better able to recognize invading viruses and other microbes.
- Once the immune system is able to maintain this ability to recognize and alert other cells about the microbes, it appears that CD8+ cells can begin to release the interferon-gamma that is critical in successfully controlling these infections.
- The next step is to test the combination of IL-2 and GM-CSF in a larger group of PLWHA to confirm the results of this study.

Activity 12: National Guideline on the Use of ARV Drugs

The National Guidelines for Initiation of ART for Adults and Adolescents

Initiation of therapy depends on availability of CD4 cell count testing.

- If CD4 testing is available:
  - WHO Stage IV disease irrespective of CD4 cell count
  - WHO Stage III disease with CD4 cell counts < 350/mm^3
  - WHO Stage I or II disease with CD4 cell counts ≤ 200/mm^3
- If CD4 testing is unavailable:
  - WHO Stage IV disease irrespective of total lymphocyte count (TLC)
  - WHO Stage III disease irrespective of TLC
  - WHO Stage II disease with a TLC ≤▫1200/mm^3

A TLC of ≤▫1200/mm^3 does not predict a CD4 cell count of ≤ 200 /uL in asymptomatic patients as such TLC of ≤▫1200/mm^3 may not be used as criterion for the initiation of therapy in asymptomatic patients (WHO Stage 1 disease).

Drug use

- For adults/ adolescents, first line regimen is d4T or ZDV / 3TC / NVP or EFV
- Alternative first line regimens are TDF or ABC/ FTC or 3TC/ NVP or EFV; ddI / 3TC or FTC / NVP or EFV
- First line regimen for children is d4T or ZDV/ 3TC / NVP
- First line recommendations for HIV/TB adult and adolescent patients is d4T, ZDV or TDF / 3TC or FTC / NVP or EFV if during non-Rifampicin-containing continuation phase d4T, ZDV or TDF / 3TC or FTC / EFV if during Rifampicin-containing intensive or continuation phase
- First line recommendations for HIV/TB in children is d4T or ZDV/ 3TC / EFV (EFV not recommended for children below 3 years)

When treatment failure occurs

- Evaluate patient for reasons for failure
- If due to non adherence, salvage therapy is not the option

For Nigeria

- When nevirapine fails, typically efavirenz will not work either. The alternative then is to initiate a protease inhibitor-based treatment. Preferred at this junction is a ritonavir boosted regimen, lopinavir/ritonavir (Kaletra®), indinavir/ritonavir, atazanavir/ritonavir, or saquinavir/ritonavir.

- If lamivudine fails, the alternative is to use tenofovir plus didanosine. There is an interaction between tenofovir and didanosine which causes didanosine levels to be increased. It is recommended that didanosine dosage be reduced from 400 mg daily to 250 mg for patients weighing >60 kg. If under 60 kg, didanosine should be dosed at 125 mg daily.
- If these alternatives fail then switch to new class of drug such as an entry inhibitor like enfuvirtide, the anti-fusion drug. It is very expensive with limited availability.
- If all treatment fails, then manage patient using prophylaxis for opportunistic infections and give palliative care.
- Changes in antiretroviral therapy can decrease future therapeutic options, however when the changes are made early, before there is multiple drug resistance it is possible to spare a class for future use.
- The same principles of antiretroviral therapy apply to HIV-infected children and adolescents.
- The treatment of HIV-infected children, however, involves unique pharmacologic, virologic, and immunologic considerations.

Activity 13: Group Activities/Discussions

Participants would be divided into groups to discuss prospects/constraints encountered in the use of HAART in

(a) Resource-limited economy;

(b) Largely illiterate society;

(c) Polypharmacy, Nutrition and its implication for HAART regimen

Module 4

Identifying the Role of Pharmacists in PLWHA Care

Objectives

1. To help pharmacists provide effective patient education and counselling
2. To help pharmacists identify their role in HIV/AIDS management beyond ARV management

Content

- Pharmacists and PLWHA education and counselling
- Pharmacists and palliative care
- Nutrition and HIV
- The future options for HIV control

Materials required

- Overhead projector
- Data/Multimedia projector
- Transparencies
- Flipcharts and flipchart stand
- Markers
- Masking tape
- Laptop
- Diskettes/Other media storage devices

Time: 200 minutes

Activity 1: The role of the Pharmacists in ARV education and counselling

This session would discuss about the importance of the education and counselling session, the role of the pharmacists and the patient and content of such education and counselling session. The need for documentation of such sessions would also be highlighted

Time: 30 minutes

Activity 2: The role of the Pharmacists in palliative care

Discussion during this session would emphasize on the role of the pharmacists in palliative care of PLWHA especially with respect to the management of narcotic drugs. The session would also highlight the role of the Pharmacists in a multidisciplinary palliative care management team

Time: 30 minutes

Activity 3: Role of nutrition in the management of HIV/AIDS

Participants would learn about nutritional management of HIV infection and the place for nutritional supplements in patients' management

Time: 20 minutes

Activity 4: Infant feeding options

The session would discuss the various infant feeding options there are for ensuring maximal growth and development of the child born to the HIV infected mother

Time: 40 minutes

Activity 5: Future control options for HIV/AIDS

Participants would understand the reasons for the recent intense international advocacy on HIV-1 vaccines and why an HIV-1 vaccine is needed. Attention would be paid to discussing microbicides, a prospective control option in the near future.

Time: 30 minutes

Activity 6: Group Activities/Discussions

Facilitator's/lecturer's notes

Introduction

This session is important because of the human and economic consequences of inappropriate medication use that has become the subject of professional, public and congressional discourse for more than two decades. Lack of sufficient knowledge about their health problems and medications is one cause of patients' non adherence to their pharmacotherapeutic regimens and monitoring plans; without adequate knowledge, patients cannot be effective partners in managing their own care. The pharmacy profession has accepted responsibility for providing patient education and counselling in the context of pharmaceutical care to improve patient adherence and reduce medication-related problems. This involves counselling outpatients about prescription medications. In future court cases may establish that pharmacists, in part because of changing laws, have a public duty to warn patients of adverse effects and potential interactions of medications. The result could be increased liability for pharmacists who fail to educate and counsel their patients or who do so incorrectly or incompletely. This session would focus on discussing the role of pharmacists in PLWHA care especially with respect to ARV use. The facilitator would then introduce the lecturers

Time: 5 minutes

Activity 1: The role of the Pharmacists in ARV education and counselling

- Providing pharmaceutical care entails accepting responsibility for patients' pharmacotherapeutic outcomes.
- Pharmacists can contribute to positive outcomes by educating and counselling patients to prepare and motivate them to follow their pharmacotherapeutic regimens and monitoring plans. Pharmacists should educate and counsel all patients to the extent possible. Going beyond the minimum requirements of laws and regulations, which is simply offering to counsel, is a component of pharmacists' responsibilities.
- In pharmaceutical care, pharmacists should encourage patients to seek education and counselling and should eliminate barriers to providing it.
- Pharmacists should collaborate with other team members, as appropriate, to determine what specific information and counselling are required in each patient care situation. A coordinated effort among team members will enhance patients' adherence to ARV regimens, monitoring of drug effects, and feedback to the health system.
- Patient education and counselling guidelines are applicable in all practice settings including acute in-patient care and home care

Pharmacists' Knowledge and Skills

- In addition to a current knowledge of the pharmacotherapy of drugs related to PLWHA care, pharmacists need to have the knowledge and skills to provide effective and accurate patient education and counselling. They should know about their patients' cultures, especially health and illness beliefs, attitudes and practices. They should be aware of patients' feelings toward the health system and views of their own roles and responsibilities for decision-making and for managing their care.
- Effective, open-ended questioning and active listening are essential skills for obtaining information from and sharing information with patients.

- Pharmacists have to adapt messages to fit patients' language skills and primary languages
- Pharmacists also need to observe and interpret the non verbal messages (e.g., eye contact, facial expressions, body movements, vocal characteristics) patients give during education and counselling sessions.
- Assessing a patient's cognitive abilities, learning style and sensory and physical status enables the pharmacist to adapt information and educational methods to meet the patient's needs. A patient may learn best by hearing spoken instructions; by seeing a diagram, picture, or model; or by directly handling medications and administration devices. A patient may lack the visual acuity to read labels on prescription containers, markings on syringes, or written handout material. A patient may be unable to hear oral instructions or may lack sufficient motor skills to open a child-resistant container. In addition to assessing whether patients know *how* to use their medications, pharmacists should attempt to understand patients' attitudes and potential behaviours concerning medication use.
- The pharmacist needs to determine whether a patient is willing to use a medication and whether he or she intends not to do so.

Environment

- Education and counselling should take place in an environment conducive to patient involvement, learning and acceptance - one that supports the pharmacists' efforts to establish caring relationships with patients.
- Individual patients, groups, families or caregivers should perceive the counselling environment as comfortable, confidential, and safe.
- Education and counselling are most effective when:
  - Conducted in a room or space that ensures privacy and opportunity to engage in confidential communication.
  - If such an isolated space is not available, a common area can be restructured to maximize visual and auditory privacy from other patients or staff.
  - Patients, including those who are disabled, should have easy access and seating. Space and seating should be adequate for family members or caregivers.
  - The design and placement of desks and counters should minimize barriers to communication.
  - Distractions and interruptions should be few, so that patients and pharmacists can have each other's undivided attention.
  - The environment should be equipped with appropriate learning aids, e.g. graphics, anatomical models, medication administration devices, memory aids, written material, and audiovisual resources.

Pharmacist and Patient Roles

- Pharmacists and patients bring to education and counselling sessions their own perceptions of their roles and responsibilities.
- For the experience to be effective, the pharmacist and patient need to come to a common understanding about their respective roles and responsibilities.
- It may be necessary to clarify for patients that pharmacists have an appropriate and important role in providing education and counselling. Patients should be encouraged to be active participants.
- The pharmacist's role is to verify that patients have sufficient understanding, knowledge, and skill to follow their pharmacotherapeutic regimens and monitoring plans.

- Pharmacists should also seek ways to motivate patients to learn about their treatment and to be active partners in their care.
- Patients' role is to adhere to their pharmacotherapeutic regimens, monitor for drug effects, and report their experiences to pharmacists or other members of their health care teams.
- Optimally, the patient's role should include seeking information and presenting concerns that may make adherence difficult.

Process Steps

- Steps in the patient education and counselling process will vary according to the health system's policies and procedures, environment, and practice setting. Generally, the following steps are appropriate for patients receiving new medications or returning for refills.
- Establish caring relationships with patients as appropriate to the practice setting and stage in the patient's health care management. Introduce yourself as a pharmacist, explain the purpose and expected length of the sessions, and obtain the patient's agreement to participate. Determine the patient's primary spoken language.
- Assess the patient's knowledge about his or her health problems and medications, physical and mental capability to use the medications appropriately, and attitude toward the health problems and medications. Ask open ended questions about each medication's purpose and what the patient expects, and ask the patient to describe or show how he or she will use the medication. Patients returning for refill medications should be asked to describe or show how they have been using their medications. They should also be asked to describe any problems, concerns, or uncertainties they are experiencing with their medications.
- Provide information orally and use visual aids or demonstrations to fill patients' gaps in knowledge and understanding. Open the medication containers to show patients the colours, sizes, shapes, and markings on oral solids. For oral liquids, show patients the dosage marks on measuring devices. As a supplement to face-to-face oral communication, provide written guides to help the patient recall the information. If a patient is experiencing problems with his or her medications, gather appropriate data and assess the problems. Then adjust the pharmacotherapeutic regimens according to protocols or notify the prescribers.
- Verify patients' knowledge and understanding of medication use. Ask patients to describe or show how they will use their medications and identify their effects. Observe patients' medication-use capability and accuracy and attitudes toward following their pharmacotherapeutic regimens and monitoring plans.

Content

- The content of an education and counselling session may include the information listed below, as appropriate for each patient's pharmacotherapeutic regimen and monitoring plan.
- The decision to discuss specific pharmacotherapeutic information with an individual patient must be based on the pharmacist's professional judgment.
  - The medication's trade name, generic name, common synonym, or other descriptive name(s) and, when appropriate, its therapeutic class and efficacy.
  - The medication's use and expected benefits and action. This may include whether the medication is intended to cure a disease, eliminate or reduce symptoms, arrest or slow the disease process or prevent the disease or symptom.

- The medications expected onset of action and what to do if the action does not occur.
- The medication's route, dosage form, dosage and administration schedule (including duration of therapy).
- Directions for preparing and using or administering the medication. This may include adaptation to fit patients' lifestyles or work environments.
- Action to be taken in case of a missed dose.
- Precautions to be observed during the medication's use or administration and the medication's potential risks in relation to benefits.
- Potential common and severe adverse effects that may occur, actions to prevent or minimize their occurrence, and actions to take if they occur, including notifying the prescriber, pharmacist or other health care provider.
- Techniques for self-monitoring of the pharmacotherapy
- Potential drug-drug (including non-prescription), drug-food and drug-disease interactions or contraindications.
- The medication's relationships to laboratory procedures (e.g., timing of doses and potential interferences with interpretation of results) especially with respect to CD4 count and viral load assessment
- Prescription refill authorizations and the process for obtaining refills.
- Instructions for 24-hour access to a pharmacist.
- Proper storage of the medication.
- Proper disposal of contaminated or discontinued medications.
- Any other information unique to an individual patient or medication.

➢ These points are applicable to both prescription and non-prescription medications.
➢ Pharmacists should counsel patients in the proper selection of non-prescription medications.
➢ Additional content may be appropriate when pharmacists have authorized responsibilities in collaborative disease management for specified categories of patients. The following should also be covered during the counselling sessions:
  - HIV prevention, transmission, progression, and recurrence.
  - Possible effects of the disease on the patient's normal daily living.
  - Recognition and monitoring of disease complications.

Documentation

➢ Pharmacists should document education and counselling sessions in patients' case notes
➢ When pharmacists do not have access to patients' medical records, education and counselling may be documented in the pharmacy's patient profiles form, or on a specially designed counselling record.
➢ The pharmacist should record
  - that counselling was offered and was accepted and provided or refused
  - The pharmacist's perceived level of the patient's understanding. As appropriate, the content should be documented (for example, counselling about food-drug interactions).

  All documentation should be safeguarded to respect patient confidentiality and privacy and to comply with applicable State and Federal laws.

Activity 2: The role of the Pharmacists in palliative care

- Pharmacists have a pivotal role in the provision of hospice and palliative care and pharmacists should be integral members of all hospice interdisciplinary teams.
- Palliative care has been defined by the World Health Organization (WHO) as "the active total care of patients whose disease is not responsive to curative treatment." WHO notes that control of pain, other symptoms, and psychological, social, and spiritual problems is paramount?
- The goal of palliative care is achievement of the best quality of life for patients and their families.
- Pharmaceutical care is defined as the direct, responsible provision of medication-related care for the purpose of achieving definite outcomes that improve a patient's quality of life.
- Medication therapy is the cornerstone of most but not all symptom control in palliative care. The goals of palliative care and pharmaceutical care are consistent, with the latter being a necessary component of good palliative care.
- Palliative care is provided by an interdisciplinary team, which provides expert medical care, pain management and emotional and spiritual support expressly tailored to the patient's wishes. Emotional and spiritual supports are also extended to the family of the patient.
- Palliative care is usually provided in the patient's home or in a home-like setting operated by a hospice programme.

The palliative care interdisciplinary team

- A palliative care interdisciplinary team should include a doctor of medicine or osteopathy, a registered nurse, a social worker, and a pastoral or other counsel. Many other professionals and support persons are often members of such teams.
- A patient's plan of care must be reviewed and updated at specified intervals.
- The team should typically meet for one or two hours, two to four times a month to review patients' care, status, and needs. Treatment plan modifications, determinations of need for additional services, and planning for consultations with specialists, changes in care settings, imminent death, and other important events are discussed.
- Education and training are often provided at these meetings as well.
- Pharmacists coordinate pharmacotherapy by making recommendations for appropriate therapy, educating patients and the team about medications, monitoring therapeutic responses and performing other medication-related functions. Adjusting drug therapy in accordance with treatment algorithms is also an identified role for pharmacists.
- A registered nurse coordinates the implementation of each patient's plan of care. They also provide personal care on a daily basis and make home visits. Social workers are responsible for the psychosocial care of patients and their families and they arrange bereavement care for families after patients die.
- Volunteer service is another essential component of hospice care. Volunteers provide needed relief for family caregivers and a broad range of services to patients and their families.
- Chaplains and Imams address spiritual and existential issues. Hospice chaplaincy is typically nondenominational and is often provided in co ordination with patients' own clergy.

Pain management

- The World Health Organization (WHO) has provided guidelines for the selection of analgesics in chronic pain.

- At the onset of pain, or mild pain, the WHO recommends nonopioid therapy (e.g. acetaminophen, aspirin, and other NSAID).
- For pain that persists or increases, an opioid for mild to moderate pain should be used (e.g. codeine, hydrocodone, and oxycodone).
- Oxycodone is the opioid used most frequently at this level, and it is preferable to use oxycodone as a single ingredient analgesic. Percocet, as well as other combination analgesics, can only be titrated to the maximum daily dose of the non opioid ingredient (e.g. acetaminophen).
- When oxycodone or any other full opioid agonist is given alone, there is no ceiling effect when titrated appropriately.
- For pain that persists or increases, the WHO recommends opioids for moderate to severe pain, such as morphine, oxycodone, hydromorphine or fentanyl.
- Adjuvant therapy should be used at any step as appropriate.

The Pharmacist's Responsibilities

- High-quality palliative care requires both traditional and expanded pharmacist activities, including a variety of clinical, educational, administrative and support responsibilities.
- One responsibility is assessing the appropriateness of medication orders and ensuring the timely provision of effective medications for symptom control.
- Pharmacists maintain patient medication profiles and monitor all prescription and non-prescription medication use for safety and effectiveness.
- Pharmacists provide patients with essential medications within a time frame that ensures continuous symptom control (especially pain relief) and avoids the need for emergency medical services.
- Counselling and educating the hospice team about medication therapy.
- Pharmacists attend team meetings to advise other team members about medication therapy, including dosage forms, routes of administration, costs and availability of various drug products. This is done through regularly scheduled educational sessions.
- Pharmacists develop and maintain a library of contemporary references about medications, dietary supplements, and alternative and complementary therapies.
- Pharmacists advise members of the team about the potential for toxicity from and interactions with dietary supplements and alternative and/or complementary therapies.
- Ensuring that patients and care-givers understand and follow the directions provided with medications.
- Pharmacists ensure that all medication labelling is complete and understandable by patients and their caregivers.
- Pharmacists communicate with patients, either through the team or in person, about the importance of adhering to the prescribed drug regimen.
- Pharmacists explain the differences between addiction, dependence and tolerance; dispels patient and care-giver misconceptions about addiction to opiate agonists.
- Pharmacists ensure the availability of devices and equipment to permit accurate measurement of liquid dosage forms by patients and their care-givers.
- Pharmacists counsel patients about the role and potential toxicity of alternative and complementary therapies. When needed, pharmacists visit patients' homes to communicate directly with patients and their caregivers and to make necessary assessments.
- Providing efficient mechanisms for extemporaneous compounding of non-standard dosage forms.

- Pharmacists communicate with pharmaceutical manufacturers to determine the availability of non-standard dosage forms. Medication-compounding needs in hospice care include the preparation of dosage forms to ease administration (e.g. concentrated sublingual solutions, topical medications), flavouring medications to promote compliance, eliminating or adjusting ingredients that patients cannot tolerate and preparing or changing drug concentrations. Whenever possible, pharmacists compound formulations for which stability and bioavailability data are available.
- Addressing financial concerns - Patients may lack coverage or benefits that cover medications and care. Pharmacists should communicate with appropriate authorities to help patient obtain medications through programmes which will assist patients.
- Ensuring safe and legal disposal of all medications after death. - Medications dispensed to patients are "owned" by the patients and should not be used for other patients. Medications remaining in patients' homes fall under a variety of hazard categories. Pharmacists are able to assist families with the removal of the medications from the home in compliance with federal and state drug control and environmental protection laws and regulations.
- Establishing and maintaining effective communication with regulatory and licensing agencies - Because patients often require large quantities of controlled substances, open communication with both state and federal controlled-substance agencies is important. Pharmacists ensure compliance with laws and regulations pertaining to medications.

Documentation of Services

- As members of the interdisciplinary health care team, pharmacists should have access to patients' health records and authority to make entries necessary for the team's co ordinated care of the patient.
- With access to the patient's health record comes the pharmacist's professional responsibility to safeguard the patient's rights to privacy and confidentiality.
- Patients should be informed that pharmacists, as well as other members of the team, have access to their records.
- Pharmacist's documentation in patient records should include drug therapy recommendations, monitoring of medication effects, patient and family education, counselling activities and other activities as indicated.
- Medication profiles should be maintained and should include information about prescription and non-prescription drug products, dietary supplements and alternative and complementary therapies.
- Pharmacists also should maintain detailed formulation files for all extemporaneously compounded dosage forms.
- Other records should be maintained in compliance with applicable federal and state laws and regulations.

Summary

- The pharmacist can:
  - Give advice on the side effects of the medication.
  - Teach the person and the family how to take the medication and what to do if there are side effects.
  - Give the doctor advice on how to give the medication.
  - Help set up a schedule for taking medications.
  - Make up the medication.
  - Ongoing monitoring of all medications.

Activity 3: Role of nutrition in the management of HIV/AIDS

The nutritional needs of HIV-infected people and the effects of HIV infection on their nutritional status may vary according to the stage in the disease.

I. Acute phase

- **Initial infection.**
  - As soon as HIV enters the body, it replicates rapidly. This rapid replication requires energy and nutrients taken from the host's body.
  - The virus relies entirely on the host for survival and will deplete the host of whatever is required for its multiplication and survival.
  - The HIV infection may have a rapid onset leading to hyper metabolism with catabolism. Although some infected people may not have any symptoms at this stage, the host's energy and nutrient need increases and food intake should increase accordingly. If the host's intake does not increase, there will be a nutrient negative balance.
  - The period during which this occurs varies from 1 to 6 weeks, depending on the person.
  -
- **Seroconversion**
  - During the seroconversion phase, the body produces antibodies to fight the virus.
  - The body needs additional energy and nutrients to mount this immune response.
  - If these are not provided by the diet, the host will use fat and muscle to provide the necessary nutrients.
  - The host will lose weight and will gradually develop malnutrition that will weaken the immune system and make the host vulnerable to opportunistic infections.
  - The seroconversion phase occurs after 6– 12 weeks.

II. Asymptomatic phase

- The length of the asymptomatic phase varies and may last several years, depending on the host's health and nutritional status before the infection.
- The asymptomatic phase is marked by hypermetabolism and increased energy needs.

III. Symptomatic phase

- Initial symptoms are marked by the onset of opportunistic infections.
- Common symptoms include fever, night sweat, tuberculosis, fungal infection of the mouth, chronic diarrhoea and weight loss.
- The onset of opportunistic infections is a sign of a weakened immune system. Negative nitrogen balance occurs early in acute infections because of the decrease in food intake and increased urinary protein losses.
- Immunologic response to infection activates cytokines, which causes fever and anorexia, thereby leading to increased energy expenditure and decreased caloric intake.
- The opportunistic infections further increase the nutritional needs of the host and continue to weaken the immune system and hasten the progression of the disease.
- The persistence of symptoms and opportunistic infections lead to increased energy and nutrient needs, reduced food intake, malabsorption of nutrients, weight loss and wasting.
- Wasting is defined as a profound involuntary weight loss > 10 percent of baseline body weight plus either chronic diarrhoea (> 30 days) or chronic weakness and documented fever (> 30 days) in the absence of a concurrence illness or condition other than HIV infection.
- Wasting is often accompanied by changes in lean body mass and body cell mass.

- The persistence of reduced food intake, malabsorption of nutrients, weight loss, and wasting will lead to AIDS.

IV. Late symptomatic phase (AIDS)

- The late phase is marked by metabolic alteration, weight loss and wasting.
- Other characteristics include high viral load, decreased CD4 count, pneumonia, Kaposi's sarcoma, systemic fungal infection, bacterial infection, and certain types of cancer.
- The stages and the symptoms described are indicative and may vary from one individual to another or overlap.

Nutritional requirements

- Good nutrition is critical for people living with HIV/AIDS. Good nutrition has the greatest impact at the early stages of the disease because it strengthens the immune system to fight opportunistic infections and delays the progression of the disease.
- Good nutritional status before contracting the virus is also important. A person with good nutritional status is resistant to many infections. Even at the onset of symptoms, good nutrition helps reduce the severity of infections and the likelihood of weakening the immune system.
- Good nutrition also contributes to weight gain, prevents wasting and enables the host's body to fight opportunistic infections.
- Good nutrition:
  - Prevents malnutrition and wasting.
  - Achieves and maintains optimal body weight and strength.
  - Enhances the body's ability to fight opportunistic infections.
  - May help delay the progression of the disease.
  - Improves the effectiveness of drug treatment.
  - Improves the quality of life.
- Dietary management of HIV/AIDS-related symptoms refers to the strategy of using food and nutritional practices to manage the effects of HIV/AIDS-related symptoms on food intake and nutrient absorption.
- The goal of dietary management of HIV/AIDS-related symptoms is to prevent malnutrition and improve the health and nutritional status of people living with HIV/AIDS, thereby slowing the progression of the disease.
- The specific objectives are to reduce discomfort, alleviate symptoms, and ensure adequate food intake using locally available foods.
- Dietary management of HIV/AIDS-related symptoms has the following advantages:
  - Enables greater food intake by adding more flavour, encouraging consumption of small but frequent quantities of food or presenting foods in a texture that can be easily eaten
  - Increases comfort and reduces pain while eating.
  - Provides more nutrients to compensate for nutrient losses.
  - Prevents dehydration during diarrhoea and fever.
  - Complements and strengthens medical treatment.
  - Reduces the severity of symptoms by providing specific nutrient needs and strengthening the immune system.
- Promote weight and muscle mass gain and nutrient repletion by limiting the intake of low-calorie foods such as tea, coffee, salads, clear soups and most fruits and vegetables because they make the patient feel full, but do not help to maintain or promote weight gain

- A source of protein should be included with each meal and snack to help maximize nutrient intake. Also, provide a multivitamin supplement daily and recommend continued physical activity. Walking can help to stimulate appetite, increase energy, preserve and build lean body mass
- Take cognizance of food and nutritional interactions with medications and also side effects of medications such as nausea or vomiting that have an impact on food intake. Maintain food intake as much as possible even during periods of acute illness and depressed appetite
- Modify the diet to take care of AIDS-related symptoms that affect the ability to eat. For example, mashing or moistening food can make it easier to chew and swallow for someone with mouth and throat sores
- When there is loss of appetite, encourage the individual to eat smaller and more frequent meals, about 5-6 meals per day; provide high protein and high carbohydrate snacks between meals and with meals; advice to drink plenty of fluids and take walks before meals, to help stimulate appetite
- When clients have sore mouths, advice to avoid citrus fruits, acidic and spicy foods and eat foods at cold or room temperature, client should also eat soft and moist foods. Client should also avoid caffeine and alcohol
- A number of HIV-infected individuals experience a loss of taste or abnormal taste sensations, in particular malnourished individuals. This is because malnutrition reduces the capacity for taste receptors to turn over. This results in the loss of a number of taste receptors which changes the taste of food. Advice on use of flavour enhancers like salt, spices and herbs to increase taste acuity and mask unpleasant taste sensations. Chew food well and move it around in the mouth to stimulate taste receptors.
- For diarrhoea management**,** dietary strategies includes eating bananas or boiled white rice, that travel slowly through the digestive tract and decrease stimulation of the bowel, which can be effective in reducing diarrhoea. Client should avoid foods with insoluble fibre (roughage), e.g. take the skin off fruits and vegetables and should drink 8-10 cups (approx. 2 litres) of liquids per day to prevent dehydration. It is also advisable to avoid eating fried foods at this time and to avoid drinking sweet drinks but rather, diluted juices instead. Food should be eaten at room temperature-Very hot or cold foods stimulate the bowels and make the diarrhoea worse. For some patients, lactose intolerance, which is the inability to digest the sugar lactose in milk, may occur but only for a short period during episodes of diarrhoea. Avoid milk and milk products to see if symptoms improve. If the diarrhoea is severe, drinking an oral rehydration solution is important to replace electrolyte losses and prevent dehydration.
- There are some foods, however, that should be avoided because they aggravate the commonly occurring symptoms that have been discussed previously.
  - Raw eggs may contain bacteria, particularly salmonella that are harmful to the already weakened immune system of the HIV-infected person.
  - Undercooked meats and chicken may have bacteria that are harmful to the already immune compromised HIV-infected person.
  - "Junk" foods such as chips, biscuits and sweets have little nutritional value.
  - Wash vegetables, fruits and tubers thoroughly with clean water
  - Never consume raw meat, poultry and fish
  - Alcohol and coffee decrease appetite interfere with metabolism and alcohol may interact with some medications therefore decreasing their efficacy.

- The dietary management of HIV/AIDS-related symptoms should be integrated in all services at health centres and in outreach activities where health workers and counsellors meet people living with HIV/AIDS.
- During counselling sessions, health workers and counsellors should always assess how clients are managing diet-related HIV/AIDS symptoms and when needed, help identify alternative options.

Nutritional supplements

- Without providing specific nutrition interventions, there is faster weight loss associated with HIV infection, faster disease progression and shorter survival time.
- Low blood levels of several nutrients, including, selenium, iron, zinc, vitamins A, B12, and E, are associated with faster HIV disease progression and reduced survival.
- Nutrition supplementation and counselling interventions reduce HIV patients' vulnerability to weight loss and muscle wasting. This effect is confirmed particularly when nutritional supplements are given in the early stages, when low dietary intake and poor nutrient absorption are the primary causes of weight loss.
- Later in the course of infection, when metabolic changes begin to play a leading role in the wasting process, other types of interventions are required. This include:
  - high energy/protein liquid supplements
  - omega-3 fatty acids, which the body needs to respond to inflammation
  - Supplement containing amino acids and several antioxidant vitamins and minerals which help to increase muscle mass.
- When single or multiple micronutrient supplements are given, these supplements improve the immune system, reduce oxidative stress, and reduce the risk of morbidity and mortality.
- Vitamin A supplementation is also shown to reduce diarrhoea and mortality and improved several indicators of immune status in HIV-infected children. However, the exact dosage for maximum effectiveness remains unknown.
- Improving vitamin B12 status improves CD4 cell counts.
- Vitamins E and C reduced oxidative stress and HIV viral load. However, taking vitamin E supplements in the late stage of the disease may not be effective because the vitamin is fat soluble and poorly absorbed.
- Multivitamin supplementation has also been shown to improve pregnancy-related outcomes and immune status.
- Selenium and beta-carotene supplements increase antioxidant enzyme functions
- Zinc supplements reduce the incidence of opportunistic infections, stabilized weight, and improved CD4 counts. Some studies in the United States however, suggest that additional zinc intake is associated with faster HIV-disease progression.

Activity 4: Infant feeding options

HIV transmission during breastfeeding

- There is a 10-20% risk of transmission of HIV through breastfeeding.
- The time that HIV transmission occurs following birth is difficult to determine precisely. The presence of maternal antibodies, combined with a period of time during which the infection is undetectable, makes it difficult to determine whether infection occurred during delivery or through breastfeeding.
- Late post-natal transmission (after 3-6 months) can be estimated with the PCR test.

- A meta-analysis of five studies concluded that the best available estimate of the risk of breast milk transmission is 14%.
- The risk of HIV transmission through breastfeeding can be calculated for a particular population with the following formula: percentage of HIV-infected mothers at time of delivery multiplied by 14 percent.
- Up to 70% of breast milk samples from HIV-infected mothers have been shown to contain cell-associated and cell-free HIV.
- Transmission is not necessarily a result of the presence of HIV in breast milk, but because of a complex interaction between the anti-infective agents—macrophages, lymphocytes, and immunoglobulin— in breast milk and HIV.
- Safe alternatives may not be available in some resource-limited settings, (e.g., unsafe or inadequate water supply may be the only sources available for mixing formulas) in which case exclusive breastfeeding for the first six months of life is recommended
- Women who require ART and are breastfeeding should continue their ongoing ART regimen
- Efficacy of potent ART for mother used solely to prevent postnatal transmission of HIV through breast milk is unknown but is currently being studied
- HAART has been shown to dramatically reduce the transmission of HIV to the infant

Breastfeeding saves lives

- Replacement feeding prevents breast milk transmission of HIV but in resource limited settings; the risk of death from artificial feeding must be weighed against the risk of HIV infection.
- Several studies have reached the same conclusion about these competing risks: with high levels of infectious disease mortality, breastfeeding is safer than artificial feeding for infants up to a certain age when the mothers are HIV infected.
- If infant mortality is < 80/1,000 live births and the risk of death from artificial feeding is < 2.5 times the risk of death of exclusively breastfed infants, infants of HIV-infected mothers are safer when fed artificially.
- The LINKAGES risk model for HIV and infant feeding assumes that if HIV prevalence among child-bearing women is 20 percent, the relative risk from not breastfeeding is 3 times that and 17 percent of infants uninfected at delivery who are breastfed by an infected mother will become infected.
- Even in situations where a greater percentage of children die from HIV-related illness, the overall risk of mortality is still greater for children who fall into the categories of no breastfeeding at all or the spill over category of mixed feeding.

HIV and infant feeding risk analysis

- Maternal viral load: Maternal viral load is higher in mothers with recent HIV infection or advanced disease. The risk of MTCT during breastfeeding nearly doubles if the mother becomes infected while breastfeeding. For mothers who became infected post-natally, there is a 29% risk of transmission through breastfeeding.
- Maternal immune status: Maternal immune status also appears to increase the risk of transmission. Immune deficiencies in the mother, including a low CD4 or high CD8 cell count, increase the risk.
- Breast health: Breast health related to mastitis, cracked and bloody nipples, and other indications of breast inflammation may affect transmission of HIV. The risk is also higher in an infant with oral lesions such as thrush. Mastitis may be caused by infectious agents, poor

positioning and attachment or weak suckling. Deficiencies in the antioxidants vitamin E and selenium also may increase the risk of mastitis. Mastitis causes junctions in the mammary epithelium to become "leaky," allowing blood plasma constituents (HIV) to enter breast milk. Cytokines and other immune reactions resulting from mastitis can damage the intestines of young babies.

- Pattern or mode of breastfeeding: The pattern or mode of breastfeeding also affects transmission. Babies who are exclusively breastfed may have a lower risk of becoming infected than those who consume other liquids, milks, or solid foods in addition to breast milk during the first months of life. At 3 months, infants who were exclusively breastfed had significantly lower transmission rates (19.4%) than mixed-fed infants (26.1%) and the same transmission rate as formula-fed infants (19.4%). There is however limited evidence to support this.
- Mucosal integrity: Studies show that the disruption of the epithelial integrity of the mucous membranes of the intestine or mouth of the infant increases the risk of transmission. Mixed feeding, allergic reactions to complementary foods and infectious illness can damage the intestine and increase risk of transmission. Oral thrush in an infant may also be associated with MTCT.
- Breastfeeding duration: The first positive PCR cannot differentiate if transmission occurred during late pregnancy, labour and delivery or the early post-natal period. Studies suggest that the risk of transmission declines with the age of the infant. It is difficult however, to ascribe increased risk only to breastfeeding duration and the age factor, as feeding patterns change over time. Breast milk intake is gradually decreased, which reduces exposure to the virus but also causes the infant to become increasingly vulnerable to other infections.
- Maternal nutritional status: Malnutrition during pregnancy *may* increase the risk of MTCT. Vitamin A deficiency may impair T and B cell function, resulting in an increased maternal viral load and reduced antibody concentrations. Vitamin A deficiency could also result from advanced HIV disease. Both malnutrition and vitamin A deficiency contribute to MTCT. Taking multivitamins, not vitamin A, significantly increased CD4, CD8, and CD3 counts. No conclusions were drawn from the findings on vertical transmission.

Safer infant feeding options

- Formative research is an important first step for PMTCT programmes for supporting safer infant feeding practices.
- Efforts must be made to understand the attitudes and practices related to breastfeeding to assess locally appropriate and feasible replacement feeding options.
- Counsellors and health providers should also be aware of stigma concerns associated with HIV in the programme area. Counselling is an important skill for service providers working with mothers in the context of HIV with respect to the nutritional needs of pregnant and lactating women with HIV/AIDS.
- Counselling on infant feeding may be conducted during the VCCT post-test session or in conjunction with MCH services.
- Peer counselling has been a successful approach in some PMTCT programmes.
- Programme experience has shown that infant feeding options beyond breastfeeding are often not feasible, sustainable, or socially acceptable.
- The following factors must be considered when discussing and counselling on infant feeding options with an HIV infected mother:

- Nutritional requirements to avoid micronutrient deficiencies

- Bacterial infections as a result of unclean water, unhygienic preparation and storage, and the risk of diarrhoea
- Costs of formula, fuel, water, and health care
- Psychosocial stimulation through mother-infant bonding

➢ Once a thorough assessment has been made of the mother, household, and community, the infant feeding options below may be discussed and evaluated for their feasibility and practicality.

➢ Food security issues must be considered for each of the options.

➢ It should be emphasized that none of the following options are easy for the mother to practice without support, especially if she is HIV infected. Many PMTCT programmes support informed choice by HIV infected mothers about their infant feeding decision.

Modified exclusive breastfeeding

➢ **Exclusive breastfeeding** of infants up to 6 months should be promoted for women who are HIV negative or of unknown HIV status. Exclusive breastfeeding should also be supported as long as replacement feeding is not a viable option for an HIV infected mother. UN guidelines state that breastfeeding should be promoted, protected and supported for all women who do not know their HIV status and for women who are not infected. Notes should be taken in addressing the policies that support exclusive breastfeeding or breastfeeding in general in Nigeria.

➢ **Early cessation of breastfeeding** is recommended after a certain period of time (an optimal time has not been determined) for HIV-infected mothers when adequate and hygienic replacement feeds are available. Cessation is especially important if a mother develops AIDS symptoms. A study showed the declining protection afforded by breast milk with age of infant. A number of factors should be considered to support a mother in the early cessation of breastfeeding. As discussed below, acceptable, feasible, sustainable and safe breast milk substitutes must be available. Appropriate complementary foods and feeding practices must also be encouraged and food security considerations taken into account. Recommend a transition period between exclusive breastfeeding and exclusive replacement feeding with the following actions to getting the infant used to the new feeding patterns.

- Getting the infant used to cup feeding
- Providing skin-to-skin contact and use of massage and other means to comfort the baby in place of offering the breast
- Teaching the infant to sleep through the night
- Monitoring the infant's urine output to detect and prevent dehydration
- Switching from breast milk to replacement foods
- Supporting and caring for the mother

➢ **Methods for treating expressed breast milk** are currently being tested. Such methods include pasteurizing the milk (heating to 62.5 degrees Celsius for 30 minutes) or boiling it briefly and cooling it immediately in the refrigerator or by placing the container in cool water. Although these methods destroy HIV, they may be difficult to sustain. Heat-treated milk retains nutritional benefits but loses some anti-infective factors. Ideally, an infant should be given the treated breast milk from a cup. This option is most likely feasible in a hospital setting for sick and low birth weight infants. Several studies have shown that expressing breast milk and letting it stand for a half an hour inactivates HIV. During this time the naturally occurring anti-HIV factors in breast milk are allowed to take effect.

Again, the feasibility and sustainability of this option must be considered. Does the mother have time (or well-being) to express and heat treat her milk and then feed her child? With an electric pump in the optimal setting, expressing and storing takes on average 20-30 minutes and the infant is fed this expressed breast milk 8-10 times a day. Can the mother afford the fuel to heat the breast milk?

- **Exclusive replacement feeding** - Replacement feeding refers to feeding a child who is not receiving any breast milk from birth to about 2 years of age with a diet that provides all the nutrients the child needs. The following conditions must be in place for safe replacement feeding:

- Access to clean water
- Availability of sterilized utensils
- A steady supply of commercial or home-prepared formula for meeting the infant's nutritional needs
- **Replacement feeding options for children 0-6 months**

  • **Commercial infant formula** is made from modified cow's milk or soy protein but lacks the long-chain essential fatty acids that are present in breast milk. Giving formula requires water, fuel, utensils, skills and time to prepare it accurately and hygienically. The average quantity needed to feed an infant for 6 months is 20 kg of powdered formula (44 tins containing 450g each). Cup feeding rather than bottle feeding is recommended for hygienic purposes.

  • **Home-prepared formulas** can be made from animal milk (e.g. cow, goat, buffalo, or sheep), powdered milk and evaporated milk. For modified cow's milk use 100 ml cow's milk; 50 ml of boiled water; and 10g of sugar (2 teaspoons). Home prepared formulas are usually deficient in micronutrients such as iron, zinc, foliate, vitamins A and C. Unmodified cow's milk increases the risk of dehydration because of greater concentration of sodium, phosphorous and other salts. Again, cup feeding is recommended for hygienic purposes (powdered full-cream milk and evaporated milk). Full-cream milk requires the addition of boiled water as described on the package. Increase water by 50 percent and add 10g of sugar for each 150mL of feed. Micronutrients are also required. Skimmed milk, sweetened condensed milk, cereal feeds, juices, and teas are not suitable for replacement feeds before 6 months. Again, cup feeding is recommended for hygienic purposes.

Recommendations for replacement feeding of children 6-24 months

- Children of this age should be given a suitable breast milk substitute and complementary foods (nutrient enriched and appropriately prepared family foods).
- Between 6 and 12 months breast milk generally provides up to half or more of an infant's nutritional requirements and between 12 and 24 months, up to one-third of requirements.
- If suitable breast milk substitutes are not available, other dairy products should be given, such as animal milk, dried skimmed milk, yogurt, meat, liver, fish as a source of iron and zinc and fruits and vegetables to provide vitamins (especially A and C).
- The guidelines for complementary feeding of children ages 6-24 months should be carefully adhered to for children given replacement feeds.
- Food quantity, consistency and variety should increase as the child gets older, while maintaining frequent replacement feeds.
- Feeding frequency should also increase as the child gets older, using a combination of meals and snacks.

- Children 6-8 months old should receive complementary foods 2-3 times a day, children 9-11 months old should receive complementary foods 3-4 times a day, and children 12-24 months old should receive complementary foods 4-5 times a day.
- It is also important to diversify the diet to improve quality and micronutrient intake.
- The mother or care-giver should practice responsive feeding, frequent and responsive feeding during and after illness, good hygiene and proper food handling.

Other breast milk options

- Breast milk from breast milk banks is generally available over a short time for sick or low birth weight babies but not in resource limited settings.
- Wet nurses should be HIV negative. HIV transmission may occur from the infant to the wet nurse, especially if she has cracked nipples.

ARV and breastfeeding

- Safe alternatives may not be available in some resource-limited settings, (e.g. unsafe or inadequate water supply may be the only source available for mixing formulas) in which case exclusive breastfeeding for the first six months of life is recommended.
- Women who require ART and are breastfeeding should continue their ongoing ART regimen
- Efficacy of potent ART for mother used solely to prevent postnatal transmission of HIV through breast milk is unknown, but is currently being studied
- HAART has been shown to dramatically reduce the transmission of HIV to the infant.

Activity 5: Future control options for HIV/AIDS

Preventive vaccine

- The success achieved in the eradication of smallpox and polio (only pockets of polio exists in few countries worldwide presently) and the significant reduction in morbidity and mortality associated with other diseases such as measles, yellow fever and chickenpox has encouraged the initiative for the development of an HIV vaccine.
- A vaccine presently presents the only long term hope for a control of the infection as behaviour control has recorded limited success in the last 20 years of the infection.
- A vaccine would also be cheap, affordable and possibly accessible by many when it is eventually developed
- HIV vaccine research has been going on for some years now. There are ongoing trials in African countries such as Botswana, Kenya, Uganda and South Africa
- The process of developing a vaccine is however long. This is because, time is needed for
    - Laboratory development of potential candidate vaccine
    - In vitro testing
    - Animal testing
    - Human testing
    - Phase I for safety and immunogenicity in 20 – 50 volunteers
    - Phase II for additional safety, immunogenicity, dose finding, and route of administration and vaccination schedule in a few hundred volunteers
    - Phase III for efficacy against infection or disease in a few thousands of volunteers
- All over the world, there is testing of candidate vaccines in various stages of trials. Multiple studies are necessary because of the potential need to develop specific HIV strain-related

vaccines at this initial stage and then work towards the development of a globally acceptable vaccine which can work against all strains of HIV-1

- Nigeria has its own HIV-1 vaccine development plans and would hope to join global efforts within the next two years.

Microbicides

- Microbicides are substances that can be applied in the vagina so as to reduce the risk of infection from HIV-1 and other STIs as well as prevent unwanted pregnancies.
- It does not eliminated the need for condom but it empowers people whose partners would not use condom or cannot use condom
- A microbicide kills microbes, viruses and bacteria.
- There are no microbicides available that have been proven safe and effective for destroying HIV-1 and as a result, HIV-1 transmission prevention depends on condom use (either male or female).
- A microbicide could be inserted into the vagina in the same way that spermicidal foams are used to prevent pregnancy and would be a woman-controlled HIV-1 prevention method.
- Microbicides are in development and with adequate financial support, could be available on the market in 2-5 years.
- There are various types of microbicides that have been developed for both
  - Vaginal applications: Some products that have been tested for vagina use are
    - Carraguard
    - Buffer gel
    - PRO 2000
    - Cellulose Sulphate
  - Rectal applications
    - This is important so as to protect individuals involved in anal sex
    - Products for rectal application may need to be different from that of vaginal application because
    - The rectal lining is more fragile than the vagina lining
    - The rectum is richer in CD4 receptors, cells particularly vulnerable to HIV-1 infection, than the vagina
    - The ecology of the rectum differs from that of the vagina
    - The vagina is a closed pouch while the rectum is an open ended cavity and thus may need greater quantity of the microbicide for use
- Four different approaches to protection are under study:
  - Broad spectrum
    - In the broad spectrum approach, all microbes present in the semen are destroyed.
    - An example of a broad spectrum microbicide is a buffer gel.
    - A buffer gel works by keeping the vagina at a low pH during and after sex.
    - A quick chemistry review: low pH means acidic (like lemon juice or vinegar). HIV prefers a basic environment, that is, an environment with a high pH. So if the vagina is kept at a low pH after ejaculation, the HIV can be destroyed.
  - Inhibitor of viral entry
    - In the inhibitor of viral entry approach, HIV-1 is prevented from infecting the cells of the vaginal wall and cervix.
    - One such method is the "invisible condom." A substance is inserted into the vagina, and body heat causes the material to thicken, creating a barrier to HIV- 1
  - Inhibitor of viral replication

  - This involves the use of anti-HIV medications in the vagina.
  - This method may be useful for people who wish to get pregnant, as the medications would be active against the virus but might not necessarily destroy the sperm.
- A combination approach: A combination approach would involve the use of a broad spectrum method plus an inhibitor of viral entry method for maximum effectiveness against HIV.

- Currently, there are twenty microbicides in preclinical development (in the laboratory) and twenty-three products in various stages of clinical trials.
- The development of one product can cost up to $50 million.
- Microbicides could be produced as
  - Gels
  - Foams
  - Creams
  - Suppository
  - Sponge
  - Vaginal ring
  - Vaginal wipe
- They also would come as contraceptive and non contraceptive options

Effectiveness issues of microbicides

- Pharmaceutical companies are hesitant to join the development effort because of liability issues, and current government funding is not adequate to ensure timely availability of these products.
- However a number of products are at various stages of clinical trials. These include those in:
  - Phase I which are initial safety trials of the product in question
  - Phase IIa is a pilot clinical trial to evaluate efficacy and safety
  - Phase IIb is a pivotal trial that must adhere to a rigorous demonstration of efficacy
  - Phase IIIa is conducted in the target population
  - Phase IIIb deals with quality of life and marketing issues
  - Phase IV focuses on issues that arise once the product is marketed and is based on observation or experience of the target population.

  Currently, there are 14 microbicide product leads in the pre-clinical phase.
  Six product leads have completed Phase I trials
  - Cellulose sulphate
  - PMPA
  - PSS
  - CSIG
  - Acidiform
  - DS
- Three products have completed Phase II trials
  - Carraguard
  - Lactobacillus crispatus
  - PRO 2000- with Phase III trials planned to begin soon.
- Only two products have undergone phase III before
  N-9 based products (conceptrol and advantage 24) - that have been discontinued as N-9 has been shown to increase the risk of HIV acquisition.
- The next three to enter Phase III trials, however, have more hopes pinned on them

- Hopefully, by 2007, the first microbicide should be in the market
- Nigeria has also been involved with trials
    - There are Phase III Savvy trials going on in Lagos and Ibadan
    - There are Phase III Cellulose sulphate trials in Lagos and Port Harcourt
    - There are plans to start a Phase 1 TMC120 trial in Abuja
    - There are also plans to start a Phase I Vivagel trial in Sagamu

Activity 6: Group Activities/Discussions

There shall be a plenary discussion on how to facilitate the mobilisation of resources for the establishment of an ARV centre where none exists. Where one is existing, discussion would also focus on how to mobilise institution support for the effective use of knowledge and skills by trained participants

Module 5
Management of Opportunistic Infections

Objectives
1. Participants will be conversant with the various types of opportunistic infections and possible co-infections associated with HIV-1 infection
2. Participants will be conversant with the appropriate management strategies for these opportunistic infections

Content
- Common bacteria infections associated with HIV/AIDS
- Common viral infections associated with HIV/AIDS
- Common fungal infections associated with HIV/AIDS
- Common protozoal infections associated with HIV/AIDS
- Malignancies in HIV infection
- Handling of specimens

Materials needed
- Overhead projector
- Data/Multimedia projector
- Transparencies
- Flipcharts and flipchart stand
- Markers
- Masking tape
- Laptop
- Diskettes/other media storage devices

Time: 300 minutes

Activity 1: Introduction

The session would briefly introduce the participants to the importance of opportunistic infections with HIV management. It will also highlights the need for management of opportunistic infection as an integral part of HIV management

Time: 20 minutes

Activity 2: Common Bacterial Infections associated with HIV/AIDS

Participants will be able to highlight and identify common bacteria infections associated with HIV-1 infection. The clinical signs and symptoms of these infections would be identified, laboratory investigations will be required identified and management highlighted.

Time: 35 minutes

Activity 3: Tuberculosis and HIV infection

Tuberculosis constitutes a major opportunistic infection in HIV infection. There are associated challenges with managing tuberculosis co-infection with HIV/AIDS. Participants would learn about this management challenges and how to effectively address them

Time: 30 minutes

Activity 4: Common Viral Infections associated with HIV/AIDS

Participants will be able to highlight and identify common viral infections associated with HIV-1 infection. The clinical signs and symptoms of these infections would be identified, laboratory investigation required identified and management highlighted.

Time: 25 minutes

Activity 5: Common Fungal Infections associated with HIV/AIDS

Participants will be able to highlight and identify common fungal infections associated with HIV-1 infection. The clinical signs and symptoms of these infections would be identified, laboratory investigation required identified and management highlighted.

Time: 35 minutes

Activity 6: Common Protozoal/Parasitic Infections associated with HIV/AIDS

Participants will be able to highlight and identify common protozoal infections associated with HIV-1 infection. The clinical signs and symptoms of these infections would be identified, laboratory investigation required will be identified and the management highlighted.

Time: 35 minutes

Activity 7: Malaria and HIV infection

The lecture would highlight research finding on HIV and malaria co-infection and its implication on the severity of Malaria, HIV infection and drug management

Time: 20 minutes

Activity 8: Malignancies in HIV infection

Participants will be able to highlight and identify common malignancies associated with HIV-1 infection. The clinical signs and symptoms of these malignancies would be identified, laboratory investigation required identified and management highlighted.

Time: 20 minutes

Activity 9: Specimen Handling

The session would take participants handling of specimens for laboratory diagnosis. Emphasis would be placed on minimum standard requirements to ensure accurate laboratory diagnosis

Time: 15 minutes

Activity 10: Group Activities/Discussions

Lecturer/Facilitator's notes

Introduction

The facilitator should introduce the objectives of the module. Give a little insight into what participants would expect from the session. Participants would be allowed to ask questions at the end of the session so as to clarify issues. The lecturer is then introduced

Time: 5 minutes

Activity 1: Introduction

- Opportunistic infections are diseases occurring in an immunosuppressed individual caused by an organism which is non-pathogenic or weakly-pathogenic in individuals with a normal host defence (e.g. PCP).It may also be a more severe form of disease than that normally seen in a normal host (e.g. TB, coccidiomycosis)
- Risk for an opportunistic infection, AIDS-related malignancy or other HIV-related complication of HIV depends on:
  - Strength of immune system (measured by CD4 counts)
  - Risk of exposure (e.g. TB, Kaposi's sarcoma)
  - Use of prophylaxis
- Certain complications are defined as AIDS defining, and reflect more advanced disease as measured by CD4 cell counts and survival (WHO clinical stage 4).
- At higher CD4 counts, many complications overlap with conditions found in general population (bacterial pneumonia, pulmonary TB), although they may be more frequent or more severe (WHO stages 2 and 3)
- As CD4 cell counts decline, the spectrum of conditions broadens and include HIV-specific and opportunistic infections.
- The risk of complications seen earlier in disease may increase as well as new HIV-related complications occurring.
- Further increases in risk are also seen for some OIs with increases in plasma HIV viral load.
- The use of effective ARV drug combinations reduces the occurrence of OIs in HIV infected individuals.
- Level of immune compromise as reflected by CD4 cell count helps predict the spectrum of AIDS-related complications to which an individual is susceptible.
- This information is critical in determining need for prophylaxis and the differential diagnosis of symptomatic patients.
- Successful use of HAART results in restoration of some part of the immune system and decrease in risks of some OIs.
- Within three to nine months of effective ART (as determined by recovering CD4 cell count and lowered viral load), risk of many OIs decline significantly.
- During immune reconstitution, worsening of pre-existing OIs and other AIDS-related conditions may occur.
- This declining risk has led to discontinuation of prophylaxis in selected groups of patients responding to HAART.
- Therefore should OI prophylaxis in the setting of CD4 recovery be stopped?
  - Risk
    - OIs decrease survival and increase viral load (VL)
    - OI-related morbidity

  - Unknown duration of HAART-related benefit
  - Discontinuation of bactrim may increase risk of bacterial infections.
- Benefit
  - Fewer pills
  - Improve adherence
  - Decrease cost
  - Decrease risk of drug resistance

When to discontinue prophylaxis

Opportunistic infection	Safe	When?
Pneumocystis carinii pneumonia	yes	CD4>200 cells/µl
Mycobacterium avium complex	yes	CD4>100 cells/µl
Cytomegalovirus	yes	CD4>100 cells/µl
Toxoplasma gondii	yes	CD4>200 cells/µl
Pneumocystis carinii pneumonia	yes	CD4>200 cells/µl
2° prophylaxis of Toxoplasmosis maintenance therapy	yes	CD4 >200 cells/µ

- Work is on going on safety of stopping treatment for toxoplasmosis encephalitis, cryptococcal meningitis and CMV retinitis in the setting of sustained CD4 cell count recover.

Activity 2: Common Bacterial Infections associated with HIV/AIDS

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*
- *Klebsielia pneumoniae*
- *Nocardia asteroides*

Activity 3: Tuberculosis and HIV Infection

- 33% of the global population is infected with TB
- Among HIV-negative population, latent TB infection carries a 10% lifetime risk of progressing to active TB.
- Among HIV-infected persons co-infected with tuberculosis, however, annual risk of progressing to active TB is 10%.
- HIV epidemic has therefore led to a general escalation of TB incidence.

Impact of TB on HIV

- Active TB accelerates progression of HIV infection
- There is a higher risk of other opportunistic infections and death among TB/HIV co-infected persons than among persons infected with HIV alone.
- TB is associated with a 5-160 fold increase in HIV viral replication.
- This risk may reduce after successful TB treatment.

- Treatment of HIV in patients with active TB or vice versa, presents several challenges to the clinician in resource-limited settings.
- It is important that all clinicians in resource-limited settings become familiar with these challenges and with options available for management of co-existing disease

Challenges to clinicians

- Diagnosis of TB in HIV infected persons
- Drug – drug interactions between ARVs and Anti-TB drugs (the NNRTI Nevirapine, and Protease Inhibitors versus Rifampicin)
- Overlapping toxicity profiles between ARVS and first line Anti-TB drugs
- Non-adherence to complicated regimens.

Diagnosing TB in HIV infection

- Active TB can occur at any clinical stage of HIV/AIDS, whereas disseminated Mycobacterium avium complex (MAC) infection can occur at CD4 cell counts drop below 50 cells/mm^3
- A typical presentation of TB is more likely with advanced HIV disease or AIDS.
- In TB/HIV co-infection, sputum smears are less likely to be positive than among HIV negative individuals.

Sputum Microscopy

- Sputum Microscopy for acid – alcohol – fast bacilli (AFBs) is the major laboratory procedure used in case-finding for the implementation of the Directly Observed Treatment. Short Course (DOTS) strategy, for TB control in resource – limited settings.
- Sensitivity of Sputum Microscopy is lowest in persons with significant immuno-suppression and progressive or disseminated disease. It can be improved by:
  - Teaching patients improved sputum expectoration techniques
  - Use of concentration methods in sputum processing for AFBs. (Culture for Mycobacteria is standard diagnostic method in many countries and molecular methods are available in advanced countries).
  - 3 Serial sputum samples should be collected: A spot, an early morning and a second spot specimen when the early morning specimen is returned to lab by patient.

Tuberculin Skin Testing

- This is a crude diagnostic tool with false positive and false negative results.
- TB/HIV co-infected persons with advanced disease may show negative tuberculin sensitivity reactions.
- A Mantoux reaction of >5mm may be significant among HIV positive persons.

Chest Radiography

- Chest radiography varies depending on degree of immuno-suppression
- Ten percent of HIV infected persons with PTB may have normal chest radiographs.
- About 90% may have abnormal chest radiographs.
- Classic apical infiltrates and cavities are seen in only 1/3 of HIV/TB co-infected persons, when CD4 counts have fallen to around 200. Hilar lymphadenopathy and pleural effusions occur in advanced disease.
- Mycobacteremia and extra pulmonary TB especially meningitis are more common in low CD4 count.

Drug treatment of HIV/TB

First line recommendations for HIV/TB patients

- d4T, ZDV or TDF / 3TC or FTC / NVP or EFV if during non-Rifampicin-containing continuation phase
- d4T, ZDV or TDF / 3TC or FTC / EFV if during Rifampicin-containing intensive or continuation phase.

Recommendations for individuals with TB disease and HIV co infection:

CD4 cell count	Recommended regimen	Comments
CD4 <200 /mm^3	Start TB treatment. Start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months)[a]	Recommend ART. EFV is contraindicated in pregnant women during the 1st trimester or women of childbearing potential without effective contraception.
CD4 200-350 /mm^3	Start TB treatment. Start one of the regimens below after intensive phase (start earlier if severely compromised).	Consider ART
	EFV-containing regimen or NVP-containing regimens in case of Rifampicin-free continuation phase TB treatment regimen.	
CD4 >350 /mm^3	Start TB treatment	Defer ART
CD4 not available	Start TB treatment	Consider ART

- Children with tuberculosis co-infection (that require Rifampicin containing regimen for TB treatment) should use d4T or ZDV/ 3TC / EFV (for children 3 years and above)

Impact of ARV drugs on TB

- ARVs reduce the risk of developing active TB
- ARVs reduce the risk of death among HIV infected persons who develop active TB.
- ARVs have reduced incidence of TB infection among persons with HIV infection.

Drug – drug interactions

- Key locus of interaction between ARVs and Anti-TB drugs is Cytochrome P450-3A in intestinal wall and liver
- The rifamycins are the most potent inducers of Cytochrome P450-3A.
- Rifampicin is the most potent, followed by Rifapentin. Rifabutin is the least potent inducer.
- NNRTIs e.g. Nevirapine and PIs (with the exception of ritonavir) are metabolized by Cytochrome P450-3A. Rifampicin reduces the concentration of PIs by 75-95%. This would cause marked reduction of their anti-viral activities in vivo and lead to the more rapid emergence of resistance to these ARVs.

- Thus among PIs, only ritonavir can be used with rifampicin.
- PIs on the other hand are potent inhibitors of Cytochrome P450-3A. They increase serum concentrations of drugs metabolized by this enzyme system, e.g. Rifampicin, Rifabutin, and Rifapentin, to toxic levels. Concurrent administration of most PIs with rifabutin causes 2- to 4-fold increases in rifabutin levels, causing clinical toxicity requiring dose modifications of rifabutin.
- Some of the drug-drug interactions are very dramatic, justifying strong contraindications to the concurrent use of certain rifamycins and ARVs.

Recommendations for Concurrent Treatment of TB and HIV/AIDS in Nigeria.

- TB is a major cause of rapid progression and death in HIV-infected persons.
- Drug treatment of active TB should be a top priority in both HIV positive and HIV negative persons.
- The aims of anti-TB drug treatment are to:
  - cure the patient of TB
  - prevent death from active TB or its late effects
  - prevent TB relapse
  - decrease TB transmission to others.
- The high potency bactericidal drugs rifampicins, isoniazid, with pyrazinamide provide sterilizing action in which all populations of tubercle bacilli are killed.
- Rifampicin is the most effective sterilizing anti-TB drug and is therefore a very essential component of any TB treatment regimen.
- HIV/TB patients in Nigeria perhaps mostly present in health care institutions as active TB patients who are simultaneously diagnosed HIV positive. They may also be individuals with established HIV infection and newly diagnosed TB. In the first category, patient is not on anti-retroviral therapy (ART), but may or may not be a candidate for it. In the second category, patient may already be on ART.
- If ART is contemplated during treatment of TB in HIV infected patients and can be delayed or deferred, **use a rifampicin-based, four-drug anti-TB regimen** in the intensive phase of treatment only (rifampicin, Isoniazid, pyrazinamide and ethambutol). **Defer ART for those two months of the intensive phase** of anti-TB treatment.
- Confirm sputum conversion to negative after intensive phase before switching patient over to continuation phase of treatment.
- In Continuation phase, patients should be on INH and ethambutol. Duration of this phase should be for the duration recommended by the National TB Control Programme for Drug Management of TB (daily, for a minimum of 6 months).
- ART can safely be initiated in the continuation phase.
- For patients already on ART, or those for whom ART cannot be deferred, rifampicin can be given with Efavirenz, an alternative NNRTI to nevirapine.
- Non- rifampicin based anti-TB regimens are inferior, and do not rapidly sterilizes sputum.
- All patients on anti-TB drugs especially those concurrently on ART, should be on daily pyridoxine 50mg p.o., as prophylaxis against peripheral neuritis.
- Thiacetazone should be avoided in HIV positive persons.
- NRTIs are not significantly affected by rifampicin, thus no change or dose adjustments are required.

Overlapping toxicity profiles

- Both ARVs and some Primary Anti-TB drugs may cause or aggravate an already existing derangement of liver functions.
- Paradoxical worsening of TB characterized by development of new signs or symptoms of TB disease, or the exacerbation of existing manifestations of TB, can occur in patients on appropriate anti-TB treatment. Its incidence is higher among HIV positive than HIV-negative persons. See section on Immune Reconstitution Syndrome.
- Monitor liver function by checking liver enzymes levels before commencement of treatment and periodically during follow-up, as in the guidelines for use of ARVs in Nigeria.

Prevention of active TB in HIV infected persons

- There is a 10% annual risk of progressing from latent to active TB in HIV infected persons.
- Controlled clinical trials have demonstrated significant reduction of the incidence of active TB among HIV positive, PPD positive patients using isoniazid prophylaxis
- In a high-burden country like Nigeria where risk of exposure to TB is high, all HIV positive persons should undergo a 5 TU Purified Protein Derivative (PPD) skin test during initial evaluation and yearly thereafter for PPD-negative individuals. This will help identify early, those co-infected with TB.
- Those with ≥5mm skin reaction should be screened further for active TB (further history, physical examination, CXR, Serial sputum microscopy for AFBs).
- For those found with active TB, full therapy should be initiated.
- For those with a positive PPD reaction and negative sputum smears and CXR, preventive therapy (chemoprophylaxis) of latent TB with isoniazid 300mg daily for 9 months, with daily pyridoxine 25-50mg.
- Measures to encourage adherence must be taken.
- Ideally, laboratory monitoring should include liver function tests at baseline and interval, including serum bilirubin and aminotransferases.
- PPD-negative individuals with recent history of exposure to active TB cases should also benefit from chemoprophylaxis of TB.

Prevention of primary infection

- Comprehensive infection control measures, should be taken in hospitals, prisons, shelters, camps, hostels and group homes to prevent transmission of TB to susceptible persons, which include HIV positive persons.
- Both sputum smear positive and negative TB cases are capable of transmitting TB
- Early identification of cases using sputum smear, CXR and culture for Mycobacterium tuberculosis and placement on curative treatment, are good measures in settings listed above.
- Isolation of suspects until fully assessed may be necessary in institutions where a large number of persons are at risk.

Mycobacterium avium **complex (MAC)**

- Risk of bacteraemia increases as the CD-4 count drops below 100 cells/uL.
- Beyond this threshold, the risk of MAC bacteraemia is 8% per year.
- Signs and symptoms are: Constitutional symptoms such as fever, night sweats, weight loss, anorexia.; hepatomegally with up to 90% having elevated alkaline phosphatase; lymphadenopathy and splenomegally; bone marrow involvement occurs early with up to 80% having anaemia

- Treatment
  - Resistance always develops in monotherapy. Triple drug regimens are indicated. When resistance develops, do not change just one drug
  - 90% respond to proper therapy
  - Substantial clinical improvement in 4-6 weeks. Sterile blood cultures by 12 weeks.
  - Consider prophylaxis when CD4 < 50 cells/uL
  - First line therapy: Macrolides which decreases bacteraemia risk by 70% e.g. Clarithomycin 500 mg bid, azithromycin 1200mg/wk
  - Second line therapy: Rifambutin which decreases bacteraemia risk by ≥ 50% e.g. Rifabutin 300 mg/day
  - Other combinations are a Macrolide antibiotic + Ethambutol + A Quinolone antibiotic [sparfloxacin > levofloxacin > ofloxacin > ciprofloxacin] or Rifambutin

Activity 4: Common Viral Infections associated with HIV/AIDS

- **Cytomegalovirus**
  - Presenting Signs and Symptoms are:
    - Fever ± delirium, lethargy, disorientation, malaise, headache (most common)
    - Stiff neck, photophobia, cranial nerve deficits (less common)
    - Oesophageal ulceration appear in 12-15% of patients
    - Respiratory symptoms, i.e., pneumonitis, present in approximately 1%
  - Management involves the use of Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h x 14-21 days; ganciclovir 5mg/kg IV bid x 14-21 days.
  - Patients without immune recovery will need to be on maintenance therapy lifelong for retinitis
  - For extra-ocular presentations, use ganciclovir and/or foscarnet

- Adenovirus
- **Herpes Simplex infection**
  - Herpes infection is caused by herpes simplex virus
  - There are two HSV types: HSV-1 and HSV-2.
  - HSV requires a moist environment for survival
  - Viral transmission occurs by direct contact, during which virus is inoculated onto a susceptible mucosal surface or through breaks in the skin.
  - During acute primary infection, the virus becomes permanently latent in the nerve root ganglia that correspond to the cutaneous or mucous membrane site of inoculation.
  - Following orolabial infection HSV becomes latent in the trigemnial ganglia.
  - After genital or anorectal infection, it becomes latent in the sacral ganglia.
  - Early in the course of infection virons travel from the site of inoculation along sensory nerves to the corresponding nerve root or trigemnial ganglia.
  - Most commercially available serologic techniques do not reliably differentiate between antibodies to HSV-1 and those to HSV-2. However, two new tests, the Western blot assay and an immunoassay specific for antibody to HSV glycoprotein G, are capable of determining accurately whether a patient has antibodies to HSV-1 or HSV-2 alone, both viruses and neither virus.

- Of the many laboratory techniques available for diagnosis of mucocutaneous HSV infection, direct virus culture of material from suspected lesions remain the diagnostic procedure of choice.
- Virus culture is more sensitive and specific than demonstration of multinucleated giant cells or inclusions by the Tzanck smear, direct staining of infected cells for virus antigen, antibody detection and identification of virus particles by electron microscopy.
- Primary or recurrent infection with herpes simplex virus (HSV) is common in HIV disease.
- Illness is often more severe, more invasive and of longer duration than the immunocompetent host.
- The clinical presentation of HSV infection in patients with advanced HIV disease may differ from that in the normal host.
- The severity of illness depends on several factors, including whether HSV infection is primary, initial and non-primary or recurrent. Severity of illness may also depend on the site of infection and the degree of HIV-induced immunosuppression.
- Although both HSV types can cause infection at any anatomic site, HSV-1 more often infects orolabial sites and HSV-2 genital and anorectal site.
- Syndromes of HSV infections in advanced HIV disease are listed below:

➢ Mucocutaneous Infections
  - Gingivostomatitis
  - Recurrent fever blister
  - Intranasal ulceration
  - Genital ulceration
  - Perianal ulceration

➢ Visceral Infections
  - Esophagitis
  - Proctitis
  - Encephalitis
  - Keratitis

➢ **Treatment**

- The antiviral drug acyclovir, a nucleoside analogue is currently the treatment of choice for HSV infection.
- Acyclovir is available in tropical, oral and intravenous preparations. Route, dosage and duration of therapy depend on the type and severity of HSV infection.
- Topical acyclovir is not effective for recurrent herpes labialis but is occasionally useful in primary genital HSV infection.
- Oral acyclovir in a dose of 200-400mg five times a day is indicated for mucocutaneous disease associated with HIV infections.
- Intravenous acyclovir should be used in patients with severe mucocutaneous HSV disease; involvement of viscera, such as brain, eye, oesophagus, neurological complications, such as transverse myelitis or atonic bladder.
- Ocular HSV infection should be treated with trifluridine.
- Acyclovir cannot eliminate latent virus from ganglia. Severe, prolonged and frequent recurrences may occur after discontinuation of therapy.
- Acyclovir-resistant strains of HSV with thymidine kinase or DNA polymerase mutations have been reported with increasing frequency. Viral cultures and sensitivity testing should be performed in patients whose symptoms do not improve with standard therapy.

- Some reports have documented that acyclovir resistant HSV isolates have been sensitive to either Foscarnet or Vidarabine and also to treatment with HPMPC, (An acylic nucleoside phosphonate analogue) or topical trifluridine.

➢ **Varicella Zoster Virus**

- Varicella-zoster virus (VZV), a herpes virus, causes both varicella (chickenpox) and zoster (shingles).
- As with other herpes viruses, VZV causes both an acute illness and chronic lifelong latent infection.
- The acute primary infection (varicella) usually occurs during childhood. In a child with normal cellular immunity, primary VZV infection is relatively benign and self limiting. In adults however, primary infection can be more severe because systemic manifestations and occasional visceral dissemination occur.
- Patients with cellular immunodeficiency, regardless of age, are at risk for severe cutaneous or visceral varicella.
- Humans are the only natural host of VZV.
- Transmission occurs through direct contact with infectious lesions or inoculation of aerosolized infected droplets onto a susceptible mucosal surface.
- Infectivity usually begins 1-2 days before the onset of rash and persists until all vesicular lesions are dried and crusted, usually for a period of 5 to 7 days.
- In primary infection, the virus usually replicates in tonsillar and lymphoid tissue.
- Primary viremia develops 4 to 7 days after initial infection, and virus then spreads to internal organs.
- A secondary more prolonged viremia occurs approximately 14 days after the initial infection, resulting in cutaneous infection and the characteristic vesicular rash of varicella.

➢ Moluscum Contagiosum
➢ Human Papilloma Virus

➢ **Co-infection with hepatitis B and or C**

- Due to shared routes of transmission, co-infection with hepatitis C virus (HCV) and hepatitis B virus (HBV) is common in those with human immunodeficiency virus (HIV).
- The overall prevalence of HCV in HIV-infected individuals is approximately 15%-20%
- This is dependent on the population, with 80%-90% of injection drug users testing positive compared to 5%-10% of those who acquired infection from male-to-male sexual activity.
- Although the prevalence of past exposure to HBV is high (90-95%), active infection with HBV is less common and occurs in 10% - 15% of those co-infected with HIV.
- Little data are available on HIV/HCV/HBV triple infection as most studies on HCV or HBV in HIV patients have excluded patients with other liver diseases. Consequently, the prevalence of HIV/HCV/HBV triple infection is not known but is estimated at 1%-5%.
- Recent data in the era of highly active antiretroviral therapy (HAART) have shown similar histology in HIV patients co-infected with HCV compared to HIV-uninfected HCV controls.
- The impact of HBV and HCV on the progression of HIV infection is unclear. Whereas some studies have shown a more rapid progression to AIDS in those with HCV co-infection, other has not been able to demonstrate such a progression of HIV in those co-infected with either HCV or HBV.

- Although there are little data on the effect of triple infection with both HBV and HCV on the progression of HIV disease, it appears that HCV infection has a greater impact on CD4 cell recovery after initiation of HAART compared to HBV infection.
- Finally, although most patients with HCV or HBV co-infection tolerate HAART well, there is an increased risk of HAART hepatotoxicity in patients with HCV or HBV co-infection.
- Treatment of HCV in the setting of HIV co-infection includes the use of interferon alpha (IFNá) and ribavirin (RBV). Although response rates have been suboptimal, with sustained virologic response rates of 20%-30%, preliminary results of ongoing clinical trials with pegylated IFNá and RBV combination therapy are encouraging.
- Treatment of HBV in HIV-infected patients is more controversial. However, all patients with active replication (HBV DNA > 100,000 copies) should be considered for therapy. In those with low-titre HBV DNA (<50,000 copies/mL) and negative for HBeAg (occult HBV infection), treatment may be of little value and these patients can be observed.
- Use of IFNá for HBV in HIV has been disappointing.
- Although short-term use of lamivudine can lead to HBV DNA clearance in the majority of patients, continued use results in a high rate (20% per year) of HBV resistance associated with the emergence of YMDD mutations. This is especially true in those on lamivudine to help control HIV infection.
- Newer medications such as adefovir are effective against HBV and are associated with low rates of HBV viral resistance. However, their use in HIV confected patients has not been well studied.
- Although there are limited data on the use of tenofovir to treat HBV in HIV co-infection, results from ongoing trials are being awaited.

Activity 5: Common Fungal Infections associated with HIV/AIDS

- These infections usually occur when the CD4 count drops < 200 cells/uL.
- These are organisms that depend upon the cellular immune system for control and eradication.
- *Pneumocystis carini (jirovesi)*
    - Although *Pneumocystis carini* has long been considered a protozoa, recent studies of ribosomal RNA from the organism have shown greater homology with fungi, suggesting that it should be reclassified.
    - Such a reclassification has no immediate importance but may suggest new therapeutic approaches.
    - Although evidence in human has not been documented animal studies suggest the possibility of persons-to- person respiratory transmission of the organism.
    - A distinct form of *P. carini* infection emerged in the mid 1950s manifesting as a diffusing alveolar pneumocystosis that affected children and adults suffering from drug-induced neoplastic or congenital immune deficiency.
    - Although sporadic in distribution, the reactivation type of pneumocystosis was the most common variety seen in the developed countries.
    - Extrapulmonary and disseminated disease was rare, almost always appearing in conjunction with pneumonitis.
    - Pneumocystis carini pneumonia (PCP) is a common opportunistic disease that occurs almost exclusively in persons with profound immunodeficiency.

- The most common underlying conditions associated with PCP were leukaemia, Hodgkin's disease and other lymphomas, primary immunodeficiencies and organ transplant.
- Available data suggested an epidemiological pattern of some seasonal periodicity in the occurrence of PCP; similar to that seen with upper respiratory tract infections.
- Patients with PCP usually experience the sudden onset of severe respiratory compromise. Such constitution symptoms as fever, anorexia and lethargy may overshadow localized pulmonary complaints.
- Although cough occurs, it is seldom productive.
- Dyspnoea is common but may go unnoticed in a sedentary patient and chest pain is rare.
- The patient may have a low-grade fever, and the lungs are either clear or reveal dry bisal rales on auscultation.
- Clinicians first recognized HIV disease as a cluster of patients with PCP who did not have any recognized immunodeficiency state.
- Prior to the widespread use of antipneumocystis prophylaxis, PCP alone accounted for 43% of all opportunistic infections in patients with advanced HIV infection seen in the developed countries.
- With or without Kaposi's Sarcoma (KS) PCP was the Centre for Disease Control (CDC) defined index diagnosis in 62% of patients with HIV in the developed countries.
- In these countries, PCP is still the most common life-threatening opportunistic infection occurring in patients with HIV-infection.
- Cases of PCP have been less reported in the developing countries like Nigeria. This is probably due to the fact that capacities for the diagnosis of PCP in these countries are very minimal or non-existent.
- Data have further shown that the lower the absolute CD4 cell count of HIV- infected patients, the higher the likelihood of developing PCP.
- It has been documented that patients with CD4 counts of 200 cells/µl or less were 5 times more likely to develop PCP compared with patients with CD4 counts of more than 200 cells/µl.
- In early stages of the infestation of the lungs, there are few cysts and no inflammatory responses. Multiplication of the organism is predominantly extra cellular. As the infestation grows, more alveoli fill with organisms and exudates, producing defects in lung function.
- Type 1 and Type 2 alveolar cells hypertrophy and mononuclear cells infiltrate. Eventually, the alveolar cells desquamate, resulting in increased

permeability of the alveolar capillary membrane with consequent pulmonary oedema.

- Extrapulmonary *P. carinii* infections are rare but do occur and usually have a wide variety of locations and clinical presentations thus posing a diagnostic problem.

➢ **Diagnosis**

- Because of the diverse presentations of PCP, patients often do not appear with a "classic" presentation.
- However, typically patients present with fever, dry cough and shortness of breath or dyspnoea on exertion, oftentimes of a gradual onset over several weeks. In HIV infected patients, the clinical presentation is often insidious with slow but steady progression of fatigue, fever, chills, sweats and exceptional dyspenia.
- Physical findings are sparse and laboratory findings are also non specific.

- Full blood counts and sedimentation rates show no characteristic pattern in patients with PCP.
- Serum chemistries are not particularly helpful, however, the serum LDH concentration is frequently increased. The serum LDH concentration, although a non-specific indicator of lung parenchymal damage, appears useful in predicting which patients do well.
- Although antibody testing is helpful as an epidemiologic tool, it presently has no place in the diagnosis of acute PCP.
- Antigen testing, although it may prove a useful adjunct to other tests presently used, needs further evaluation before it is recommended as a routine diagnostic test.
- Serologic testing for *P. carinii* suggests that infection with the organism is widely prevalent in the general population; however, the use of serologic tests for diagnosis has been disappointing.
- A study on the usefulness of an enzyme-linked immunosorbent assay (ELISA) for IgG antibody to *P. carini* and a latex agglutination test for *P. carini* antigen found that although the mean IgG antibody titres of patients with and without acute PCP were not statistically different, antigen titres were both sensitive and specific in identifying patients with acute PCP. In addition, antigen titres appeared to parallel the patients clinical course during acute therapy.
- Diffuse interstitial infiltration, occasionally, with peripheral sparing, is the most common radiographic presentation of PCP, occurring in 75% of patients with advanced HIV disease and PCP.
- However, all of the following presentations have occurred: abscesses, cantation or cystic lesions, Lobar consolidation, nodular lesions, effusions, pneumothorax and a normal chest radiograph.
- Rare radiographic presentations include patchy upper lobe consolidation imitating tuberculosis, a miliary pattern and mediastinal and hilar enlargement.
- The radiographic appearance of PCP commonly worsens early in the course of therapy; in more severe cases, early PCP may progress to air space consolidation.
- However, clinicians should consider deterioration that continues beyond 7 to 10 days, a failure of therapy.
- A diffuse interstitial pattern can occur in other infections common to patients with advanced HIV disease, including CMV, histoplasmosis, TB and MAC infections. These cases of pneumonitis were clinically indistinguishable from cases of PCP, although the radiographic abnormalities were generally less serious and histological study showed less alveolar damage than those in patients with PCP.

- Clinical studies have shown gallium scanning of the lung (using gallium 67 and scanning 48-72 hours after injection of gallium) to be very sensitive (90-100%) for PCP but the specificity was as low as 20%.

- **Management**
- Prophylaxis against and treatment of acute PCP have advanced rapidly in recent years.
- The therapeutic regimens for acute PCP are all for 21 days unless indicated otherwise.

➢ **Drug Dose**

- Trimethoprim (TMP): 15-20mg/kg/d in combination with Sulfamethoxazole (SMX) 75-100gm/kg/d (IV or Oral) divided doses of 6 hourly. A rare percentage of patients have adverse effects necessitating change of therapy.

- Sulfamethoxazole (SMX) SMX: 75-100gm/kg/d
- Pentamidine 3-4mg/kg/d. (IV once daily). A large percentage of patient have adverse reaction necessitating change of regimen
- Dapsone (DS): 100mg/d. with TMP: 15-20mg/kg/d (both oral).Screen for G6PD when starting dapsone

➢ *Cryptococcus neoformins*

- Distributed world-wide.
- Present in soil that is contaminated by birds
- There are multiple other hosts.
- A characteristic thick capsule (anti-phagocytic) capsule with budding of smaller, "daughter cells".
- About 2% of patients with AIDS present with Cryptococcal infection, and over 10% of HIV-positive patients eventually develop it during the course of their illness.
- For such patients CD-4 count is almost always < 100 cell/uL unless there are concurrent risk factors.

➢ *Histoplasma capsulatum*

- In some parts of the world, it is the second most common opportunistic infection.
- Lives in acidic soils contaminated by bats or birds.
- May remain viable in soil for years.
- At the initial stage of infection, inhaled microconidia yeast form within airways and/or alveoli. Then macrophages ingest the yeast. The yeast proliferates within the macrophages. A specific cell-mediated inflammatory response then occurs. A reticulonodular pneumonitis may result.
- If the cell-mediated inflammatory response is successful, the organism is contained within granulomas. Granulomas may heal with irregular, stippled, or laminated calcifications.
- This develops in about 10% of HIV-seronegative patients. The exact incidence in HIV-seropositive patients is not known.
- About 30% of HIV positive patients who develop progressive pulmonary disease have a negative or unimpressive chest X-ray. The Chest X-ray may show hilar and mediastinal adenopathy, and patchy infiltrates. Of those with progressive disease: 33% have no known risk factor, 50% are immunosuppressed, and 17% are over the age of 55 years.
- Symptoms include: Fever, dyspnoea, pleuritic chest pain, anorexia, cough that may be productive and haemoptysis may occur.
- Other manifestations include: Bone marrow invasion, increased LFTs, skin lesions, adrenal involvement, endocarditis
- Reactivation of the disease typically occurs when the CD-4 count drops lower than 200 cell/uL. Only 30% of HIV-positive patients with reactivation disease have fevers. Most have non-specific constitutional symptoms such as weight loss and fatigue. A fibrotic response to the presence of live or dead fungal organisms may occur.
- Diagnosis is by culture of involved tissue(s), serology is positive in 75% of normal hosts. Urine or serum antigen is positive in approximately 90% of normal hosts. Tissue biopsy shows macrophage involvement
- Therapy is in almost cases indicated. Amphotericin: Drug of choice for induction treatment.

- Maintenance therapy: Itraconazole > amphotericin > fluconazole

➢ *Blastomycosis dermatitidis*
- Endemic to areas with warm, moist soils rich in organic material
- The lung is the primary site of infection. Dissemination may involve any organ, but most common are: Lung > Skin > Bone > Gastrointestinal System
- Skin is involved in 40-80% of cases. A characteristic response is pseudo epithelial hyperplasia with micro-abscesses. The organism is found in the periphery of the skin lesions.

➢ *Coccidioides immitis*
- Spherules that reproduce by internal sporulation.
- One of the few invasive fungal infections that can be transmitted by vectors.
- Symptoms: Cough > Fever > Chest pain > headache > dyspnea > rash
- About 1% of normal hosts develop extra-thoracic disease. Higher proportion of immunosuppressed hosts develops this. Sites of extrapulmonary disease include ; Skin (often the face) > Subcutaneous soft tissues >Musculoskeletal (30% of patients) > CNS (10% of patients) (sub acute or chronic meningitis)

➢ *Aspergillus* **spp**
- Typically occur with advanced AIDS associated with other risk factors such as neutropenia.
- Usually pulmonary infections that cavitate.
- Often associated with hemoptysis.
- Other common sites of infection: Brain and Para nasal sinuses.
- Causes tissue infarction due to the propensity to invade blood vessels

➢ Dermatophyte infections

➢ *Candidiasis*
- Candidiasis is a disease condition that is caused by infection with some species of Candida.
- Although there are many species of Candida, only a few are important pathogens in humans.
- Pathogenic species include *C. albicans*, *C. tropicalis*, *C.parapsilosis* with a few other less common isolates.
- Candida Species are the most frequent fungal pathogens in HIV-infected patients.
- The frequent occurrence of mucous membrane candidiasis in HIV-infected patients underscores the importance of T-cell mediated immunity in protection against superficial Candidal infections.
- Thus immunosuppression, rather than a novel or hyper virulent strain of Candida causes the high frequency of candidal infections in HIV-infected patients.
- Candida infections can be divided into these two broad groups:
- Mucocutaneous; often the common form of infection.
- Systemic; a rare form of the infection.

- Chronic mucocutaneous candidiasis is a syndrome characterized by T-cell dysfunction and persistent recurrent candidal infection of the skin, nails and mucocutaneous membranes.
- The major sites of infection are the oral cavity, the gastrointestinal tract (GI) and the vagina.
- Oral candidiasis (thrush) is the most common infection of the oral cavity. They appear as cordlike patches on the tongue and buccal mucosa. Although relatively common in normal, non-HIV-infected newborns (approximately 5%), oral thrush in adults usually involves some predisposing risk factor, such as steroid use, chronic illness (e.g. diabetes) immunodeficiency and antibiotic use.
- Oral Candidias is the most common fungal infection in patients with HIV/AIDS and is independently predictive of progression to AIDS. The likelihood of thrush, which generally develops in patients with CD4 counts less than 500 cells/mm^3 and increases as the CD4 counts decline.
- Candidiasis of the GI frequently involves the oesophagus.
- Most cases of candidal oesophagitis occur in patients with obvious risk factors for fungal infection.
- About 50% of non HIV-infected patients with oesophagitis present with oral thrush. Thus the absence of thrush does not rule out the diagnosis of candidal oesophagitis.
- In patients with advanced HIV disease with oesophageal candidiasis, oral thrush is almost always manifested.
- The most common symptoms include painful swallowing (odynophagia), dysphagia, retrosternal pain and nausea.
- Candida infection of the stomach and of the small and large intestines in less frequent than oesophageal candidiasis in both HIV and non-HIV-infected subjects.
- Most cases occur in non HIV infected patients with haematological malignancies treated with cytotoxic agents or corticosteroids.
- Candida vaginitis is a common infection in women that is characterised by a thick vaginal discharge pruritus and erythematous swelling of vaginal membranes and labial region.
- Women infected with HIV have more frequent episodes of candidal vaginitis The duration of their episodes is considered prolonged in any patient with unexplained thrush.
- Thrush can be easily diagnosed clinically as they present as creamy plaques that can be partially scrapped off the mucosal surface with tongue blade or spatula.
- Identifying the yeast and pseudohyphae in the oral scrapings treated with 10% KOH (potassium hydroxide) should be used for clinical diagnosis and confirmation of oral candidiasis.
- Culture of swabs of oral lesions is not useful as Candida exists in the mouth of persons without Candidiasis.
- Observation and biopsy during oesophagoscopy lead to the definitive diagnosis of candidal esophagitis.
- Characteristic endoscopic findings include patchy white plaques overlying a friable mucosa.
- Vaginal candidiasis should be suspected in a woman with known HIV infection or appropriate risk factors, who complains of increased vaginal discharge, or vaginal and vulvae pruritus.

- Vaginal examination usually shows a thick discharge from an erythematous membrane.
- KOH preparations of the discharge allow identification of hyphae and pseudohyphae indicative of candidal infection.
- Cultures of vaginal discharge should not be performed since they often indicate the presence of candida in women who have no evidence of vaginitis.

Management

- The standard treatment for thrush is clotrimazole troche (10mg) allowed dissolving slowly in the mouth 3 to 5 times a day for 7 to 14 days. Nystatin is also available though a less effective anticandidal agent. It available as pessaries, vaginal tablets or suspension (containing 100,000 to 1,500,000 units) and can be used as mouth wash every 4 to 6 hours. A short course of systemic antifungal therapy often leads to rapid clearance of infection and may be cost-effective in comparison to daily topical agents.
- Systemic therapy with Ketoconazole (200-400mg) given daily for 7-14 days is usually effective.
- In patients who do not tolerate Ketoconazole due to toxicity, fluconazole is an effective and well tolerated (but more costly) alternative.
- Oral antifungal therapy is the preferred mode for candidal oesophagitis.
- Treatment with Ketoconazole or fluconazole should continue for at least 2 weeks, or for at least 1 week after symptoms have resolved. Some data indicated that fluconazole was more effective than ketoconazole in patients with advanced HIV disease with oesophagitis.
- Tropical preparations of antifungal agents such as Nystatin and Clotrimazole, should be the initial therapy for Candida Vaginitis. Oral antifungal therapy is indicated if tropical therapy fails or vaginitis recurs readily after therapy. Ketoconazole (400mg per day orally for 14 days) is frequently effective. In women who are unable to tolerate ketoconazole or in whom ketoconazole has failed, fluconazole (200mg per day orally) is an effective alternative. Ketoconazole is embryo toxic and is contraindicated in pregnancy.
- Disseminated candidiasis is treated with standard doses of intravenous amphotericin B (0.6 – 0.8mg/kg/day) for 6 to 8 weeks.

Activity 6: Common Protozoal/Parasitic Infections associated with HIV/AIDS

- For parasites and HIV co-infection, there are a few opportunistic parasites and others which could be classified as weakly or not opportunistic.
- To date, the major parasitic infections of humans, (malaria and helminths), have not been strongly associated with exacerbation of disease.
- The opportunistic organisms are associated with diarrhoea (microsporidia, cryptosporidia, cyclosporidia, etc.) and pneumonia (pneumocystis).
- In addition to these opportunistic infections, patients in western countries may also have re-activation disease, such as toxoplasmosis and leishmaniasis
- Opportunistic protozoan causes diarrhoea and weight loss in AIDS

- Small bowel-biopsies of AIDS patients with chronic unexplained diarrhoea have shown intracellular microsporidia in up to 20-30% of cases.
- *Entamoeba histolytica*

- *Gardia lamblia*
  - Clinical symptoms may evolve and present as enteritis, watery diarrhoea ± malabsorption, bloating and flatulence
  - It is a common cause of diarrhoea in general population, but may be recurrent or more severe in HIV patients
  - Most cases are readily treated with sulfamethoxazole/ trimethoprim (960 mg qid for 10 days) followed by 1 double strength tablet (960 mg bid for 3 weeks), then chronic suppression with sulfamethoxazole/ trimethoprim (960mg daily)
  - High dose of pyrimethamine with calcium folinate is needed to prevent myelosuppression
  - Long-term maintenance therapy may be required to prevent relapse

- **The Helminths**
  - Helminth infections tend to bias the immune response towards Th2-type. This has been considered to be deleterious to HIV co-infected patients immune system.
  - Several studies have suggested that helminth and HIV co-infected patients have higher viral loads than do non-helminth infected cohorts.
  - Filariasis increases susceptibility to HIV infection in peripheral mononuclear cells in vitro
  - Schistosomes are potent Th2 drivers and inducers of IL-10.
  - There are suggestions that helminth co-infection subjects have higher viral loads than do non-helminth infected individuals. The data to support this is poor.
  - Viral load is shown to actually increases when schist some infected patients are treated.
  - Does HIV/AIDS increase the pathology of schistosomiasis? Increase pathology is caused by the host immune response to parasite eggs trapped in the liver, lungs or the bladder.
  - Egg granuloma formation protects against hepatotoxic antigens and is CD4+ mediated.
  - Also, individuals with low CD4+ T cell counts pass fewer eggs than individuals with normal CD4+ T cell counts with the same worm burdens.
  - These patients also have high liver enzyme levels, suggesting progressive liver damage.
  - Good news is that praziquantel treatment is still effective in patients with AIDS.

- *Toxoplasma gondii*
  - Toxoplasma gondii is an ubiquitous protozoan parasite of birds and mammals and an obligate intracellular parasite. Human infection is common, but in general poses a risk only to the immunodeficient patient and the infant in utero.
  - Infection occurs by ingestion of tissue cysts in poorly cooked meat or oocysts shed in faeces of cats. Infection of intestinal epithelial cells is followed by dissemination throughout the body; tachyzoites invade cells, replicate and destroy cells. As host

develops immunity, parasites become dormant within tissue cysts, generally remain dormant unless immunosuppression occurs.
- Transmission also transplacental, via organ donation or blood transfusion.
- Reactivation occurs in 30-45% of seropositive AIDS patients, usually when CD4 count is < 100/mm3. A minority of cases of active toxoplasmosis among AIDS patients due to acute acquired infection. Rates of active disease decreased among persons taking HAART.
- Congenital toxoplasmosis (usually with HIV co-infection) is seen in infants of HIV-infected mothers, even if infection with toxoplasmosis occurred years before conception.

➢ *Trypanosoma cruzi*
- Trypanosoma cruzi infects approximately 20 million persons in Latin America, and over 300,000 Latin American immigrants living in the United States.
- Most reported cases of co-infection with HIV and *T. cruzi* were the result of reactivation of chronic trypanosomiasis in persons with low CD4 counts.
- Treatment with use of Nifurtimox (no longer manufactured, only available from CDC, Atlanta)
- Benznidazole (Rochagan), which is available in Latin and South America, reduces parasitemia but does not usually eliminate parasite.

➢ *Sarcoptes scabiei*
➢ *Cryptosporidium spp, isosporiasis, and cyclosporiasis*
- All three cause a self-limited diarrhoeal illness with flu like symptoms in healthy persons and persistent diarrhoea with potentially massive fluid loss and malnutrition in persons with AIDS.
- Transmission by ingestion of contaminated food and water; cryptosporidia is also transmitted directly from person to person (especially in day care centres) and from animals (especially livestock) to persons.
- *Cryptosporidium* has caused city-wide waterborne outbreaks, such as that which affected thousands of persons in Milwaukee in April, 1993. Recent outbreaks of cyclosporiasis in various US cities attributed to ingestion of poorly washed imported fruits.
- Isosporiasis and cyclosporiasis are found in developing countries, cryptosporidiosis common in temperate and tropical areas.
- Isopodan and cyclospora respond to trimethoprim and sulfomethoxazole or pyrimethamine and sulphonamide.
- No consistently effective treatment for cryptosporidia.
- As with microsporidia, HAART may be the best therapy if immune re-constitution is observed.

Activity 7: Malaria and HIV Infection

- Current understanding of the human immune response to malaria and HIV leads us to expect that either infection might influence the clinical course of the other.
- Many other types of infections are associated with at least a transient increase in HIV viral load. Hence, it is logical to expect malaria to do the same and potentially to accelerate HIV disease progression.
- On the other hand, the control of malaria parasitaemia is immune mediated, and this prevents most malarial infections from becoming clinically apparent in semi-immune adults in endemic areas. The immune deficiency caused by HIV infection should, in theory, reduce the immune response to malaria parasitaemia and, therefore, lead to an increased frequency of clinical attacks of malaria. Surprisingly, evidence of the association between HIV and malaria is scanty, and it is only in the past 10 years that a clearer picture of this association has begun to emerge.

The Association Between HIV and Malaria

- Clinical studies show an increased rate of placental malaria in HIV-infected pregnant women.
- Infection with HIV-1 causes progressive cellular immunosuppression, and any resulting impairment in immune response to malaria might be associated with failure to prevent infection or to suppress parasitaemia and clinical disease. However, laboratory-based studies have found that some components of the human immune response to Plasmodium falciparum are modified by HIV-1, but that others are unaffected. On the other hand, P falciparum has been shown to stimulate HIV-1 replication through the production of cytokines (IL-6 and TNF-alpha) by activated lymphocytes. It has also been shown to increase the potential reservoir for HIV in the placenta by increasing the number of CCR5+ macrophages.
- In pregnancy, there is more peripheral and placental parasitaemia, higher parasite densities, more clinical malaria, more anaemia, and increased risks of adverse birth outcomes.
- HIV-infected women remain susceptible to the effects of malaria whether or not they are pregnant.
- Placental HIV-1 viral load is increased in women with placental malaria especially those with high parasite densities.
- However the effect of malaria on mother-to-child transmission of HIV is unclear, with the results of published studies to date giving conflicting findings.
- Recent studies in non pregnant adults show that the underlying epidemiology and intensity of malaria transmission seem to be critical for determining the consequences of co-infection. In areas of stable malaria, transmission is intense and continuous, although seasonal variations may occur. Immunity develops early in life, and young children and pregnant women are at greatest risk of malaria mortality and morbidity. In these areas, HIV-related immunosuppression may increase rates of malarial infection and clinical malaria disease, however there is no clear evidence of an increase in rates of severe or complicated malaria.
- The odds of parasitaemia and risk of malarial fever increase with decreasing CD4 cell count and increasing viral load. These findings suggest there may not only be interference with parasite control, but also, perhaps more importantly, loss of antitoxic immunity, which protects persons with parasitaemia from clinical disease.

- In regions of unstable malaria, transmission is intermittent, less predictable, and epidemics may occur.
- The disease burden is similar in all age groups, because pre-existing anti-malarial immunity is limited. As a result, malarial fever rates are a direct function of parasite transmission rates. Thus the impact of HIV co-infection is on disease presentation, with an increased risk of complicated and severe malaria and death.
- Studies of malaria and HIV interactions in children living in areas of stable malaria epidemiology have been inconclusive.

Response to Treatment and Drug Interactions

- Antimalarial therapy is most effective in individuals who have acquired some immunity to malaria.
- It would be predicted that response to therapy will be decreased in immunosuppressed HIV-infected individuals living in regions of stable transmission.
- More recent studies suggest treatment with artemisinin, sulfadoxine-pyrimethamine (SP), and artemether-lumefantrine is less effective in HIV-infected non-pregnant adults.
- No information is available on the most effective antimalarial therapy for non-immune HIV-infected individuals, although case reports of travellers suggest chemoprophylaxis may be less effective.
- Interactions between anti-malarial drugs and antiretroviral drugs (ARVs) mostly involve protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).
- The anti-malarial drugs halofantrine, artemether, and/or lumefantrine should not be given to patients receiving PIs (or the NNRTI delavirdine) because of excessive risk of toxicity.
- For patients receiving other NNRTIs (nevirapine or efavirenz) lower concentrations of lumefantrine and artemether may lead to increased risk of treatment failure.
- There is also potential for an interaction between quinine and NNRTI or PI drugs. However, the magnitude and clinical significance of these potential interactions need further research.

Public Health Implications of Co-infection

- The association between the 2 infections has important implications. Malaria and HIV-1 are 2 of the most common infections in sub-Saharan Africa and to a lesser extent, in other developing countries. It is estimated that 25.4 million Africans are infected with HIV, whereas 300 million to 500 million suffer from malaria each year. Therefore, any interaction between these 2 infections will be of public health significance, even if the statistical effect is modest.
- On a population basis, an increased prevalence of malaria and increased parasite density in HIV-infected individuals could lead to increased malaria transmission affecting both HIV-positive and -negative individuals. (This assumes that the frequency, duration, and density of gametocytemia rise in parallel with asexual parasitaemia, which is currently unproven.)
- The increased risk of clinical malaria in HIV-positive subjects could increase the burden on clinical services in areas where HIV-1 is prevalent. The population-attributable fraction of adult malaria due to HIV-1 would be expected to rise in parallel with HIV-1 prevalence.
- In a region with an HIV-1 prevalence of 30%, such as parts of southern Africa, the population-attributable fraction could reach 20% for parasitaemia and 35% for clinical malaria.
-

Implications for Clinical and Public Health Management

- In endemic areas, the most relevant immediate action would be to encourage HIV-infected patients to avoid malaria infections, because it appears that these patients are at increased risk of infection and clinical disease. Clinicians should advise their HIV-infected patients to avoid mosquito bites, perhaps most effectively by sleeping under an insecticide-impregnated bed net.
- Alternatives include using mosquito repellents on skin or clothing or sleeping in a room with burning mosquito-repellent coils or tablets. These alternatives are likely to be too expensive for regular use by people living in endemic areas, but may be considered by visiting travellers. Visitors to malaria endemic zones should take prophylaxis, whether HIV-infected or not.
- The use of anti-malarial chemoprophylaxis should be stressed in endemic areas. People living with HIV in these areas may be understandably reluctant to take regular preventive medications, but at-risk groups such as pregnant women and their foetuses are particularly likely to benefit. Intermittent presumptive treatment with at least 3 doses of SP given monthly at routine prenatal clinic visits during the second and third trimesters of pregnancy is probably the most practical public health approach to prevention of malaria-related maternal anaemia, low birth weight, and the subsequent higher risk of infant mortality.
- Clinicians need to be aware that HIV infection reduces the effectiveness of anti-malarial treatment. Pharmacovigilance and additional evidence on the efficacy of anti-malarial drugs in HIV infection are urgently needed.
- As a result of studies of cotrimoxazole (trimethoprim-sulfamethoxazole) prophylaxis showing significant reductions in morbidity and mortality in HIV-infected adults, daily cotrimoxazole prophylaxis is recommended for all symptomatic adults and children living with HIV in Africa. The antifolate drug combination cotrimoxazole is quite similar to SP and has a similar effect on malaria parasites.
- There is a risk that widespread use of cotrimoxazole will hasten the development of resistance in malaria parasites to SP, as there is some evidence of P falciparum cross-resistance between trimethoprim and pyrimethamine at the molecular level.
- The WHO recommends that pregnant HIV-infected women should not receive intermittent presumptive treatment with SP if they are already receiving cotrimoxazole prophylaxis. It also follows that HIV-infected individuals receiving cotrimoxazole prophylaxis should be treated with antimalarial drugs other than SP.

Activity 8: Malignancies in HIV infection

Kaposi's Sarcoma

- The prevalence of Kaposi sarcoma is 20,000 fold higher in HIV-1 infected patients as compared with general population.
- The lower the CD4 cell count the higher is the risk for Kaposi's sarcoma
- Prevalence in Nigeria is not known
- It often presents as brown black macular patches, nodules and papules on the limbs, face, oral cavity and the genitals
- Diagnosis is based on the histology of the lesion.
- Basic fibroblast growth factor concentration in the plasma may be micro active.
- Serological testing show rise in antibody to human herpes virus type

Lymphomas

- Non Hodgkin's lymphoma has been reported at increased prevalence in HIV infection.
- Common reported subtypes are
  - small non-cleaved B-cells (Burkett's type) 40%
  - large cell lymphoma 30%
  - immunoblastic plasmacytoid lymphomas 30%.
- Diagnosis is predominantly by histological examination of biopsy tissue.
- Fine needle aspiration of fluid from the cavity of lymphoma may help with the making of a diagnosis
- Effusion can be tapped and subjected to cytological examination.

Carcinoma of the Cervix

- Invasive carcinoma of the cervix has become an AIDS defining illness
- Squamous intraepithelial lesion, a forerunner of carcinoma of the cervix, occur in 33 to 40% of HIV-infected patients as compared with 7 to 14% of HIV-negative persons
- Screening for squamous intraepithelial lesion is by PAP smear
- PAP smear is recommended as a baseline investigation and to be repeated at 6 months and thereafter once a year.
- Diagnosis of cervical cancer requires one biopsy for histological study.

Activity 9: Specimen Handling

- Proper specimen collection is pivotal for the provision of meaningful clinical laboratory information
- Though rigorous laboratory quality assurance procedures are required to assure technically accurate results, such techniques can not safeguard against incorrectly labelled tubes or improperly drawn specimens.
- If the specimen is not correctly labelled or has been compromised by improper collection or handling, results may be misleading or dangerous.
- Blood and other body fluids from people are to be treated as if known to be infectious for HIV, HBV, and other blood borne pathogens.
- All specimens should be put in a well constructed container with a secure lid to prevent leaking during transport.
- All persons collecting and processing specimens should wear gloves. Gloves should be changed and hands washed after completion of specimen collection.
- All blood specimens received by the laboratory must have a permanently attached label with the appropriate information written in black indelible ink, including the patient's ID number and the date of collection. Additional information may be required by individual labs.
- Confidentiality should be maintained at all times.
- It is important to be certain that a tube is filled with the prescribed minimum volume in order to avoid spurious results due to an inappropriate anticoagulant to specimen ratio.

Summary

- Major opportunistic infections remain Protozoan infection remains the major OI leading to diarrhoea. This is responsive to HAART.
- Re-activation is still major problem leading to TE and disseminated leishmaniasis.
- HAART does not interfere with anti-malarials.
- Little conclusive data that malaria or helminth infections exacerbate HIV.
- In contrast, HIV may exacerbate helminth infections.

Activity 10: Group Activities/Discussions

Participants would discuss case reports of OIs in AIDS. The objectives of this discussion are to highlight the need for care/vigilance in drug combinations (dangerous interactions), good nutrition to boost immune system and specific attributes of some drugs used in OI.

Module 6
Pharmaceutical Care in HIV/AIDS

Objectives
1. Participants are expected to acquire the necessary knowledge and skill for the provision of pharmaceutical care in the prevention and management of HIV/AIDS
2. Be able to provide pharmaceutical care in their respective pharmacy settings

Content
- Definition of Pharmaceutical Care
- Scope and Concept of Pharmaceutical Care
- Goals of Pharmaceutical Care
- Patient data collection
- Patient data evaluation

Materials required
- Overhead projector
- Data/Multimedia projector
- Transparencies
- Flipcharts and flipchart stand
- Markers
- Masking tape
- Laptop
- Diskettes/Other media storage devices

Time: 200 minutes

Activity 1: Role of communication in patient care

The session would discuss how to ensure effective communication which is vital for effective functioning within a multidisciplinary team

Time: 20 minutes

Activity 2: Pharmacist's Role in the multidisciplinary care of PLWHA

The pharmacists have identified roles to play in the care of PLWHA. This session highlight these roles as well as define the practising scope within a multidisciplinary team. It discusses how to ensure the information on clients are kept confidential, as well as the role of pharmacists in accessing ARVs and care in a resource-limited setting

Time: 30 minutes

Activity 3: Monitoring and evaluation(M&E)

The session would focus on the how and why of monitoring and evaluating the various programmes. It would also discuss the various tools for monitoring and evaluation.

Time: 20 minutes

Activity 4: Ethical and legal Issues

The lecturer would be discussing on issues related to patient rights, pharmacist's right, informed consent, and litigations. Participants would learn about patients and service providers rights and how to address abuse.

Time: 30 minutes

Activity 5: Group Activities/Discussion:

Draw up a Pharmaceutical Care Plan and describe how to execute it. Practical experience to a recognized centre for Pharmaceutical Care practice would be organised and facilitated.

Time: 60 minutes

Lecture/Facilitator's notes

Introduction

The facilitator would introduce the objectives of the module. At the end of the module, the pharmacists should be able to identify his/her role in the management of PLWHA, understand also his/her limitations and learn to link up with appropriate institutions for effective care even when functioning as a community pharmacist

Time: 5 minutes

Activity 1: Role of communication in patient care

Goals of communication

- To give information and achieve understanding
- Persuade/convince the patient to adhere to the regimen prescribed so as to attain compliance

How to communicate

- Verbally
- Speaking and writing
- Non verbally e.g. Eye contact, facial expressions
- Use of gestures
- Body movement e.g. nodding, pointing
- Use of space
- Both verbal and non verbal are usually used. Congruency between the two is necessary

Verbal communication- listening

- When we speak one must listen
- When we write one must read
- Listening is very important in communication.
- Both the pharmacist and the patient must be good listeners

Non Verbal Type of Communication

- Check /observe /watch for non verbal actions/responses from patients e.g. You start talking to the patient the patient bursts out crying. Do not continue talking she/ he may not listen. Or patient stares at you: You need to be sure whether the patient is listening to you or not.
- Facial expression- Is the person angry? (blame, care taker)
- But also be careful with your own actions e.g. do not show that you are avoiding the patient who is coughing (TB) or has a rash e.g. By keeping a distance (use of space). Patient can easily detect this action and this may lead to break down in communication.

Probing

- When communicating with the patient you will need to ask questions in order to get certain information
- Phrasing of the question is important
- Why type of questions should be avoided as they make the patient feel he/she has to justify his/her actions.
- Close ended type of questions should also be avoided. The answer to these is in most cases is a YES or NO
- Leading type of questions should also be avoided. Since the patient judges what you want to hear and answers accordingly, e.g. "You do not forget to take your medicine do you?"

- Open ended questions are preferred. This allows the patient to express himself/herself
- Timing of the question is also important
- Do not ask too many questions at a go before getting the answer for the first one, the patient may feel he/she is being interrogated.
- Use of silence; there are times when you and the patient will stop talking. A moment of silence will pass. Treat these as normal. This gives time to the patient to think over what he has been asked or told
- Too much silence however may mean either the patient did not understand or he/she understood everything.
- May require that the question/information be repeated

Meaning and communication

- Your understanding/meaning of certain words/phrases may not be the same as that of the patient
- Look for feed back to make sure your intended meaning has been understood by the patient. For example, telling the patient to take the medicine with food. To the patient, food may mean lunch but breakfast is not food

Barriers in communication

- Environmental barriers
- Physical barriers e.g. set up of the pharmacy (privacy)
- People
- Noise
- Patient barriers
- Relates to patient perception
- The way they perceive the pharmacist
- Some patient feel that since the doctor has written the prescription to cover their situation they need to know nothing more than what is written on the prescription label

Patient barriers

- Perception of the medical condition
- The patient may be upset about the condition and does not want to talk about it, e.g. patient not willing to reveal his HIV status (patient pretending to be another person)
- need to use your probing skills to be able to get information
- Time barriers
- Choose the appropriate time to talk
- Some patient think their time is too valuable to waste listening to the pharmacist who provide them with information perceived to be unimportant.
- The challenge to the pharmacist is to change this perception

Pharmacist barriers

Non verbal actions of avoiding the patient or ignoring his/her questions may stop the patient from talking

- Lack of confidence
- Lack of sufficient knowledge on ARVs and HIV/AIDS in general

Activity 2: Pharmacist's Role in the Multidisciplinary Care of PLWHA

- Several years have seen the approval of two or three new antiretrovirals. With these rapidly changing and complex therapeutic options, it is a challenge for many primary care providers to keep abreast of state-of-the-art strategies for managing HIV infection and provide comprehensive treatment.
- The advent of effective antiretroviral therapies has increased the need for clinicians with a broad knowledge of and experience in managing HIV infection's concomitant diseases. In addition, important drug-drug interactions exist between antiretroviral agents and drugs used to treat opportunistic infections, between antiretroviral agents and drugs used to treat non-HIV-related co-morbidities, and among the antiretroviral agents themselves.
- Failure to recognize these drug-drug interactions may result in additional or exacerbated adverse effects, non-adherence, therapeutic failure, or irreversible drug resistance.
- HIV-infected patients require extraordinary counselling and education regarding their treatment, from the importance of adherence to ways to recognize and cope with long-term consequences of therapy.
- The complexity of pharmacotherapy for patients with HIV infection presents special challenges and opportunities for pharmacists interested in developing a specialized knowledge base about HIV treatment.
- Pharmacists are frequently at the frontline in helping HIV-infected patients deal with barriers to medication access, managing adverse effects and drug interactions, and adhering to medication regimens.

Responsibilities

- Pharmacists involved in the care of HIV-infected patients participate with other members of the health care team (e.g., physicians, nurses, dieticians, social workers, case managers, and pastoral care providers) in the management of patients for whom medications are a focus of therapy.
- The pharmacist's responsibility is to optimize the patient's medication therapy. Because of the rapid changes in HIV treatment, pharmacists involved in the care of HIV-infected patients should commit themselves to weekly if not daily education from journals or other sources.
- Pharmacy services should be designed to support the various components of the medication-use process (ordering, dispensing, administering, monitoring, and educating) as individual steps or as they relate to one another in the continuum of care.
- Pharmacists should evaluate all components of the medication-use process to optimize the potential for positive patient outcomes. Particular care is needed in the prescribing and dispensing phases because the names of many antiretroviral agents sound and look similar, especially when they are handwritten, and some physicians continue to refer to antiretroviral agents by their chemical or investigational names.
- Verification of the appropriateness of the antiretroviral cocktail and its dosages are important because dosing recommendations change frequently as more become known about individual drug pharmacokinetics and because drug-drug interactions may be used clinically to simplify or increase the efficacy of drug regimens.
- Pharmacists should screen the medication profile for potential drug-drug and drug-food interactions. A number of antiretroviral drugs cannot be taken with certain foods, and it is the responsibility of the pharmacist to ensure that the patient and caregivers (dieticians, nurses, family members, and friends) are aware of these dietary restrictions.

- Pharmacists are responsible for assessing patients' readiness to adhere to drug therapy, assisting in the design of therapeutic plans to increase the likelihood of adherence, assisting the patient in successful implementation of drug therapy, intervening when the patient states or intimates that he or she cannot or will not adhere to treatment and providing ongoing monitoring of adherence.
- The pharmacist can promote patient adherence by considering the patient's history of adverse effects when recommending a regimen; helping to develop a daily medication administration schedule that accommodates the patient's sleep, work, and meal schedules; providing memory aids for medication taking; recruiting an adherence coach; and educating and motivating patients and caregivers.
- To ensure a consistent supply of antiretroviral medications, patients need to be counselled to plan for medication refills so they are never without these medications. Pharmacists, along with other health care professionals, are responsible for post marketing surveillance of adverse drug events.
- Suspected adverse drug events should be reported to the patient's primary care provider and to NAFDAC pharmacovigilance programme. Many antiretroviral medications are marketed with scanty data about their long-term effects because FDA's accelerated drug approval process allows certain drugs to be approved with only six months of clinical (Phase III) data. Pharmacists should also be aware of the potential for adverse events or drug interactions caused by dietary supplements and should report those as well.
- In addition, pharmacists have an obligation and an opportunity to educate members of the community about prevention of HIV infection and may be in a position to recognize persons undertaking high-risk behaviours. The pharmacist should recommend testing of persons at high risk for HIV infection and help educate patients infected with HIV about how to modify their behaviour to prevent disease transmission.
- Pharmacists need to be prepared to recognize, prevent, and treat the acute opportunistic infections associated with advanced AIDS. The extended survival of those undergoing antiretroviral therapies introduces new co-morbidities, such as diseases of the liver, malignancies, hyperlipidemia, and diabetes mellitus, which pharmacists must take into account as they provide pharmaceutical care.
- Care for dying patients is also part of the continuum of pharmaceutical care that pharmacists should provide to patients.
- Pharmacists have a professional obligation to work in a collaborative and compassionate manner with patients, family members, care-givers, and other health care professionals to help fulfil the pharmaceutical care needs – especially nutrition support; the management of diarrhoea, electrolyte imbalances, pain and depression; and other quality-of-life needs – of dying patients.
- When more than one pharmacist is involved in delivering care, practice standards for the group should be adopted and should serve as a guide for all.
- Pharmacists should also establish methods of communication among themselves in order to provide and ensure continuity of pharmaceutical care on behalf of the patients served.
- Methods for referral to other health care providers should also be defined.

Functions

- In general, pharmacists perform the following functions in collaboration with physicians and other members of the health care team
    - Perform patient assessment for medication-related factors.
    - Provide drug information to physicians and other members of the health care team.

- Identify potential and actual drug-drug interactions and make recommendations for dosage modification or alternative therapies, if appropriate.
- Interpret data related to medication safety and effectiveness.
- Initiate or modify medication therapy or patient care plans on the basis of patient responses.
- Provide information, education, and counselling to patients about medication-related care.
- Document the care provided in patients' records.
- Identify any barriers to patient adherence to medication regimens.
- Communicate with prescribers about known instances of non-adherence to medication therapy and propose strategies to the prescriber and patient to improve the likelihood of success of subsequent regimens.
- Communicate relevant issues to physicians and other members of the health care team.
- Participate in multidisciplinary reviews of patients' progress. Hospice caregivers and volunteer community service organizations should be included in this review as appropriate.
- Communicate with payers to resolve issues that may impede access to medication therapies.

- The pharmacist may have a range of practice privileges that vary in its extent of authority and responsibility. Pharmacists who participate in the collaborative care of patients with HIV should meet the health care organisation's competency requirements to ensure that they provide appropriate quality and continuity of patient care.
- They should demonstrate required knowledge and skills that may be obtained through practice-intensive continuing education, pharmacy practice, and specialty residencies.
- The specific practice of pharmacists who participate in collaborative practice should be defined within a scope-of-practice document or similar tool or protocol developed by the health care organization. The scope-of-practice document should define activities that pharmacists would provide within the context of collaborative practice, as well as limitations when appropriate.
- The document should indicate referral and communication guidelines, including the documentation of patient encounters and methods for sharing patient information with collaborating medical providers.
- Pharmacists participating in collaborative practice should remember that, although diagnosing is not within the pharmacist's scope of practice, the pharmacist must be able to recognize the manifestations of opportunistic infections and complications of HIV infection and treatment in order to know when to refer a patient to the appropriate practitioner.
- Also included in the scope-of-practice document should be references to activities that will review the quality of care provided and the methods by which the pharmacist will maintain continuing professional competency for functions encompassed by the scope-of-practice document.
- A process should be in place, and responsible parties identified, to review and update the scope-of-practice document as appropriate.

Documentation of Pharmacists' Care

- The professional actions of pharmacists that are intended to ensure safe and effective use of drugs and that may affect patient outcomes, should be documented in the patients' medical records.

- Pharmacists in every practice setting should routinely document the quantity and quality of services provided and the estimated effect on patient outcomes.
- Confidentiality of medical data is protected by common law and by constitutional rights to privacy. Confidentiality for the HIV-infected person is a critical issue because of the stigma that is sometimes still associated with the illness.
- Pharmacists should always take extreme care in discussing drug therapy to ensure that confidential medical information is not overheard by other individuals. Information about medications should be disclosed only to appropriate individuals and only with authorized consent from the patient.
- Before counselling anyone other then the patient about medications, the pharmacist needs to ascertain that the person with whom he or she is speaking has been authorized by the patient. Pharmacists are urged to explore their local and state laws that may apply to the confidentiality of medical records.

Confidentiality of Patient Health Care Information

- All medical information is sensitive and should be given the utmost protection. Pharmacists can have access to patient health records in order to provide quality care and ensure the safe use of medications. With access to the patient's health record comes the pharmacist's professional responsibility to safeguard the patient's rights to privacy and confidentiality.
- Within health systems, all authorized practitioners should be encouraged to communicate freely with each other but to maintain patient confidentiality and privacy. Uniquely identifiable patient information should not be exchanged without the patient's authorization for any reason not directly related to the provision of health care services.
- There is no potential for a breach of patient confidentiality when patient information is aggregated for use in legitimate research and statistical measurement and is not uniquely identifiable. Therefore, specific authorisation by individual patients for access to this information is not needed.
- Pharmacists participate extensively in clinical trials of drugs. All clinical trial data must be recorded and stored in such a way that the subjects' rights of privacy and confidentiality are protected.
- The current process for storage and retrieval of clinical trial data contains adequate safeguards to protect patient information. As part of the established procedure for obtaining informed consent, patients receive a statement describing the parties that will have access to patient-identifiable information. These parties include institutional personnel who audit the information for quality, financial integrity and personnel from the study sponsor and or NAFDAC who monitor compliance with regulations.
- Pharmacy training programmes must implement policies and procedures to ensure the confidentiality of patient medical records while allowing pharmacy students and trainees access to these records in the course of their training.
- There should be strict governmental protections, with appropriate penalties for violations, in place to preclude dissemination of patient-identifiable information outside the health system (i.e., to an unauthorised third party) for any purposes that do not involve the direct provision of patient care or administration of health benefits.
- Health systems must have written policies and procedures in place to guard against the unauthorised collection, use, or disclosure of protected health information. Strict governmental penalties, including criminal sanctions for egregious violations, should be considered. However, inadvertent infractions with no intent to harm should be subject to the health care organisation's disciplinary process or civil penalties.

Activity 3: Monitoring and Evaluation (M & E)

Monitoring

- Monitoring is an important management tool. It involves, amongst other things:
  - Keeping records of what we are doing
  - Analysing the quality of what we are doing
  - Analysing the impact of what we are doing
- The purposes of monitoring are:
  - To check on progress and challenges
  - To make sure we are doing what we are doing well
  - To help in day-to-day case management - keep on-going record of client's progress
  - To learn more about ongoing needs of client(s) – respond better to people in need of care and support including their families
  - To report on progress and challenges to supporters and donors
  - To share experiences and lessons learned with others – including those providing us with training and technical support, so that they can better respond to needs
  - To avoid duplication of work which others are doing
  - To change what is not working
  - To feed into evaluation processes
  - To plan for the future e.g. how to increase the scale and scope of our work for example
  - Information from the field about what work can inform stakeholders/partners to better channel their support
- It is important to monitor the quality and quantity of work as it progresses. This means gathering accurate and up-to-date information that can tell some useful stories about what we are doing and what is happening.
- Methods of monitoring include:
  - Quantitative methods which are used to collect data that can be measured in numbers. They answer the questions such as: who? What? When? How much? How many? How often? For example, numbers of patients visited, number of visits to each patient drugs dispensed, community health education and awareness talks given.
  - Quantitative methods will generally tell how much work is keeping appropriate records but they do not provide much information about the quality of what is being done. For instance if someone is visiting a lot of clients, you can record how many clients received visits, however it does not tell us how well the carer counsel the client, help the client and their family, or responded to different support needs?
  - It also does not tell how well the carer explained to the client and their families the different ways of looking after they nor whether the clients understand and remember what they have been told?
  - Also, quantitative data does not necessarily tell us about the impact and stress of the work on the carer.

How to achieve quantitative monitoring

- Careful record keeping is essential to allow monitoring of quantity by providing accurate numbers that can be analysed to produce statistical information about the work.
- Records such as the following can be useful when monitoring care and support work:

- the different types of problems brought by patients
- the different types of care or treatments given.
- the number of follow-up appointments made and kept

- This type of information is also essential for making sure the person receiving support is followed up properly - it is a tool for the support work rather than just a tool for monitoring in its own right.
- The aim of record keeping is to maintain records that are actually relevant to the goal and objectives of the work. Programme implementers should understand why the records are important. This will help to ensure that they are accurately kept.

Qualitative methods

- Quality is less easy to identify than quantity but it is possible to find this out it through the use various skills.
- In order to get an honest appraisal of how good or bad some aspect of support activities might be, it is necessary to find methods that will tell the story about people's behaviour, abilities, attitudes, values and motivation in carrying out their activities. These factors strongly influence the strengths and weaknesses of a programme and help in understanding how and why particular decisions and activities came into being.
- An example: In a busy health centre prescriptions were being dispensed at a rate of less than one minute per patient. Quantitatively, things were going well - the queues were short, dispensing was quite accurate and the patients moved on quickly. Qualitatively, things were not going well at all. Patients did not remember being told anything about how to take their drugs and the dispensers said they felt under pressure to keep the queues short - they worried that their supervisor always criticized them if a long queue formed. Understanding the whole story helped the manager to work with the dispensers and their supervisor to find new ways of managing queues and to allow a little more time to check that patients understood their medication.
- Exchanging anecdotes and problems with other carers – in a confidential way – can often help programme implementers in monitoring their own work and in seeing what they can do or how they can respond differently to issues they face.

What do we monitor?

- It enables programme implementers to assess the impact of their own work. The monitoring process helps in many other ways to ongoing development of care, treatment and support projects.
- Can be used in programme evaluation.
- Can help to identify new and changing needs in the community thereby, identifying what resources are needed and what linkages can be made with other groups – bearing in mind that no group can expect to respond to every need.
- Changes are an important factor in the HIV/AIDS epidemic in addition to responding to changes in the world around you, it will be important to assess from time to time if change is necessary within an organisation, its projects and its objectives. Key questions to ask in a changing situation:
  - Does the work still need doing?
  - Should something different be done?
  - Should someone else be doing it?
  - What will happen to our group if we take on extra work?
  - What will happen to our group if we reduce or limit our work?

Evaluation

- Evaluation can be defined as judging the value of effectiveness of your programme. This is usually done periodically or at the end of a particular process (of every activity) or programme
- It is a way of assessing whether the activities have achieved their objectives and this will determine whether the objectives have achieved the aim. If the programme is successful you will find it easier to do more. If it is less successful you will need to make changes and measure whether new activities are achieving your aim.
- Methods used in evaluation include:
  - **Designing a questionnaire:**
    - The questionnaire needs to be structured in a way to measure the impact of the programme and addressing key issues in the project
    - Decide what you want to find out, who will collect the information, from whom and how many people.
    - When you need to collect the information, how the information will be collected (personal interviews or written questionnaires), how the information will be analyzed and what will be done with the information you have collected.
    - Then, think carefully about what information is needed. The information should relate to programme goal and objectives
    - Keep questions brief and use simple language.
    - A question is easiest to understand when it addresses one idea at a time.
    - Use exact words, which cannot be misunderstood. To obtain precise answers. and accurate information, ask "how many times have you had diarrhoea in the last week? Rather than "How many times recently?"
    - Most importantly, keep the questionnaire short by avoiding unnecessary questions.
  - **Focus group discussion:**
    - The use of focus group discussions in assessing the impact of project activities has been widely accepted.
    - However there is need to develop a few question for the discussion. The question should be designed to cover the main areas of the project, the impact, what should have been done better and recommendation.

Activity 4: Ethical and Legal Issues

- The primary mode by which HIV is acquired is via mother-to-child transmission for children and sex for adults
- Acquisition through blood transfusion, intravenous drug usage, rape, or human bites are possible and account for a number of cases
- Thus, people mainly acquire HIV in a manner that relates to the survival of families and communities
- In the attempt to control the HIV epidemic, governments, health and other workers risk:
  - Being intrusive into personal privacy and families
  - Being on collision course with communities' survival needs
  - Antagonising traditional and religious beliefs
  - Being overbearing or authoritarian
  - In the end, losing the trust and confidence of patients their families

- In Nigeria, there is no public legislation dealing specifically with HIV/AIDS
- The existing Public Health Act focuses on infectious diseases, but may be inadequate for HIV/AIDS
  - It is not clear whether HIV is notifiable or not
  - Yet, coded test reporting is frequently done
  - It should authorize but not require that healthcare professionals DECIDE, whether to inform their patients' sexual partners of the HIV Status of their patients
  - Such a decision to inform should only be made in accordance with the following criteria that - The PLWHA in question has been thoroughly counselled; Counselling of the HIV-positive person has failed to achieve appropriate behavioural changes; The PLWHA has refused to notify, or consent to the notification of his/her partner(s); A real risk of HIV transmission to the partner(s) exists; The PLWHA is given reasonable advance notice; and that follow-up is provided to ensure support to those involved

  Whether testing infringes on fundamental human rights is interpretive and remains a legal minefield

  It depends on the circumstances of each case and the interpretation of the laws in question

  Human rights are guaranteed in the Constitution of Nigeria to all persons, regardless of race, place of origin, colour, creed or political opinion

  These rights are subject only to respect of freedoms of others and public interest

  The right to life includes the right to live in dignity and safety; subjecting anyone to inhuman treatment is prohibited by the Constitution

  The right to privacy is meant to protect the dignity of persons, including their honour and reputation. Confidential information relating to HIV/AIDS falls under this right

  Any violation of the right to privacy must be justifiable. However, although the foregoing rights are guaranteed, the rights of other persons exposed to the possibility of infection are not sacrificed in the process of trying to protect the rights of those that are infected

  Detailed guidelines regarding testing are contained in the Ministry of Health Policy on HIV/AIDS

  The following principles should be observed:
  - Testing should not be done without the knowledge of the subject except when screening of blood, in patients presenting with HIV suggestive symptoms and during anonymous surveillance
  - All testing should be voluntary and pre- and post-test counselling should be done in all cases
- The following principles should be observed:
  - Consent for testing must be given by persons with the capacity to understand after adequate information has been provided
  - Persons with HIV/AIDS should be made aware of their responsibility to prevent onward transmission to others
  - The responsibility of PLWHA to their sexual partners is paramount; penalties are prescribed for deliberate spread
- Generally, information regarding HIV status should be treated confidentially and should not be divulged to others without the consent of the person concerned
- There is no obligation for the employee to inform the employer, however, where an employee feels that sharing the information with an employer or supervisor is helpful, they should be assisted to do so

- The principle of "shared confidentiality" applies to those (usually family) who need to know in order that proper care may be provided. This requires:
  Timely involvement of family members
  Making efforts to involve family members during pre-test phase

Confidentiality

- Like all other patients, PLWHA have the right to the greatest possible confidentiality with regard to their illness and test results. PLWHA has the right to expect that information shared with the doctor and other members of the team will remain confidential both while alive or following his or her death.
- However, strict or absolute confidentiality is not regarded as being either necessary or desirable, e.g. need to inform the spouse or members of the family
- There are general obligation to maintain confidentiality therefore rests on good reason
- There is need to balance the rights of those in a spousal relationship or those involved in the care of the PLWHA with the threat of discrimination against the PLWHA

Human rights and social justice

- HIV infection has the greatest impact on marginalised populations and groups such as women, sex workers and drug addicts. This aspect of an individual's life must be taken into consideration when providing nursing interventions.
- It is however important for the individual doctor to examine and be clear about one's own beliefs, prejudicial attitudes and limitations
- The clinician then has the responsibility to fight against sexist, racial or cultural prejudices that fuel stigma and discriminatory actions
- It is equally important for the clinician to help ensure that PLWHA have access to care, treatment and support regardless of gender, race, sexual orientation, lifestyle, economic status or place of residence

Children and the Laws of Nigeria

- The UN Convention on the Rights of the Child enjoins all nations to take necessary measures to protect children for all forms of physical and mental violence, abuse or negligent treatment
- Although this right is not specifically mentioned in Nigeria's Constitution, the essence is expressed in the Children's Act
- The UN Convention grants the right to access to health care and requires state parties to ensure such access
- The Constitution of Nigeria does not guarantee the right to health or other socio-economic rights (the right to work and to education)
- Socioeconomic rights are considered difficult to enforce as their enforceability depends on the country's financial capacity
- In conclusion, like adults, children have a right to confidentiality and to be consulted according to their maturity and capacity to understand the issues that pertain to their health

Disclosure of HIV Status to Children

- A nagging and difficult issue is when and how to disclose the illness to the child and who should do the disclosing
- Generally, the parents alone or parents together with the health care provider are the key participants
- Nonetheless, the physician cannot escape the responsibility in working with parents and other professionals to ensure disclosure is done appropriately
- Disclosure can be effected at any age depending on the child's capacity to understand. What is important is the language and detail of content
- "Chronic illness needing regular medication, regular laboratory sampling and regular visits to the doctor" to "...you have HIV acquired this way..."
- Help sensitize the child against who needs to know

Activity 5: Group Activities/Discussion

Divide participants into homogeneous groups. Each group should draw a pharmaceutical care plan and discuss how to execute it. Site visits would be organised to a recognized centre where pharmaceutical care is practiced

Module 7
Adherence to Antiretroviral Therapy

Objectives
1. Have a good understanding of adherence and its importance in ARV therapy
2. Acquired the necessary knowledge and skill to ensure adherence to ARV therapy

Content
- Goals of adherence
- Factors influencing adherence
- Strategies to enhance adherence
- Adherence counselling
- Support for adherence

Materials required
- Overhead projector
- Data/Multimedia projector
- Transparencies
- Flipcharts and flipchart stand
- Markers
- Masking tape
- Laptop
- Diskettes/Other media storage devices

Time: 200 minutes

Activity 1: Overview of adherence

Participants would understand what adherence means and the difference between adherence and compliance. .

Time: 10 minutes

Activity 2: Goals of adherence

The lecturer would define the goals of ARV drug adherence for HIV management and the need for strong adherence to drug therapy

Time: 20 minutes

Activity 3: Factors influencing adherence

The various factors influencing the possible success of clients adhering to drug regimen would be discussed

Time: 20 minutes

Activity 4: Strategies to enhance adherence.

The session would focus on how the ARV management team can enhance client's ability to adhere to drug regimen. The lecturer would discuss the factors that can enhance adherence. Issues to discuss during client's education would also be discussed

Time: 30 minutes

Activity 5: Adherence counselling

Counselling has a role to play in ensuring client's successfully adhere to their drug regimen. The session would focus on how to counsel client's on drug use and possible ways to help ensure drug adherence and compliance with regimen

Time: 20 minutes

Activity 6: Support for adherence

This session would discuss how to provide possible support for client to help ensure drug adherence. This session would highlight the role of the family and the community in ensuring drug adherence

Time: 10 minutes

Activity 7: Group Activities/Discussions

Cases studies to facilitate the understanding and identifying of adherence problems would be undertaken. Activities to illustrate various adherence intervention models and practical demonstrations on adherence counselling would be done.

Time: 40 minutes

Lecturer/Facilitator's notes

Introduction

The facilitator would introduce participants to the objectives of the module. S(He) would also highlight the importance of the session. The two main thrust of ARV drug administration is for the health management team to understand the principles of drug administration and for clients to comply wit drug regimen. This session would help pharmacists have an overview of the importance of ARV drug adherence as well as identify their roles in ensuring clients' compliance and adherence with drug regimen. The lecture would then be introduced

Time: 5 minutes

Activity 1: Overview of adherence

- Adherence can be defined as the extent to which a client's behaviour coincides with the prescribed health care regimen as agreed upon through a shared decision making process between the client and the health care provider.
- The term "compliance" is defined as acting in accordance to a command. In healthcare it is often perceived as obeying providers instructions while adherence is perceived as a patient agreeing to make behaviour changes that improves his or her health.
- General observations about adherence have been acquired from studies in the disease areas of diabetes, coronary heart disease, TB and in the geriatric population
- Adherence to drug regimes is poor across all populations and diseases
- The proportion of patients who fail to self-administer medication as prescribed can range from 20% to 100%. The average is 50%.
- Clinicians consistently overestimate the percentage of patients who will adhere and generally are unable to predict who will adhere or not adhere to recommended drug regimen.
- Everyone has trouble taking medication in every disease.
- Non-adherence accounts for a significant % of admissions in pts being treated for heart disease.
- Directly observed therapy (DOT) has been used in other diseases (TB) to improve adherence.
- More frequent dosing lower adherence. Increased number of pills may have same effect.
- Adherence is difficult over the short and long term

Activity 2: Goals of adherence

- The accepted definition of successful adherence for most other chronic diseases is >80% of pills taken. This standard does not apply to HIV disease and antiretroviral therapy. With HIV therapy, greater than 95% is the goal
- Less than excellent adherence may result in virus breakthrough and emergence of drug resistant strain of HIV. Even short-term non-adherence to an aggressive therapy may result in rapid virus re-population in lymph nodes.
- Taking less than between 60 and 90% is associated with development of resistance i.e., taking some medication is worse than taking none in the long run
- Reasons for missing doses change over time (initiation period versus maintenance)
- Adherence in most patients will decrease over time as new problems and side effects arise and pill fatigue sets in

- High levels of adherence are critical to prevent resistance and improve health
- Adherence is hard to predict
- Factors that impact adherence must be identified and addressed
- Certain factors are likely to be universal (dosing frequency, knowledge, side effects) while others will be specific to the population or individual

Activity 3: Factors influencing adherence

Factors related to the drug regimen:

- Cost of the regimen
- Complexity of the regimen
- Storage of drugs, e.g. refrigeration
- Duration of the therapy
- Extent to which the regimen interferes with the patient's daily life
- Model of regimen delivery
- Side effects associated with the regimen

Factors related to the patient and/or the provider:

- Provider not familiar with antiretroviral therapy, side effects, drug-drug interactions, etc.
- Lack of understanding on part of patient/provider of relationship between adherence and resistance
- Poor communication between provider and patient
- Lack of trust between patient and provider/health care system
- Lack of self-efficacy (belief in self and therapy)

Psycho-social issues:

- Depression or stress related to living with HIV (stigma or discrimination)
- Fear of disclosure
- Active alcohol or drug use
- Lack of support from family, friends, community
- Unstable living environment, lack of food or shelter, other basic needs
- Cultural beliefs and practices regarding disease and treatment

Reasons for missed doses

- 36% do not understand their regimen (women with children were less likely to understand)
- 43% forgets
- 36% slept through dose
- 32% travel
- 27% change daily routine
- 11% felt sick
- 9% depression

Activity 4: Strategies to enhance adherence

Reasons for poor adherence to drug therapy

- Multiple drugs to be administered
- Pill burden may be high
- Frequent dosing
- The regimen may be complicated

- Toxicities are common
- Drug interactions may occur
- There are often food restrictions
- Medications are expensive
- There is an enormous social and psychological burden for many patients
- Therapy is life-long.

Need to improve adherence

- Reason
    - Less than 95% adherence to a regimen can lead to viral resistance and ultimately treatment failure.
    - For every 10% decrease in adherence, there is a corresponding 16% increase in mortality.

Factors that make adherence successful

- To succeed, a patient must have access to, take and tolerate ARV therapy
- To prepare for ARV Therapy and adherence, all potential barriers should be identified and begun to be addressed
- Reassessment for new barriers should occur at every visit. Many of these barriers will impact adherence and could ultimately result in therapy failure
- For patients who need therapy and are able to access the medications, the question is not whether to start therapy, but when and how to start therapy. This must be a mutual decision

Strategies to improve adherence

- Reasons for poor adherence are multifaceted; therefore, a combination of interventions must be considered
- Strategies that enhance adherence must be tailored to individualized needs
- Regimen Related strategies
    - Cost of Regimen
    - Prior to initiating ARV therapy, explore with the patient his/her ability to financially secure medication for both the short and long term…develop a plan!
    - Insure medication availability
    - Adherence often decreases over time due to "pill fatigue". Assess adherence at every visit/interaction with the patient in a non-judgmental manner
    - The more complex the regimen, the poorer the adherence. Make every effort to simplify the regimen in terms of number of pills and dosing frequency. If possible, minimize dietary (food and water) requirements and minimize drug - drug interaction
    - Tailor regimen to individual lifestyle. Adherence is enhanced if the regimen fits into a person's daily routine
    - Discuss detailed daily schedule with patient
    - Assist patient to coincide doses with daily routine
    - Assist patient to look for "cues" (daily activities) that fit medication intervals
    - Provide timed reminders (inexpensive beepers, watches, labelled pill boxes)
    - Assist patient to plan ahead for changes in routine (e.g. travel, weekends, holidays)
    - Directly Observed Therapy was pioneered to improve adherence to anti-tuberculosis treatments. Like HIV therapy, TB treatment requires multiple drugs, and non-adherence can lead to resistance development. High rates of non-adherence led to

the development and transmission of MDR-TB. DOT was implemented and found to achieve improved adherence in setting of tuberculosis. Much interest in this model for HAART delivery due to high rates of co-infection and the success of DOT for TB programmes. Unlike TB treatments however, HAART must be given life-long, may have increased and more severe adverse effects and may have a greater degree of stigma attached.

- Side effects
  - Side effects of ARV are a major barrier to adherence. All medications have side effects ranging from minor to life threatening. Side effects are the most common patient reported cause for protease inhibitor discontinuation. Impact of side effects varies from minor but impacting quality of life to life threatening .Over time side effects change (early mostly GI, later metabolic complications including lipodystrophy)
  - Discussion and balancing of risk and benefit is critical to prepare for side effects and toxicities
  - Aggressive education, intervention and support may decrease side effects and increase adherence
  - Use multiple routes to teach (community/clinic educators, support groups, written and oral information)
  - Inform patient, anticipate and treat side effects: prepare patients for side effect and pre-empt problems
  - Educate clinic staff on management and palliation of side effects and recognition and which mandate discontinuation of ARV therapy and which will decrease with treatment (e.g. Nelfinavir and diarrhoea) or decrease with time (e.g.. AZT and nausea)
  - Adherence is a learned skill. Before a patient can comply with their regimen, they must fully understand it. Give information on the basics of HIV Infection, purpose of antiretroviral therapy , all the names of each medication, reasons for dose and administration requirements; connection between adherence and resistance; potential side effects and treatments
  - Provide culturally, linguistically and literacy appropriate materials, both written and pictorial
  - Education must be ongoing, repetitive and revised to address the changing needs of patient
  - Enhance Self-Efficacy. The patient, who understands the therapy regimen, understands the relationship between adherence and resistance, believes in the effectiveness of the medication, believes in his/her ability to take the medications as prescribed, has trust in health care provider and has a better chance of success.

Some critical points for patient education

- Some drug is NOT better than no drug
- Do not share medications
- Continue taking medications even when feeling “well”
- Do not stop medications due to side effects without consulting your provider
- The medications do not cure HIV
- The medications do not keep HIV from spreading through sex and other routes
- Remember to use protective measures all the time

Rewards for successful adherence:

- Positive feedback- decreased viral load, increased CD4 cells
- Verbal support/encouragement from provider
- Use of incentives, e.g. food, transportation vouchers
- Social support - If possible, involve and educate family/friends to provide support for adherence
- Community based support groups
- Peer support!!

Provider related strategies

- Provider education
- Therapeutic relationship
- Tailor strategies to the individual
- Acknowledge successes
- Social support
- Provider should have up to date knowledge of HIV disease and therapy regimens; knowledge regarding the management of potential side effects; understanding the relationship between adherence and viral resistance; understand factors associated with adherence and non-adherence:
- Establishing patient readiness before first prescription
- Skills in patient education
- Therapeutic relationship:
  - Establishment of a trust
  - A strong provider-patient relationship can be a very powerful tool that can greatly affect adherence
  - Reduction of stigma by non-judgmental attitudes
  - Respect client privacy and confidentiality!!
  - Availability for follow-up and support
  - Positive attitude regarding therapy by client and patient
  - Collaborate with client in goal setting and adherence goals
  - Work to develop open and honest communication
  - Encourage involvement of family, friends and peers for support
  - Pro-active management of adverse side effects
- Tailored interventions
  - Each patient will present their own individual issues related to their ability to adhere
  - Listen, recognize and address concerns
  - Consider traditional and cultural beliefs
  - Help patient take medications as prescribed
  - Acknowledge Successes. Positive feedback when achieving clinical/virologic benefit
  - Prepare for failures. Be supportive and understanding. Aggressively work with the patient to make effective adjustments
  - Support
- A multidisciplinary approach to support for patients is essential
  - Use health care team approach
  - Seek support from NGOs
  - Refer to peer support groups
  - The health care provider shares the responsibility for successful adherence
- Psychosocial Issues

- Once in care and eligible for therapy, multiple psychosocial and concrete barriers to adherence may remain
- A holistic and multi-disciplinary approach to address these issues is essential
- Treatment of co-existing behavioural or psycho-social issues is crucial
- Patients who are isolated without the support of family, loved ones, or friends are less likely to be adherent. Explore with the patient if family or friends could provide support.
- Assist in the education of family members or friends regarding HIV and ARV Therapy
- Explore with the patient the option of one to one peer (buddy) support
- Refer to peer support groups where available
- Consider initiating support group
- Before a patient can consistently adhere to ARV therapy, their most pressing basic needs must be addressed. Access to food and stable shelter must be assessed.
- A patients safety must be assessed
- Need for childcare and transportation to seek care
- Refer to NGOs or government programmes
- Nurses and social workers, home-based care volunteers, and other community based counsellors can work together to assure continuity of care and support
- On-going evaluation of needs
- The ethno-cultural beliefs and practices of the patient must be incorporated into the therapy plan.
- Explore the relationship between the patient and the traditional healer.
- Assess cultural beliefs and practices regarding disease and therapy.
- Incongruence should be addressed, e.g. sharing medications
- Efforts should be made to ensure collaboration between traditional healers and modern medical care providers to enhance adherence.
- Mental health counselling should be considered for addressing depression or stress of living with HIV.
- Denial of status will result in non-acceptance of therapy or decreased adherence
- "Readiness" is not only clinical status, but also psychological acceptance of disease and need to take therapy.
- Stigma and fear of discrimination may interfere with patient taking medications as prescribed or seeking care.

Improving adherence

- Do not rush to treat – assess carefully
- Start with twice or once daily regimens
- Lower pill burden
- Pay attention to minor side effects these might be important
- Consider on site dispensing
- Encourage patient diaries
- Intensify counselling and patient education
- Improve patient – care provider interaction
- Consider DOT (?early in therapy, ?selected population)
- Explore possibility of family and community support

Key Points

- Multiple potential barriers even before ARV therapy is started will impact adherence and will need to be addressed
- These challenges include psychosocial (readiness, knowledge, fear), concrete/structural (reliable access to therapy and care, competing social issues), and medication demands (dosing, side effects)
- Education and linkage into resources, combined with support and strong provider-patient relationship, can decrease the impact and improve adherence
- Education plays a critical role for both patients and (all) providers
- Role of multidisciplinary team with linkages to other HIV service and support organizations can decrease the clinic burden and increase resources needed to overcome barriers
- As adherence can decrease over time and new challenges arise, adherence assessment and support must continue at every encounter
- The response and support of all care providers and community is critical for success
- The development of care system which incorporates these interventions is crucial

Activity 5: Adherence counselling

It is important to note the following for successful counselling

- Do not rush to treat…assess "readiness" carefully
- Counsellors must help in ensuring that their patients have the knowledge and skills needed to meet the challenge of adherence to ARV therapy
- Success requires a strong provider-patient relationship based on a mutual respect, trust and openness
- Patient must feel confident that their confidentiality will be respected
- Two-way collaborative relationship, provider as guide, both invested in the outcome
- Provider's belief about the efficacy of ARV Therapy and the importance of adherence significantly impacts a patient's ability to adhere
- The counsellor must understand the pathophysiology of HIV and the basics of ARV therapy, importance of adherence and factors that influence adherence
- Attitudes, feelings, prejudices towards PLWHA should be clarified and addressed (values clarification)
- Broader context of the lives of their patients (poverty, lack of food, shelter) needs to be well understood
- Need for an empathetic, non-judgmental approach in counselling
- The counsellors must understand and continue to understand:
  - There is no such thing as a single session approach…counselling must be on-going
  - Need to be flexible and open to new strategies
  - Cultural beliefs about illness and health impact adherence
- Need for interventions to include cultural values, customs, and traditions.
- Need for their patients to identify their barriers to adherence and be involved in the development of strategies
- A multi-disciplinary team collaboration is needed to meet the needs of the patient
- Integrate clinical care and counselling support
- Research shows that social support and peer support is effective and important
- Explore with patient the possibility of involving family for support
- Be aware of referral sources: NGOs, community based organizations, peer support groups

Activity 6: Support for adherence

- Patients on treatment should receive support to facilitate their adherence to the prescribed treatment. This can be facilitated by:
  - Community based volunteers and family members who are enlisted to assist in patient support.
  - Each patient has a support person assigned.
  - Support persons are trained to assist the patient with his/her drug regimen.
  - Whenever possible, the support person accompanies the patient to the appointment with the care-giver and reports on progress as well as on barriers encountered.
- Patients on treatment could be referred to organizations or individuals who can help address their social needs. Such organizations should:
  - Have a policy to support patients with their social needs.
  - Have a mechanism and operating procedure to assist patients with their social needs.
  - Have an effective referral mechanism to other organizations or individuals in place to support social needs of patients.

Activity 7: Group Activities/Discussions

Participants would undertake some case studies on adherence. The activities would illustrate various adherence intervention models. There would also be practical demonstrations on adherence counselling during visits to ART sites.

Module 8

Managing Procurement and Logistics of HIV/AIDS Drugs and Related Supplies

Objectives

1. To enable participants identify approved antiretrovirals and their sources, methods and means of quantifying, procurement and distribution, storage and inventory control.
2. To enable participants address the issue of quality assurance of ARVs in DSM chain.

Content

- Intellectual property rights
- Pharmaceutical systems
- Selection and quantification
- Quality assurance
- Procurement
- Financing and pricing
- Priority setting and effectiveness

Materials required

- Overhead projector
- Data/Multimedia projector
- Transparencies
- Flipcharts and flipchart stand
- Markers
- Masking tape
- Laptop
- Diskettes/Other media storage devices

Time: 320 minutes

Activity 1: Priority setting and effectiveness

Discussants would learn about the economic and ethical issues surrounding different care interventions, share experience in prioritizing eligible populations for access to ART, understand different policy options for scaling up access to ARV drugs and the constraints to scaling up care and support services.

Time: 30 minutes

Activity 2: Intellectual property rights

Participants would understand how an Intellectual Property Right (IPR) - patent - can impede medical supplies for the treatment of HIV/AIDS. They would also explore avenues by which governments and supply agencies can obtain quality low-priced, safe, and effective HIV/AIDS medicines by *lawfully* surmounting obstacles created by patents.

Time: 40 minutes

Activity 3: Financing and pricing

Participants would understand how the pharmaceutical supply chain works including comprehension of who the components and key players are. They will also understand price discrimination and pricing differences both within and across countries and how international programmes have sought to implement programmes with the goal to allow countries with widespread access to antiretroviral medicines at the lowest possible prices

Time: 30 minutes

Activity 4: Product selection and quantification

After this session, participants will be able to initiate a rational selection of HIV/AIDS care package including Anti Retroviral Treatment Supplies, quantify ARTS and adapt selection and quantification processes to rapidly changing contexts

Time: 30 minutes

Activity 5: Quality Assurance

Upon completion of this activity, participants will be able to Explain the need for a systematic quality assurance process for pharmaceutical products, describe key elements of the quality assurance process for pharmaceuticals, discuss the procedures and standards for prequalification of suppliers of pharmaceuticals and apply quality assurance and supplier selection principles to case discussions

Time: 30 minutes

Activity 6: Procurement planning and management

Upon completion of the activity, participants should be able to identify specific components involved in the procurement of the HIV/AIDS care package and their interrelationship and be able to initiate an evaluation of the implementing capacity of a procurement system. Participants would also be able to identify appropriate procurement strategies and key elements of planning

Time: 30 minutes

Activity 7: Supply chain management

Participants would be able to identify some commonly faced constraints (Storage, LMIS and Inventory Control), and examine some of the interventions that have been developed to face those constraints

Time: 30 minutes

Activity 8: Logistic system for ART

The session would discuss the logistic issues related to managing ARV and other HIV/AIDS supplies.

Time: 30 minutes

Activity 9: Pharmaceutical systems

The lecture would highlight the importance of the pharmaceutical system in the overall health system. Participants would also get to understand and identify the key components of supply chain management, identify the determinants of pharmaceutical system failure and understand and identify the key considerations of ART supply chain management

Time: 30 minutes

Activity 10: National guideline on ART procurement & management

Participants would learn about the national requirements on procurement and management of ARV

Time: 30 minutes

Activity 11: Group Activities/Discussions

The session would discuss life experiences that bring out the importance of a good pharmacy practice environment in ARV therapy and management. Case studies would highlight possible interventions to remedy the situations.

Time: 40 minutes

Lecture/Facilitator's notes

Introduction

Facilitator would introduce the objectives of the module. S(he) would highlight the importance of the session. ARV drug procurement management is of great importance because of the huge funding that goes into its procurement. It therefore becomes very important for the pharmacists to management this procedure and the drug storage with great skill so as to prevent fund wastage and drug expiration. The lectures for the session would then be introduced

Time: 5 minutes

Activity 1: Priority setting and effectiveness

When prioritizing Programmes of Care for People with HIV/AIDS, there are various considerations that need to be made when deciding what kind of treatment to offer. These include issues related to ethics, economic analysis, demand, political pressure, acceptability, biomedical needs and technical challenges

Ethical Principles that are related to priority setting

- **Justice** - Justice is the moral virtue of constant and firm willingness to give to one's neighbour that which his or her due is. Justice promotes fair, equitable, and appropriate treatment in light of what is owed to the individual.
- **Human rights and dignity** - Human dignity is the principle that accepts that humans deserve a certain standard of respect, free from needless degradation.
- **The common good** - The common good demands that actions be taken that benefit the community. Beneficence includes any form of action to benefit another.
- **Fair opportunity** - Fair opportunity is the rule of social distribution that attempts to decrease unjust forms of allocation

Care Options for People with HIV/AIDS in Africa

Ways of improving the quality of life for people with HIV and AIDS in Africa include:

- Palliative care: providing supportive care and pain control
- Prophylactic care against opportunistic infections
- Treatment of opportunistic infections
- Antiretroviral therapy
- Costs of palliative Care, prophylaxis and treatment of OIs and cost effectiveness of HAART for People with HIV/AIDS in Africa are all high. It is therefore pertinent to prioritise population for the distribution of ART.
- Considerations to be made when deciding which populations are offered ART first depends on the following issues:
  - deciding a fair process
  - economic consideration
  - community involvement
  - economic productivity
  - social productivity
  - likelihood of adherence
  - potential for transmission
- Other issues that arise are:

- Deciding on who should be the first recipients of ARVs
- What process must be followed in priority setting for fairness?
- What Criteria? - Policy guidance on populations to be prioritized
- Involving Communities in decision making

The elements of fair process

- Transparency
- Community access for rationale decisions making
- Relevant reasoning is discussed among stakeholders
- Room for revising the criteria
- Accountability for enforcing the criteria are adhered to

Potential Recipients of Scaled up ARV Programmes

- First Come/First Served
- Groups of People Based on Characteristics
  - The economically or socially productive sector
  - The poor
  - Those likely to adhere to therapy
  - Health care workers
- ARV Drugs can be used to Prevent HIV transmission in
  - Exposed health care workers and rape victims
  - HIV infected mothers (PMTCT)
  - Those at risk of transmitting HIV
  - Sex workers/High risk men
- When prioritising the poor to receive ARVs issues to consider include:
  - Identifying the poor
  - Cost of testing for HIV
  - Cost of out-patient visits
  - Illiteracy
  - Poor nutrition
- When prioritising The economically or socially Productive to receive ARVs, issues to consider include:
  - Identifying the economically or socially productive
  - Some may be able to afford the drugs without subsidization (issues of fairness)
  - Likely to be literate and able to support other associated costs of care

Preventing the spread of HIV Using ARVs

- ARVs have demonstrated reductions in transmission when used for occupational post-exposure prophylaxis and the prevention of mother-to-child transmission
- ARVs are likely to reduce HIV transmission by reducing viral load, thereby making HIV less sexually transmissible
- In post-exposure prophylaxis (PEP) for occupational exposure
  - Risk of HIV transmission after a needle stick injury from an HIV infected source is about 1 in 400 (or 0.25%)
  - Zidovudine (AZT) lowers the risk of HIV transmission from a needle stick exposure by 80%
  - PEP may result in cost savings in developing countries
- Post-Exposure Prophylaxis (PEP) for post-rape

  - Estimated risk of HIV infection in unprotected heterosexual sex between HIV discordant couples is about 0.2% (if the male partner is HIV+)
  - Risk of acquiring HIV from unprotected receptive anal sex with an infected partner is estimated to be 0.8 %
- Risk of HIV infection in a rape situation would likely be higher as:
  - There is a greater potential for other sexually transmitted diseases, trauma, and inflammation.
  - The risk is multiplied if more assailants are involved
- Prevention of Mother-to-Child Transmission
  - The infection rates of children born to HIV infected mothers in the absence of any intervention is about 25 - 40%
  - Several studies have demonstrated that short courses of AZT or Nevirapine during pregnancy, reduce transmission by 50%
- Supplying ARVs to those most at risk for spreading HIV can effect population-level prevention. This is because ARV can:
  - reduce the viral load of HIV, a major determinant of HIV transmission
  - potentially be used to prevent the spread of HIV at a population level
- Possible adverse effects exist with the use of ARVs. This include:
  - increases in risky behaviour
  - Resistance
  - side-effects
  - over-reliance on ARVs

Adverse Behavioural Change

- Even with effective viral suppression due to HAART, infection can occur
- 33% of men on ARVs continue to shed virus in their semen
- Transmission benefits gained from a programme covering 50-90% of HIV positive people with effective HAART is reversed with a 10% increase in risky behaviour
- Actual coverage with HAART does not usually exceed 30% of HIV positive people in industrialized countries
- Risky behaviour is on the rise among MSM in North America in the post-HAART era
- For years, North American MSM had declining rates of HIV and STI. Some cities in the late 1990's reported an upturn in both epidemics, especially among young MSM
- In Kenya, on two separate occasions immediately following wide media coverage of "quack cures", 100% condom use among female sex workers decreased and with increased HIV incidence

Mitigating Against Adverse Behaviour Change

- Step up prevention activities that are highly effective
- Healthy media messages
- Positive living, but with scaled up preventive behaviour
- Counselling: encourage safe behaviour and adherence to therapy

Side Effects

- Most HIV-infected people on HAART experience some side effects
- A study from Botswana found that the side effects were so serious that they interfered with adherence to therapy in 9% of people on HAART

- Poor management of side effects may lead to purposeful non-adherence, which in turn could lead to lowered effectiveness of the treatment and resistance

Mitigating Against Side Effects
- Make a number of standard regimens of medications available
- Treat side-effects. Offer good overall care, not just drugs
- Encourage adherence to therapy
- Offer appropriate nutritional support

Resistance to ARVs
- There is a concern that there will be widespread antiretroviral resistance resulting in mass treatment failure
- One of the key accelerators of resistance is lack of adherence
  - A study from Botswana found that only 54% of people on ARVs reported that they had adhered to the therapy regimen
  - A Ugandan study reported that 70% of patients enrolled in their study had virus that was resistant to at least one antiretroviral drug
- Drug resistant HIV strains are transmissible
- "HAART for all" may lead to resistance in drug regimens which are used to prevent mother-to-child transmission
- Nevirapine should be reserved for mother to child treatment

Mitigating Against Drug Resistance
- Use standard regimens with fixed dose therapies
- Monitor drug resistance using simplified diagnostics
- Improve clinical management and build infrastructure
- Work with communities to find strategies that encourage adherence to therapy

Conclusion

Policies written to guide ARV programmes must address the following
- the level of treatment to be offered
- the process to be followed in prioritization
- those who will be prioritised for treatment
- the potential adverse effects
- how those side-effects can be mitigated against

Activity 2: Intellectual Property Rights

IPRs in Medicines Procurement

- Intellectual property rights (IPRs) provide the basis for "market exclusivity" in medicines and related supplies
- The extent of market exclusivity directly affects the price and availability of medicines
- IPRs holders view strong enforcement of market exclusivity as important to profitability, and will act to defend their perceived interests
- It is critical for medicines procurement specialists to understand the key "flexibilities" afforded under international agreements and national law that can be used to reduce the impact of market exclusivity on affordability and access 4

National Law and International Agreements

- Each country or region has its own set of IPRs laws and regulations that govern actions taken within the national or regional territory
- It is the "in-country" legal situation that most directly affects procurement authorities
- On January 1, 1995 the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights ("TRIPS Agreement") entered into force
- The TRIPS Agreement provides the basis for member countries to make claims against each other at the WTO
- TRIPS Agreement rules do not directly apply in most national legal systems, but instead are implemented by legislation

The TRIPS Agreement

- Establishes minimum standards of IPRs protection for all member countries of the World Trade Organization
- Provides various "transitional arrangements" in favour of "developing" and "least developed" members
- Recognizes that IPRs protection must be balanced with public health needs, and it allows Members to take steps to reduce the adverse impact of IPRs on affordability
- Attempts at aggressive and unjustified application of TRIPS rules led developing Members to demand that the WTO affirm the right to use the "flexibilities" built into the Agreement, as well as to negotiate important new flexibilities

The Doha Process

These affirmations and new flexibilities are in:

- .The Doha Declaration on the TRIPS Agreement and Public Health, adopted November 14, 2001
- The Decision on Implementation of Paragraph 6 of the Doha Declaration, adopted on August 30, 2003
- The Doha Declaration acknowledges the right of all countries to protect public health and "to promote access to medicines for all"

The Doha Declaration confirms:

- TRIPS Agreement does not limit grounds on which WTO members may issue compulsory licenses
- Each member to determine if a national emergency or circumstance of extreme urgency exists within its territory, and recognizing that HIV/AIDS (among other situations) may constitute an emergency, providing special flexibility under TRIPS rules
- Members free to permit "parallel importation" of medicines

The Declaration provides

- Maximum flexibility for least developed members to misapply patents and data protection rules at least until January 1, 2016
- For further negotiations to allow members with insufficient or no capacity in the pharmaceutical sector to make effective use of compulsory licensing

Importance of Understanding the Rules

- Because TRIPS Agreement flexibilities reduce the market exclusion power of pharmaceutical patent holders, efforts are made to persuade or prevent governments (including procurement authorities) from taking advantage of them, including by misstating the terms of the TRIPS Agreement
- It especially important that procurement specialists understand what "is" permitted, and/or seek expert guidance from those who are familiar with the rules

Rules at the National or Regional Level

Because procurement activities take place within a national and/or regional legal system, it is important that:

- National and/or regional rules include the flexibilities permitted under the TRIPS Agreement
- Procurement specialists become familiar with the national and/or regional legal IPRs situation
- Procurement authorities may need to act as "advocates" with other parts of the government to explain what steps should be taken

Relevant IPRs

- Patent: a right granted to the inventor of a new product to exclude others from its making, using, selling, offering for sale or importing (importing rights depend on exhaustion rule).
    - Patents also granted for processes, giving right to exclude others from use of process, and from sale or import of products made by process
    - Minimum term of 20 years from date of patent application
    - Patents for pharmaceutical products the subject of special TRIPS "transition" rules in favour of developing and least developed countries
- Trademark: a right granted to exclude others from the use of a sign that creates confusion in distinguishing the goods or services of one enterprise from those of other enterprises (e.g., Coca-Cola)
    - Medicines typically have "brand names" or trademarks used for marketing by specific companies (whether originator or generic), and a "generic" name (usually an International Non-Proprietary Name or INN)
- Copyright: right granted to author of "expressive" work (e.g., book or song) to prevent others from copying and distributing
    - Does not provide protection for technical information or data
    - Medicines producers - sometimes asserted "copyright" in doctor and patient brochures accompanying medicine (such claims appear outside scope of copyright)
- Rights in Data: TRIPS Agreement has rule requiring protection against "unfair commercial use" of data submitted for marketing approval of new chemical entities
- Reliance by developing country regulatory authority in approving treatment for HIV/AIDS does not represent "unfair commercial use", - addresses urgent public health problem

Important Features of the International IPRs System

- Patents are granted on national and/or regional basis
- A medicine may be (and often is) "on-patent" in some countries and "off-patent" (or generic) in others. The patent situation in the importing and exporting country is relevant to the procurement authority

- The patent situation in the exporting country may determine whether "generic" alternatives are available
- The patent situation in the importing country will determine what steps, if any, are needed to authorize importation and distribution
- Trademark, copyright and data protection rules are also granted and enforced on a country-by-country basis.
- Trademark and copyright rules less likely to be an obstacle to procurement of HIV/AIDS medicines and supplies because generic producers can take relatively low-cost steps to avoid conflicts. Nonetheless important to be aware of potential claims. Unless international exhaustion rule is adopted, trademarks and copyrights may be invoked to block parallel imports (if the same mark and/or designs are used)
- Patents do not prevent submission of data for regulatory approval. WTO has already recognized exception to patent right for this purpose (should be implemented in national law)

IPRs in Procurement of Generics

- Procurement policies favours lowest cost lawful purchase of safe and effective medicines. There is no preference for "originator" or "on patent" products. When generic medicines of suitable quality are available, World Bank funds may be used to purchase them
- Whether such purchase is "lawful" will depend on patent situation in exporting and importing country

Exporting Countries

- India does not yet provide pharmaceutical patent protection - essentially all medicines "lawfully produced" there from patent standpoint
- Situation will change, become more complex after January 1, 2005
- Certain lawfully produced generics should remain available, but there are grounds for serious concern
- India may increasingly rely on TRIPS Agreement "flexibilities", e.g., compulsory licensing for domestic and/or export
- Whether generics are lawfully available in other exporting countries will depend on whether patents were obtained and/or are in force on specific medicines
- Because TRIPS Agreement patent rules did not apply before January 1, 1996 in developed countries, and have been phased-in in developing countries, the patent situation varies by country and by medicine
- Least developed countries do not need to enforce patents until at least January 1, 2016, and may increasingly become viable exporters
- August 30, 2003 WTO "medicines deal" opens possibility of compulsory licenses granted for export

Importing Countries

- Situation varies depending on patent status within country and developmental category
- Most countries, including least developed countries, provide for possibility of obtaining pharmaceutical product patents but
    - Many products that are under patent in developed countries are not under patent in developing countries
    - Procurement authority should determine which medicines are under patent in-country

- If medicine is not "on-patent" in importing country, there is no patent-based obstacle to importation

Sources for Patent and Pricing Information

- Pricing: Sources and Prices of Selected Medicines and Diagnostics for People Living with HIV/AIDS from UNICEF, UNAIDS, WHO, MSF – http://www.who.int/medicines (and others)
- Patents: Drug Patents Under the Spotlight – MSF – http://www.accessmed-msf.org
- Pricing: Untangling the Web of Price Reductions – MSF – http://www.accessmed-msf.org

Importing Least Developed Member

- Situation easiest for "least developed" WTO Members which enjoy maximum flexibility
- Pursuant to Paragraph 7 of Doha Declaration and WTO implementing acts may elect not to enforce patents and/or data protection at least until January 1, 2016
- Effectively gives government a "free hand" from standpoint of international obligations
- Government should take appropriate steps within national legal framework to "disapply" patents
- Executive or parliament may, for example, delegate decision to Health Minister or procurement authority
- When patent is not enforced, a patent holder conceivably could assert some claim to compensation under national law. Such claim would be unreasonable. Research is not conduced in least developed countries, and a least developed country cannot afford to support expensive developed country marketing efforts
- In any case, this is a matter for the authorities in the least developed country to decide, and the decision entails no obligation under the TRIPS Agreement
- A patent holder claim for compensation would be manifestly inconsistent with WTO decision to relieve least developed countries of patent burdens and would shock the conscience. Least developed countries have option to use the same more burdensome flexibilities as developing countries (e.g., compulsory licensing), but no reason to do so

Importing Developing Member

- Developing countries remain subject to TRIPS Agreement rules, subject to transition arrangements and to Doha confirmation and addition of flexibilities
- Situation for developing Members more complicated than for least developed.
- If a medicine is not under patent "in-country", there is no patent barrier to producing locally or importing
- If a medicine is under patent "in country", then government may issue a "government use" authorization or "compulsory license", and/or authorize "parallel importation"
- May also seek voluntary license from patent holder (or price break)

Government Use

- WTO TRIPS Agreement permits granting of "compulsory" or "government use" licenses (Article 31)
- National patent law typically provides that the government (and third parties acting on its behalf) may use private patents. A "government use" license may authorize importation or local production without the consent of the patent holder

- The procedural requirements for government use licensing are normally much less burdensome than for compulsory licenses requested by private parties.
- U.S. patent law authorizes the government or its contractors to use any patent without notice to the patent holder and with no possibility to be enjoined. It is automatic
- Prior negotiations with the patent holder are not required when addressing urgent situations such as HIV/AIDS or for public non-commercial use
- Adequate remuneration in the circumstances of the case must be paid to the patent holder, but this may be determined after-the-fact
- The remuneration level may take into account the public health budget and the severity of the problem
- Private enterprises may apply for compulsory licenses, and procurement authorities may purchase from them, but the procurement authority would ordinarily for itself rely on a government use license

WTO "Medicines Deal" of August 2003

- The Decision on Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health was adopted by consensus vote of the members of the WTO at a meeting of the General Council on 30 August 2003. It was accompanied by a Statement of the Chairperson of the General Council setting out certain shared understandings of the members
- The Decision is in the form of a "waiver" applicable to Article 31(f) and (h) of the TRIPS Agreement regarding compulsory licensing. It is without prejudice to other rights, obligations and flexibilities under the TRIPS Agreement. It provides for further negotiations toward the adoption of an amendment to the TRIPS Agreement based, where appropriate, on the Decision
- Technically, Decision applies to WTO Member countries, but provision may be made for non-WTO members Intellectual Property

Genesis of Paragraph 6 Negotiations

- Problem of conjoined expiration of TRIPS Agreement transition period for pharmaceutical patents and Article 31(f) compulsory licensing limitation recognized by developing WTO Members well before Doha Ministerial
- As of January 1, 2005, world supply of off-patent (generic medicines) will substantially contract as mailbox applications processed and new medicines under WTO-wide patent
- For compulsory license issued under Article 31, TRIPS Agreement, "(f) any such use shall be authorized predominantly for the supply of the domestic market of the
- Member authorizing such use;"
- Compulsory licenses serve dual function of (a) permitting production or importation of products under patent (b) providing leverage in price negotiations as "background" possibility, or explicit lever (as in U.S.-Bayer/Canada-Bayer cipro negotiations or Brazil-Roche ARV negotiations)

Paragraph 6 Negotiations Involved Limited Problem Set

- Negotiations NOT about whether WTO members may issue compulsory licenses for production or import of medicines. Article 31, TRIPS Agreement, allows compulsory licensing on any grounds, establishing certain procedural and substantive requirements that vary in context

- Paragraph 6 negotiations ONLY concerned the LIMITED case of members wishing to export predominant part of production under compulsory license (CL), which itself may not be a common phenomenon (because major suppliers, e.g., Brazil, China, Egypt, India, may have substantial local requirements). If a predominant part of CL supply is furnished for domestic supply, the Paragraph 6 solution would NOT APPLY. Article 31, TRIPS Agreement would apply without subparagraph (f) effect 28

Elements of the Solution

- Applies broadly to "pharmaceutical product[s]", meaning "any patented product, or product manufactured through a patented process, of the pharmaceutical sector needed to address the public health problems as recognized in paragraph 1 of the Declaration. It is understood that active ingredients necessary for its manufacture and diagnostic kits needed for its use would be included."
- Establishes procedures for importing and exporting members making use of the "system"

- **Importing Members**
- Least developed WTO members automatically eligible as importing countries. Other Members - one time notification to TRIPS Council of intention to use required (may notify intent to use in whole or limited way). Notification may be modified at any time
- When using system, notify TRIPS Council of names and expected quantities of product(s) needed
- Establish insufficient or no capacity in the pharmaceutical sector for the product(s) in question in one of the ways set out in an Annex
  - Least developed countries automatically included
  - Other countries self-determine that they have "no capacity" or, where some capacity, self-determine that capacity is currently insufficient to meet their needs
- If product under local patent, indicate intention to grant compulsory license (except least developed countries that may rely on right not to enforce pharmaceutical patents at least until 2016). When compulsory license issued, remuneration obligation waived (paid in exporting Member)
- Take reasonable and proportional measures to prevent diversion

Exporting Members

- Issue compulsory license within prescribed conditions
- Production limited to needs of importing member(s) and exported to that member(s)
- Products identified as produced under the system
- Post on website information identifying product(s) and distinguishing features
- Notify TRIPS Council of license and terms
- Provide for remuneration to patent holder "taking into account the economic value to the importing member of the use that has been authorized in the exporting member"
- Additional flexibility for certain regional arrangements
- Otherwise comply with provisions of Article 31 of TRIPS Agreement (not subject to waiver)

Intellectual Property Rights: Registration and Marketing Approval

- Most or all countries require that a pharmaceutical product be "registered" and/or granted "marketing approval" by a national or regional authority before being distributed for use

- Approaches vary widely, from payment of a fee for registration to extensive scientific evaluation of product prior to registration and marketing approval
- Registration and marketing approval raise patent and data protection issues
- In recent years, pharmaceutical producers have increasingly sought to block entry of generic medicines at the registration and marketing approval stage

Registration and Patents

- WTO dispute settlement panel has already determined that members may provide exception to patent law to allow for development and submission of data to medicines regulatory authorities
- The "regulatory review exception" (allowed under Article 30 of the TRIPS Agreement) can be put in national legislation or regulation, but it may also be recognized as "common law" by courts (as it is in a number of countries)
- The regulatory review exception is sometimes referred to as a "Bolar exception" since this is the name that is used for the exception in the United States. "Bolar" has no English-language meaning. It is the name of a pharmaceutical company that was involved in a patent dispute (Roche v. Bolar)
- If not already in place, the procurement authority should advocate for a regulatory review exception to the patent law

Data Protection

- Marketing approval of a new medicine in a developed country typically involves submission of a "dossier" that includes data concerning the results of clinical trials
- For approval of follow-on generics, the dossier is typically more limited, such as to bio-equivalence and bio-availability. Many developing countries do not require the development of a country-specific dossier for marketing approval. Some rely on the fact that a medicine has been approved for marketing by a developed country authority
- Since clinical trials are costly and time-consuming, and since developed country regulatory authorities are generally reliable, the requirement for a new dossier would involve social waste
- Article 39.3 of the TRIPS Agreement provides limited protection to data submitted for regulatory purposes: "Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize *new chemical entities*, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data *against unfair commercial use*."
- The scope of the obligation under Article 39.3 is controversial. However, in no event would Article 39.3 appear to preclude reliance by public health authorities in developing countries on foreign registrations to address HIV/AIDS. The procurement and distribution of medicines under such circumstances would not involve "unfair commercial use" of the data. Where a compulsory license is issued and the patent holder is paid adequate remuneration in the circumstances of the case, such remuneration should address any claim of commercial unfairness
- Developing country reliance on the "prequalification" programme of the WHO Essential Drugs and Medicines Division may provide a useful mechanism for avoiding data protection controversies

Parallel Importation

- Pharmaceutical companies often hold patents on the same medicine in many countries, and these are referred to as "parallel" patents
- A country may decide to follow "international exhaustion" of patent rights. If so, the patent holder cannot block the importation of the medicine after it is lawfully first sold in ANY country
- The procurement authority may look for the lowest price patented medicine on the world market and "parallel import" it
- WTO members confirmed this right in the Doha Declaration on TRIPS and Public Health

Differential Pricing

- A patent-holder company may offer to sell ARVs or other medicines to a developing or least developed country at a discount to its developed country price(s), provided there is a contractual commitment not to re-export the lower-priced medicines. A commitment not to export in these circumstances is reasonable. However, the procurement authority should be careful to put in place adequate control mechanisms to meet its commitments
- Rules permitting parallel imports and rules restricting exports of differentially-priced medicines are not inconsistent. Developed countries may elect to block parallel imports to prevent low-priced medicines from entering their markets. This should not affect imports into developing countries Intellectual Property Rights Training Long Form

Trademark and Copyright

- Originators may assert trademark rights in the colour and/or shape of a medicine. Although colours and shapes may be the subject of trademark protection, trademarks may not protect "function"
- Medicines colours and shapes become known to pharmacists, doctors and patients to identify a treatment and, particularly for elderly or impaired patients, colour and/or shape may be main means of identifying the proper medicine. Trademark law may exempt colours and shapes of medicines from protection on functional grounds, or alternatively may permit third party use under a "fair use" exception to trademark law acknowledged in TRIPS Agreement
- Similar issues arise regarding copyright and informational materials accompanying medicines. Data and information are not prosecutable by copyright, and copyright also allows for "fair use"

Brazil's Patent Legislation relating to Medicines Procurement

- National HIV/AIDS prevention and treatment programme includes universal free access to ARV treatment
- Brazilian Ministry of Health purchases ARVs from originator-patent holders, produces ARVs at its own national pharmaceutical enterprise (Far-Manguinhos) and at five state enterprises, and may under compulsory license import generic versions of medicines on patent in Brazil
- Brazil has effectively used its compulsory licensing/government use legislation
  - As a lever in price negotiations with patent holders
  - Based on a practical threat to reverse engineer and produce
- New legislation adopted in 1996 (Law No. 9,279, of May 14, 1996, effective May 15, 1997) adds coverage of pharmaceutical products and processes

- Allows prior use to continue (art. 45)
- Prohibited pipeline patenting of medicines already introduced on any market by originator (art. 230)

➢ Provides for compulsory licensing (Section III), including government use
- Expedited procedures for grant of license for "public non-commercial use" in cases of emergency or "public interest" (Decree No. 3,201 of October 6, 1999)
- "Public interest" considered in relation to public health
- Determination of public interest made by Minister responsible for subject matter
- In circumstances of extreme urgency, prior determination regarding patent holder capacity to fulfil the situation and terms of license unnecessary
- New Decree permits importation of generics to satisfy license (Decree No. 4,830 of September 4, 2003)

South Africa and Parallel Importation

➢ South Africa has adopted legislation (Section 15C of the Medicines and Related Substances Control Amendment Act, No. 90 of 1997) pursuant to which its Minister of Health (through the Medicines Control Council) has issued regulations that establish the conditions for the parallel importation of medicines into the country. In addition to the regulations, the Council has issued a Guideline for Parallel Importation of Medicines in South Africa

➢ The regulations provide that: "parallel importation" means the importation into the Republic of a medicine protected under patent and/or registered in the Republic that has been put onto the market outside the Republic by or with the consent of such patent holder

➢ The regulations and guideline provide procedures under which a parallel importer must obtain a permit to undertake importation. These procedures are intended to assure that parallel import medicines are duly approved and registered by the Department of Health, and that the parallel importer will comply with requirements ordinarily imposed on vendors of medicine in South Africa, such as using an approved storage facility and having in place a recall procedure. The guideline also establishes that, "The parallel importer may use the proprietary name approved in South Africa as well as any trade marks applicable to the medicine in order to ensure the public health interests."

➢ Example of use of South Africa and Parallel Importation: Assume that the procurement authority in South Africa seeks to purchase an anti-infective medicine used to treat opportunistic infections associated with HIV/AIDS and that medicine is under patent in South Africa and Thailand. The anti-infective is sold by the patent holder's authorized distributor in Thailand to wholesale purchasers at $1.00 per capsule. The same anti-infective is sold by the patent holder's authorized distributor in South Africa to wholesale purchasers at $2.50 per capsule. The procurement authority in South Africa can purchase the anti-infective from a wholesaler in Thailand and import it. The patent holder in South Africa will not be able to block the importation based on its local patent because its patent rights are "exhausted" when the medicine is first sold in Thailand

Country Case Study

➢ Country A is recipient of World Bank Multi-Country Acquisition Programme (MAP) funds.

➢ Procurement authority seeks most cost-effective use of funds and asks Bank whether it may purchase generic ARVs from India

- World Bank policy is that there is no preference for purchasing from originator/patent holder or generic producer, provided that procurement is lawful and that ARVs meet standards of quality, safety and efficacy

Lawful Availability of Generics?

- WTO TRIPS rules do not require pharmaceutical product patent protection until January 1, 2005 for developing countries. India does not yet provide such protection. ARVs are available lawfully from Indian generic producers
- This situation will change in 2005 as new medicines come under patent and some in "mailbox" pipeline also are protected, but a number of important ARVs will not be under patent
- The changed circumstance in 2005 was addressed in the "Paragraph 6" negotiations

Are ARVs Patented in Country A?

- Even though ARVs may be off-patent in India, they may be under patent in Country A. Patents are granted on country-by-country basis
- Country A has a patent law in force that allows for the patenting of pharmaceutical products, including ARVs
- MSF maintains a list of the ARVs under patent in a number of countries, including Country A. Ten ARVs were found to be patented in Country A, several of which are on Country A's standard HIV-AIDS treatment list

Features of Country A's Patent Law

- The law of Country A allows the Minister that administers patents to direct that any patent may be exploited by the government "in the vital public interest", including the "public health" interest, and to fix adequate remuneration for the patent holder
- If Country A were a developing country, the procurement authority could request use of this government authority. However, Country A is a "least developed country", giving the procurement authority greater flexibility

Least Developed Country Option

- Because it is "least developed", Country A can elect not to "enforce" existing patents under paragraph 7 of the Doha Declaration. This is a decision that should be taken by the appropriate governmental authority in Country A
- The World Bank advised the procurement authority that if Country A exercised its discretion not to enforce patents and to import generic ARVs from India this would raise no concerns from the Bank's standpoint

Role of Procurement Authorities

- Procurement authorities should evaluate national IPRs situation and determine whether changes are necessary to take advantage of TRIPS Agreement flexibilities
- Procurement authorities should act as advocates among government agencies, some of which may have different priorities
- Procurement authorities should monitor the patent and registration situation. This situation will directly affect procurement options
- When questions arise, do not hesitate to seek guidance from the Global HIV-AIDS Programme

Activity 3: Financing and pricing

- There is only one price for which planned market demand is equal to planned market supply, which is known as equilibrium price or market clearing price
- Shifts in demand and supply can cause this equilibrium condition or price level to shift

Types of market

- Perfect Competition
  - Multiple small buyers and sellers in the market - no one buyer or seller is large enough
  - Freedom of entry and exit into the market
  - Buyers and sellers have perfect knowledge about market prices and output
  - The price of a good is ascertained through regular interactions between demand and supply
    - Short-run
    - Long-run
- Monopolistic Competition
  - Same conditions hold as for perfect competition except that firms produce differentiated products with close substitutes
  - Firms have a certain degree of market power as they can raise prices without losing all of their customers
- Monopoly
  - There is only one firm in the industry (the monopolist)
  - There are many barriers to entry
  - Monopolist maximizes profits in the short-run

The Pharmaceutical Supply Chain: Key Players

- Manufactures
  - Innovative Pharmaceutical Firms
  - Generic Manufacturers
- Wholesalers/Distributors
- Retailers
- Governmental & Non-Profit Sellers

Innovative Pharmaceutical Firms

- Multinational companies: brand name drugs
  - Conduct their own R&D and own many patent portfolios: however, also typically spend more money on marketing and administration than research and development
  - Bayer, Boehringer Ingleheim, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Pfizer and Schering-Plough

- Generic Manufacturers
- Generic manufacturers that compete in the production of off-patent drugs
- Produce drugs that are marketed under approved non-proprietary and proprietary names
- Major generic producing nations include Brazil, China, India, South Africa and Thailand

Equity Pricing

- An equitable price structure may take the following form:
- 'Market' pricing by manufacturers in different markets, according to the ability to pay

- Voluntary out-licensing and generic competition
- Subsidization of drugs by international programmes or donors
- Compulsory licensing and generic competition

➢ Price Discrimination
- *First degree* – charging whatever the market will bear
- *Second degree* – quantity or versioning
- *Third degree* – separate markets and customer groups

Explanation of Pricing Differences

➢ Explanation of Pricing Differences
➢ There are pricing differences within and across countries this depends on:
- Amount of state intervention - Originator antiretroviral drugs and generic locally manufactured drugs coexisting
- Marketing, sales, and volume - Companies can sell high volume of drugs at discounted prices

➢ Pricing Differences Within Countries
- Once patent expires, generic manufacturers can enter market
- Some companies produce only "Copy" molecules already developed (no R&D costs).
- The prices of these are usually about 35% cheaper

➢ Pricing Differences Across Countries
- Differences in living standards - Clear relationship between Gross National Product and drug prices
- Regulatory systems and tax levels
  - Price differences not uniform due to federal regulation
  - Over the counter price differences due to regulation in pharmacy markets
- Differences in purchasing power - Comparison – Purchasing Power Parity based on Gross Domestic Product and Health Purchasing Power Parity

Description of Current System Design
Additional strategies

➢ International Programmes: Accelerating Access Initiative
  - The Initiative was launched in 1997 between three pharmaceutical companies, the United Nations and health officials in Chile, Cote d'Ivoire, Uganda and Vietnam
  - In each country, clearing house for placing orders and receiving antiretroviral drugs
  - In 2001, Accelerating Access Initiative became responsibility of World Health Organization
  - Despite reductions in drug prices, prices offered by companies participating in the Initiative are still more than double the prices of generic companies
  - As a result few patients are gaining access to antiretroviral therapy – less than 1% of the HIV-positive population is receiving antiretroviral therapy

➢ Legal Remedies
  - Compulsory Licensing
    - Country may request patent holder permission to begin domestic manufacturing

- Local government could ask domestic firm to manufacture generic version of drug in domestic country
- Exporting firm could agree to manufacture drug in domestic country
- Decrease in drug prices case examples are India and Brazil

- Voluntary Licensing - Examples of Voluntary Licensing is that of Boehringer Ingelheim which licensed Aspen Pharmacare to produce nevirapine and GlaxoSmithKline agreed to license three antiretroviral drugs to Aspen Pharmacare

➢ Other Remedies

- Domestic Production of antiretroviral drugs. Examples: Brazil, India, Thailand
- Bulk Purchases
  - Bulk purchasing can lower drug prices
  - Reduction in the risk of capital equipment investment
  - Economies of scale
  - Reduced market and distribution costs
  - Improved production planning from better demand forecasting

Donations

- Two main types of donations - Form of money or drugs
- For example, in 2000, Pfizer announced it would provide Diflucan free of charge to AIDS patients diagnosed with cryptococcal meningitis
- However it is to be noted that there are several problems with drug donation, mainly from restrictions on type of use, and from strict reporting.

Reducing Drug Prices

"*Prices are an important factor, especially in developing countries, since while in developed countries pharmaceuticals are largely publicly funded through reimbursement and insurance schemes, in developing countries, typically 50%-95% of drugs are paid by the patients themselves. Thus in developing countries, prices of medicines have direct implications for access*" (HIV/AIDS Antiretroviral Newsletter, December 2002, Issue No. 8, WHO)

Case study of Brazil: Strategies Used

➢ Brazil is the first developing country to have implemented a large-scale universal antiretroviral therapy distribution programme
➢ The public health system provides free antiretroviral therapy to approximately 125,000 patients
➢ The savings from out-patient and hospital costs outweigh the costs of implementation by more than US $200 million

Factors that Contribute to Brazil's Success

➢ 1971 Law suspending intellectual property rights
➢ Large scale experimentation without legal restrictions
➢ Domestic national laboratories with the capacity to manufacture large quantities of antiretroviral drugs
➢ Negotiation of drug prices with pharmaceutical companies that are exclusive producers - Deals were made with Abbott, Merck and Roche cutting prices of four drugs by more than 50%

Antiretroviral Prices in 2002: The Impact of Increased Competition

Price Per Pill	Accelerated Access Initiative	Brazil	Lowest Generic Price
Zidovudine 100mg	0.26 US$	0.13 US$	0.10 US$
Nevirapine 200mg	0.60 US$	0.34 US$	0.28 US$
Lamivudine 150mg	0.31 US$	0.29 US$	0.17 US$

Factors that Prevent Success

- Most developing countries lack manufacturing capacity building to produce local drugs under compulsory licensing
- Strengthening and capacity building require much funding
- Reduction of customs and tariffs over time – fierce competition
- High prices constitute necessary incentive for efficient R&D
- Still not perfectly universal system

Take-Away Lessons from Brazil

- Gather financial resources
- Confront cultural, religious, and legal barriers
- Compulsory licensing
- Local production by local laboratories
- Increased advantage in negotiating drug prices with patent holder pharmaceutical firms

Conclusions

There are many ways in which drug prices can be reduced

- Stages of production
  - For countries that have the capability of producing their own generic products, it is important to bear in mind the various stages of production
    - Production of raw materials and intermediates
    - Production of active principles
- Negotiations with patent holder firms
- Once countries are able to produce generic drugs, they will have an advantage with regards to negotiations with patent holders

Activity 4: Product selection and quantification

Six Therapeutic Goals in HIV/AIDS Treatment

- Reduction of HIV related morbidity and mortality
- Improved quality of life with effects for the individual, the family and the society
- Restoration and preservation of immunology functions
- Maximal and durable suppression of viral replication
- Reduced need for medical intervention and support
- Prevention/reduction of drug resistant strains of HIV and OI's

Clinical Goals
- Improved overall health status
- Viral load reduced to <20c/ml, CD4 within normal range
- Reduction and control of drug side effects and support for adherence

Pre-Conditions for Treatment
- Adequate social support and patient care taker available
- Adequate food supplies
- Adequate health facilities nearby
- Appropriate education for the patient re: adherence and side effect issues
- Adequate testing and monitoring available

Basic Components of HIV/AIDS Treatment
- Use of Antiretrovirals to prevent replication of the Human Immunodeficiency Virus (HIV) in cells
- Treatment of Opportunistic Infections caused by a weakened immune system
- Monitoring, evaluation and adjustment of treatment to prevent drug resistance; to maximize effects of ART and to minimize consequences of toxicity and side effects.

Treatment of HIV Infections in Various Population Groups
- Adults and adolescents
- Pregnant women or women of child-bearing age
- Children
- People with TB & HIV Co-infection
- Health and emergency workers after occupational exposure
- Victims of sexual assault

Treatment of Adults and Adolescents
- First line combination therapy of three ARV's
- Second line combination therapy
- Customized treatment for patients who cannot tolerate the first and second line regimes

Treatment of Women (pregnant/child-bearing women) aims at:
- reducing viral load and disease progression in the mother
- reducing the risk of toxicity to the foetus
- preventing the transmission of infection to the neonate
- A separate treatment protocol needs to be agreed upon

Prevention of Mother-To-Child Transmission (PMTCT)
- During pregnancy use ARV either as mono-therapy or combination therapy
- Birth - Caesarean section
- Breastfeeding - Avoid breastfeeding if appropriate alternatives are available: in term of HIV transmission, exclusive artificial feeding>exclusive breastfeeding>mix feeding

Treatment of Children and Infants
- Similar regimes as for adults
- Paediatric dosage is problematic

- Monitoring of children under 6 yrs different

Other special Groups of Patients

- People who have been exposed to HIV contaminated materials or fluids due to occupational hazards, i.e., healthcare workers)
- Victims of sexual assault by HIV infected people
- People with TB and HIV co-infection

Basic Elements of the Product Selection Process

- Selection committee should be multi-disciplinary - representatives of AIDS council, national drug formulary committee, HIV specialists (doctors, nurses pharmacists, procurement specialists) and PLWHA
- Drug selection should be based on pre-determined criteria
- Fixed dose combination should be considered to optimize adherence
- Important to use INNs (int'l non-proprietary names instead of brand names)
- Selection of ARV's should be based on National Treatment Protocols
    - First line ARV treatment
    - Second line ARV treatment
    - PMTCT
    - Post Exposure prophylaxis

Considerations that Informed the Choice of First-Line ARV Regimens

- Potency
- Side effect profile
- Maintenance of future options
- Predicted adherence
- Availability of fixed dose combinations of antiretrovirals
- Coexistent medical conditions (TB, and pregnancy or risk thereof)
- Concomitant medications
- Presence of resistant viral strain
- Cost and availability
- Limited infrastructure
- Rural delivery

Problems with second-line ARV regimens

- Multiple resistance mutations
- High pill burden
- Limited experience
- TDF availability
- ABC hypersensitivity
- Cold chain for RTV
- High cost

PEP therapy

- Start PEP as soon as possible after exposure to HIV (within 72 H) for a duration of 28 days (4 weeks).
- Most commonly used for PEP:
    - Bitherapy: AZT + 3 TC (Zidovudine, Lamivudine) (combivir)

- 300mg AZT+150mg 3TC twice per day for 28 days
- Triple combination: AZT + 3 TC + IDV
- Twice per day Combivir and 3 times IDV 800mg per day
- or other PI such as NFV, LPV/r

Non ARV's Essential commodities for care of PLWHA

- Essential HIV and related testing materials and reagents
- Essential medicines for Opportunistic Infections
- Medicines for pain relief, palliative care, and mental health problems
- Condoms
- Medical supplies: gloves, syringes, needles

Some Key Principles of Quantification

- Try to use two quantification methods to validate your estimations
- Do not forget that initially you will have to constitute a security stock as well as to fill the supply pipe line (lead time!)
- Rate of expansion may be bigger than you expect
- Some Key Principles of Quantification (Cont'd)
- Define the units in which quantities are expressed clearly: try to use basic units as tablets, vials or capsules etc
- Calculate/estimate losses/waste
- Use VEN if necessary
- See formula table 4.4 in "Battling HIV/AIDS"
- Drugs to be included need to be defined for each type of health facility whose requirements are being estimated
- Standard treatment protocols need to be there to set the consensus about the appropriate use of these drugs.

Quantification Methods for HIV/AIDS Drugs

- Consumption (Usage) Method
  - Based on past consumption records to estimate future needs, adjusted for stock-outs, expiration of overstocked items and projected changes in utilization.
  - Cannot be used for rapidly changing or new programmes (at this moment ART programmes)

- Adjusted Consumption (Usage) Method
  - Relies on past consumption records from other facilities or even other countries
  - Data is extrapolated and adjusted to local circumstances like population coverage or service level provided
  - Can be very useful in start-up situations
  - Advantages:
    - Less complicated, easy to calculate
      - Can be very accurate when based on accurate statistics and conformity to treatment guidelines
  - Disadvantages:
    - Difficult to adjust for changes in demand and use
    - May perpetuate irrational use of medicines and lab tests

- Patient Morbidity Standard Treatment Method
  - Based on the number of expected patients x the drugs and materials consumed according to the standard treatment protocol
  - In new ART programmes capacity is often the limiting factor
  - Advantages
    - Works well in new programmes
    - Encourages conformity to treatment guidelines
    - Prompts periodic evaluation of needs
  - Disadvantages
    - Time consuming, more complex
    - Requires reliable and up to date morbidity and patient attendance records
    - Requires sound professional judgment on target treatment population

Conclusions

- The selection process of ARV is subject to frequent reviews as a result of fast changing products and treatment guidelines
- The quantification of ARV will likely be more dependent on the capacity of ART programmes and associated funds than on morbidity numbers

Activity 5: Quality Assurance

Quality Assurance

- Is a process, not an end-point
- Must be independent of financial pressures
- Must ensure that quality policies are followed
- Must have final authority in product acceptance, rejection and release to public
- Integral to production, not an add-on
- Responsible for day-to-day operations and for longer term goal settings
- Quantitative discipline with specified parameters

Definitions

- Quality - The totality of features and characteristics of a medicinal product and its ability to satisfy stated and/or implied needs
- Quality Assurance -The sum total of the organized arrangements made with the object of ensuring that medicinal products are of the quality required for their intended use.
- Good Manufacturing Practice (GMP) -That part of QA which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use.
- Quality Control - That part of GMP which is concerned with sampling, specifications and testing.

Factors in Drug Quality Assurance

The following factors affect the drug product quality

- Legislative Framework –Regulations
- Import and Export Control
- Packaging
- Labelling and Product Information

- QC and analysis
- Transport, Distribution, Dispensing and Use
- Storage
- Manufacturing Processes & Procedures
- Raw Materials – Active and Inactive
- Human Resources - Professionals

Quality Assurance

This is achieved through:

- Quality Control - Analytical testing of products
- Active and Non active material control - Sampling, inspecting and testing of incoming raw materials
- Packaging and labelling components - Bottles, caps, foils, labels, measures, cartons
- Physical inspection of product and operations at critical intermediate stages - In-process controls, HHACCP
- Control of product through its distribution - GSP, GDP ETC

Quality Must Be Designed Into A Product

- Quality is not an add-on: it begins with research and development
- Product quality criteria must be established
- Detailed specifications provide quantitative parameters for measurement
- Written procedures document how quality is attained and maintained
- Continuous monitoring (sampling, testing) to confirm quality is being built-into product

Quality Assurance: Essential at All Stages

- Research
- Development
- Prototyping
- Documentation
- Raw Materials
- Facilities
- Equipment
- Personnel and Supervision
- Monitoring, Feedback, Follow-up

Analytical Control Laboratory: Heart of Quality Management in Pharmaceuticals

- Academically trained and certified staff
- Experienced supervision/management
- Capable of performing complex analyses
- Able to report honestly and in a timely manner
- Equipment and instrumentation must be suitable for performing testing
- Access to reliable power, water and other stable infrastructure

Quality Control and Analysis

- Qualification - Design, Installation, Process and Operational
- Calibration - Daily and periodic
- Validation - Equipment, Method and process
- SOPs - Authorized, used and updated

- Documentation - Systematic and well kept
- Quality Manual - Quality manager, staff trained and motivated to comply.
- Safety measures

Quality Assurance throughout the Manufacturing Process

- Monitoring environmental conditions under which products are manufactured/stored
- Monitoring of air and water systems to prevent contamination– Air Handling Units
- Monitoring of humidity
- Monitoring of personnel
- Feedback and follow-up

Manufacturing Process and Procedures

- Dispensing / Weighing
- Mixing / Granulation / Preparation
- Compression / Encapsulation / Filling
- Equipment, Operational & Process Qualification
- Validation and calibration
- Documentation and record keeping
- Yield Reconciliation

A Guiding Philosophy for Quality Assurance in the Pharmaceutical Industry

Poor Quality Medicines:

- Are a health hazard
- Waste money for governments and consumers
- May contain toxic substances that have unpredictable, unintended consequences
- Will not have a desired therapeutic effect
- Does not save anyone any money in the long term
- Hurt everyone – patients, health care workers, policy makers, regulators, manufacturers

Consequences of quality assurance breaches

- Poor Treatment outcomes
- High Health Bills
- Treatment Failures & Deaths
- Loss of Confidence in the Health Services
- Enormous Economic Losses
- National Security Issue

What is GMP? (WHO)

- Comprehensive system for ensuring products are consistently produced and controlled according to quality standards
- Designed to minimize risks involved in any pharmaceutical production that cannot be eliminated through testing of final product alone

Major Risks in Pharmaceutical Production

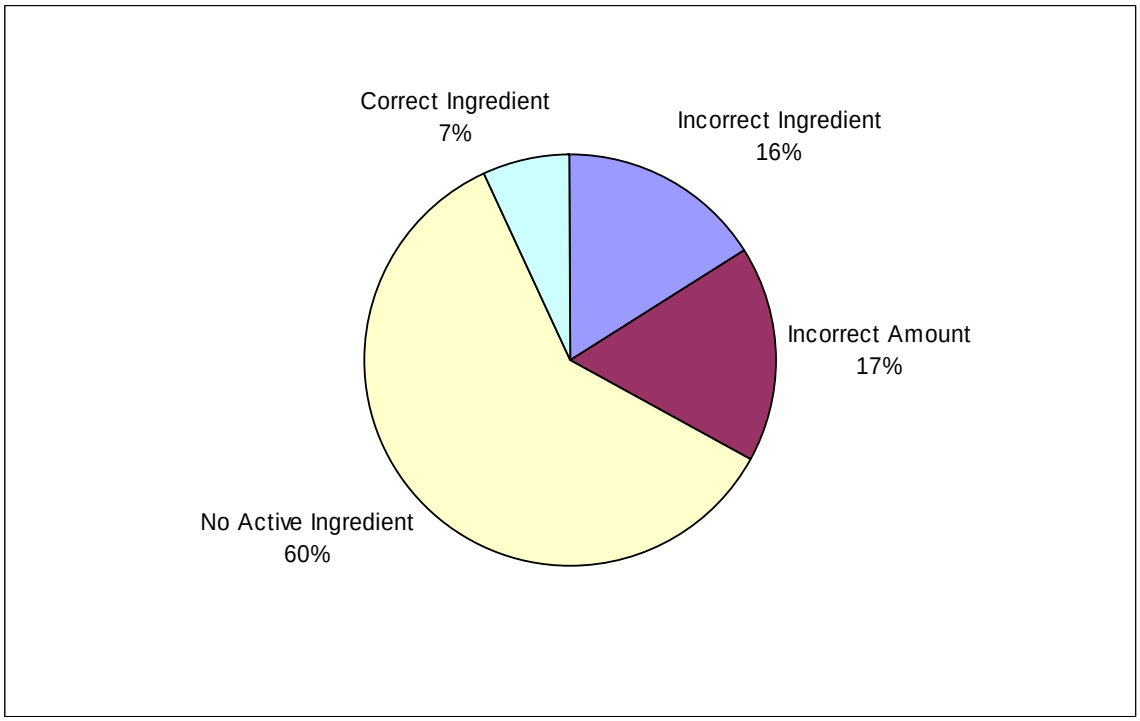
- Contamination of products (microbial, particulate or other)
- Incorrect labels on containers
- Insufficient active ingredient

- Excess active ingredient
- Poor quality raw materials
- Poor formulation practices

The Breadth of GMP

- Covers all aspects of production including
- Raw or starting materials
- Finished products
- Premises and environment
- Equipment
- Personnel
    - Training
    - Hygiene

Analysis of Substandard Medicines



GMP Principles:

- Must be built into manufacturing process
- Prevents errors that cannot be eliminated through quality control of finished product
- Ensures all units of a medicine are of the same (within specified parameters) quality
- Poor medicines leads to loss of credibility for everyone: manufacturers, health care workers and governments

WHO Technical Guide to GMP: General Consideration

"Licensed pharmaceutical products should be manufactured only by licensed manufacturers whose activities are regularly inspected by competent national authorities"

WHO Technical Guide to GMP: Key Concepts

- Validation - Action of proving (in accordance with principles of GMP) that any procedure, process, equipment, material, activity, or system actually leads to expected results
- Qualification - Action of proving that any premises, system, and items of equipment work correctly and actually lead to expected results
- Associated Concepts
  - Good Laboratory Practice (GLP)
  - Good Clinical Practice (GCP)
  - Clear language use
  - Effective record keeping
  - Design, installation, operational and process qualification (DQ, IQ, OQ and PQ)
  - Self-inspection and self-regulation
  - Good Distribution Practice (GDP)
  -

Key elements of GMP

- Sanitation and hygiene
- Qualification and validation
- Complaints
- Product recalls
- Contract Production and Analysis
- Self-Inspection and Quality Audits

Product Selection Issues

- Unique nature of medicines heightens need for effective quality assurance
- All medicines used must be safe, effective, and of consistent quality
- Failure to select proper products will lead to treatment failure, drug resistance, wasted resources and human suffering
- Selection of product and goal of treatment may vary depending upon patient group

Successful treatment for HIV with quality medicines will:

- Improve general health status/well-being
- Reduce viral load to <20 cells/mL
- Maintain CD4 within normal range (550-1400 cells/mL)
- Prevent/reduce drug resistance
- Manage and minimize drug-related side-effects
- Reduce need for medical intervention

Sources of Pharmaceutical Products

- Multi-source - Well-established products, long history of use, no longer subject to patent protection (e.g. Rifampin)
- Single source - Newer products still subject to patent protection in many countries (e.g. Saquinavir)
- Limited source - More than single source/supply possible (e.g. AZT); may be difficult to manufacture (e.g. amphotericin); may be unprofitable drug with limited market potential

Identifying Product Suppliers

- Systematic Approach
  - Pre-qualification of suppliers and products

  - Specifying supplier conditions in contract
  - Monitoring quality of product and processes
  - Continuous evaluation of supplier performance and product performance in clinical practice
- Selecting and Sourcing Multi-Source Products
  - Innovator vs. generic issues
  - Prequalification systems
  - Specific issues related to interchangeability of products - stability, bioavailability, bioequivalence, etc.
- Procedures for Prequalification of Suppliers
  - Rationale - More meaningful, effective, efficient and less expensive to eliminate sub-standard manufacturers and products at the opening of bidding/tendering than during the process
  - Purpose - To ensure that products are manufactured in compliance with GMP and products meet established quality standards
- Procedures for Prequalification of Manufacturers
  - Local Procurement Committee comprising managerial, technical, and professional staff
  - Manufacturers submit dossiers for review; must be reviewed/re-inspected every 3-5 years to ensure adherence to policies
  - Review/re-inspection also performed if product changes occur that may impact on safety, efficacy, quality, manufacturing method, or location of manufacturing
  - Evaluation of Product Dossier
  - Random testing of samples
  - Verification of compliance with GMP
  - Verification of compliance with good distribution practices
  - Role of national drug regulatory organizations (in compliance with WHO standards)

Prequalification: Evaluation of Product Dossier

- Specifications in WHO guidelines
- Must include details regarding:
  - Regulatory status
  - Pharmaceutically active ingredient(s)
  - Manufacturing processes
  - Finished product specifications (stability, bioavailability, interchangeability etc.)
  - Packaging/labelling/storage details
  - Product/patient information

Prequalification: Evaluation of Product Dossier- Multi-source Products

- For products manufactured and registered in countries with a stringent regulatory authority, the product dossier presented may be the same as that presented to the regulatory authority
- Appropriate documentation/certification provided if product differs in any way from product registered in original country (e.g. packaging, formulation, strength, manufacturing site, etc.)

Prequalification: Evaluation of Product Dossier- Single/Limited Source Products

- Include specifications of in-house quality-control and quality management practices in sufficient detail to allow replication by another laboratory
- Validation of in-house methods must be provided by manufacturer
- Quality assessment of products to be undertaken by external laboratory

Prequalification: Random Testing of Samples
- Undertaken to verify compliance with standards and references provided in dossier
- Test samples should be from supplies, not from pre-supply batches
- On-going random sampling and quality control analysis post-supply

Prequalification Verifications
- Compliance with GMP - Inspections and certification of facilities or reliance on national regulatory authorities
- Compliance with good distribution practices - Quality assurance methods for selection of raw material suppliers, storage of products, transportation delivery of final product, etc.

Options for Prequalification
- WHO Prequalification
- Regional Prequalification
- International Low-cost Suppliers
- Development of international consolidated prequalification system

Pharmaceutical Stability - GMP state there must be a written testing programme designed to assess stability characteristics of drugs. Results of stability testing are used to determine appropriate storage conditions and expiration dating

Stability Definitions - Capability of a particular formulation of a pharmaceutical in a specified container/closure system to remain within specified physical, chemical, microbiological, therapeutic and toxicological specifications. The time from the date of manufacture and packaging of the formulation until its chemical or biological activity is not less than a predetermined level (generally, 90%) of labelled potency and its physical characteristics have not changed appreciably

Stability Issues
- Time-related harmful events include
- Deterioration of therapeutic activity below specified threshold
- Potentiation of therapeutic activity above specified threshold
- Appearance of toxic substance forming as a degradation by-product

Factors Affecting Stability of a Pharmaceutical Product
- Stability of active ingredient
- Interaction between active/inactive ingredients
- Manufacturing process
- Dosage formulation
- Container/Liner/Closure System
- Environment during storage, handling
- Length of time between manufacturing and usage

Evaluation of Therapeutic Equivalence of Generic Products

- Basic Assumption - Drug quality is a function of consistent and optimal release, dissolution, and absorption of active ingredient from a dosage form: this impacts upon chemical equivalence, lot-to-lot uniformity in manufacturing, stability, etc.
- Bioavailability - Measurement of both the rate of drug absorption and total amount (extent) of drug that reaches the general systemic circulation from an administered dosage form
- Equivalence - More general, relative term indicating a comparison of one drug with another along a set of established standards/criteria
- Bio-equivalence
- Clinical equivalence
- Therapeutic equivalence
- Pharmaceutical equivalence

Therapeutic Equivalence

- Two different brands of a drug product are expected to yield the same clinical result
- Factors Affecting Equivalences
    - Properties of the Drug
    - Properties of the Dosage Form
    - Properties of Inactive Ingredients (e.g. binders, fillers, disintegrants, lubricants)
- Bio-Equivalence - Indicates that a drug in two or more similar dosage forms reaches the general circulation at the same relative rate and the same relative extent
  Does not necessarily demonstrate clinical or therapeutic equivalence (but does not necessarily rule it out either!)

Evaluation of Equivalence

- Products frequently tested in small samples, not whole populations
- Individual variations may emerge
- Must adhere to GMP
- Appropriate and accurate labelling (e.g. generic or brand-name product)

Conclusions

- GMP as a quality management system
- Ensure appropriate infrastructure encompassing organizational structure, procedures, processes, and resources
- Ensure systematic actions necessary to provide adequate confidence that product will meet quality standards and expectations
- Good Manufacturing Practices are
    - Pivotal to quality assurance
    - Everyone's responsibility (manufacturers, purchasers, distributors, consumers)
    - Clear, transparent, documented, readily observable
    - On-going, consistent, reproducible
- GMP are aimed at reducing risks inherent in pharmaceutical production
- Qualification and validation provides confidence in manufacturers' processes
- Prequalification provides greatest assurance regarding quality of pharmaceutical products, based on GMP and product dossier

Activity 6: Procurement planning and management

- Procurement is the process of acquiring
- the right quantity
- of the right health products
- of the right quality
- for the right customer
- at the right time
- in the most efficient, safest and least costly way possible.
- Procurement as part of the Supply Cycle
- Multiple stages involved and thus, careful scheduling needed
- Better planning can reduce wastage, shortages, costs
- Simultaneous global demand affects supplier lead times
- Product shelf-life impacts planning
- Many stakeholders, many opportunities
- Procurement options differ depending on products
- Health Products:
  - Pharmaceuticals
  - Laboratory
  - Medical Devices
- Goods - Office Equipment, air conditioners, Vehicles, etc.

Procurement options differ

Services are sub-contracts, engagement of technical advisers, MIS developers, pharmacists, doctors, trainers, facilitators, security, assessment works, other individual/firm experts, etc.
Works are things like office renovations, shelves, installations, minor civil works, etc.
Steps

- Make sure everybody knows exactly what you need
- Avoiding confusion when procuring products
- Requirements are defined as "Specifications"
- Can be defined based on:
- Quality standards / Commercial Standards
- Design Specifications, Labels, Packaging
- Performance Specifications, shelf life, expiry
- Brand or Trade Names
- Samples: Lazy person's method
- Requirements for services are defined in the *"Terms of Reference (TORs)"*
- TOR should be clear and precise enough for the contractors/bidders to prepare a responsive offer
- TOR also provides the basis of evaluation after completion of Contract
- Requirements for works are defined in the "*Statement / Scope of Works (SOW)"*
- SOW is a much more detailed and refined version of the TOR.
- Thorough supervision is required, and performance is bonded/secured financially

Minimum requirements for TORs/SOWs

- Background / Context of Procurement
- The aim and objective of the assignment
- Scope of the work: Outputs/ Deliverables required of the contractor

- Institutional arrangements, requirements for supervision, progress reporting and time schedule
- Training requirements where appropriate
- Additional References (Annexed) to guide the offerors
- Duration of the work/Implementation timetable
- Level of details of price breakdown
- Data, local services, personnel and facilities required from the buyer
- Recommended Presentation of Proposal
- Criteria for Evaluation of Proposals

Procurement methods

- *Request for Quotation (RFQ)* - most flexible and least formal
- *Request for Proposal (RFP)* - used in the procurement of services and complex goods (e.g., functional specifications cannot be expressed)
- *Single Source /Direct Contracting / Waiver of Competition* - there is no competitive market for the requirement, previous tender failed
- *Invitation to Bid (ITB)* - normally used when entity is not required to propose technical approaches to a project activity (i.e., goods, civil works)
- National Competitive Bidding (NCB) with prequalification
- International Competitive Bidding (ICB) with prequalification
- Limited International Bidding (LIB)
- *International Shopping (IS)* - Use of specialized low cost international procurement suppliers or UN
- Use of Pooled Procurement (PP)
  - Group Contracting
  - Central Contracting
- Single Source or Direct Contracting
- Advantages
  - Availability of product guaranteed
  - Simplified procurement rules
  - Expeditious process
- Disadvantages
  - Usually less competitive prices
  - Dependent on one supplier
  - Less transparent
- National Competitive Bidding with Prequalification
- Only applicable if there is a robust and fully qualified local industry
- Not recommended for procurement of medicines
- Limited International Bidding (LIB)
- Advantages
  - Competitive prices
  - Supply of particular product assured
  - Quality control procedures assured
  - 'Good' relationship with supplier
- Disadvantages
  - Purchaser should actively follow developments in Pharmaceutical market (e.g. should be very knowledgeable of the market)
- International Competitive Bidding with Prequalification

- Advantages
  - Assurance of getting the lowest price offers
  - Transparency
  - Multi source products
  - Quality control procedures assured
- Disadvantages
  - Expensive process
  - Lengthy process
  - HR intensive
  - Requires highly technical expertise for evaluation of applicants and bids

➢ International Shopping

- Advantages
  - Speedy and simple process
  - Negotiating room on non-price issues
  - Useful for emergency orders
  - Practical in case of particular products with few suppliers
- Disadvantages
  - Less competitive prices
  - Limited options
  - Less transparent
  - Suppliers don't take you serious

Adherence to Procurement principles

- ➢ Divide key functions among different offices
- ➢ Procurement should be transparent with SOPs
- ➢ Procurement should be planned and monitored
- ➢ Limit medicines to EML or formulary
- ➢ List products by INN
- ➢ Quantities should be based on actual need
- ➢ Ensure reliable financing
- ➢ Procurement should take advantage of economies of scale
- ➢ Use competitive procurement methods
- ➢ Purchase only from supplier awarded tender
- ➢ Pre-qualify suppliers
- ➢ Procurement procedures should assure all drugs are quality assured

Choosing the 'Right' Procurement Method

- ➢ Adherence to Procurement principles
- ➢ Ensure reliable financing
- ➢ Procurement should take advantage of economies of scale
- ➢ Use competitive procurement methods
- ➢ Purchase only from supplier awarded tender
- ➢ Pre-qualify suppliers
- ➢ Procurement procedures should assure all drugs are quality assured

Procurement in context

- ➢ Best practices must balance between:

- Distribution capacity
- Storage capacity
- Procurement staff capacity
- Health delivery capacity
- Available finances
- Time

Structures for Storage and Distribution

- Government Central Medical Store
- Autonomous supply agency
- Direct delivery system
- Prime vendor system
- Private supply system

Procurement Planning

1. Identify requirements to initiate and complete your procurement

- Clarify *scope of the task/specifications*
- *Time* required for each task
- *Staffing* levels
- *Resources*: financial, storage, logistics
- External *dependencies*

2. Schedule all tasks

3. Scheduling procurement

- How long will procurement take?
- When to start?
- How often to procure?
- What to do if shortages are possible?
- How to monitor the process?

4. Identify and Manage Cost Factors

- Interval between orders
- Safety stock levels
- Increased costs from emergency orders
- Bulk procurement
- Reliable payment
- Hidden costs

5. Identify critical path items

- Identify tasks that can disrupt schedule
- Develop strategies to monitor and keep:
- critical path items on schedule
- *external* dependencies on schedule
- Monitoring of contract terms, and application of penalties

6. Expedite: Product available for use

Is the Procurement of ARVs something special?

- Technical Issues
- Each single treatment needs an uninterrupted life long supply of ARTS
- ARVs are combination medicines
- Need to be combined with other drugs to treat Opportunistic Infections (OIs)
- Need to be combined with proper lab testing facilities
- Decentralisation to community level
- ARVs are scarce and valuable

- Development and Research Issues
- Service provider, client and community education are in an early stage of development
- Treatment protocols and ARVs are subject to continuing research: changes can occur quickly and can be significant

- Financial Issues
- ARVs are scarce and (still) expensive, prices change frequently: procurement planning difficult
- These ' *small* ' and often ' *vertical* ' programmes have a HUGE impact on the health budgets and probably the economy of small countries

- Political & Social Issues
- AIDS = Politically sensitive
- AIDS = Stigma

- Product Registration
- ARVs change rapidly and often need "fast track" registration
- Special "fast track" procedures should be encouraged

- Legal Issues
- International: TRIPS
- National: existing legislation, fast track registration of medicines, quality control, procurement

Assessing the Capacity of a Procurement Agency

- Why is capacity of a procurement agency important? Procurement of ARVs is critical to:
  - Successful project implementation
  - The attainment of the objectives of the project
  - Sustainability

Objectives of Assessment

- To evaluate capability of the implementing agency and adequacy of the procurement systems in place
- Assess the risks (institutional, political, organizational, legal, procedural etc)
- Develop an action plan to address deficiencies and to ensure coordination
- Propose a suitable procurement supervision plan, now and in SCALE UP

Elements of Assessment

- Existing infrastructure and capacities
- Compliance with guidelines, local & international
- Organization / organizational capacity
- Bureaucracies: Approvals procedures, Practices
- Human Resources
- Physical Resources
- Record keeping, good management information

Results of Assessment

- Procurement capacity sufficient
- Activities to introduce new commodities / Deficiencies that can be addressed
- Third party required? (procurement agent, distribution agent)

Assessing the robustness of Procurement Planning

- HIV-AIDS procurement needs are difficult to plan in advance for a complete programme. The assessment tries to identify how strong these links are?
  - Funding
  - Capacity
  - HIV testing programmes
  - Community involvement
  - Changing protocols and prices
- Are there sub-projects or – components, taking policy priorities into account
  - Plan for those components?
  - For a limited period?
- Planning to expand capacity, how will it be updated?
- Procurement Scheduling
  - When are goods and services needed?
  - Was a time frame prepared, working backwards from desired date of delivery?
  - Then determine if and how procurement can / should be arranged
- Procurement Strategy for Each Product Category
  - Multi source/ generic products
  - Limited source products
  - Single source products
- Prequalification of Suppliers
  - Is prequalification of suppliers' part of the strategy?
  - What are the benefits of prequalification to the programme?
    - Registration
    - Quality control

Key determinants

- Value of the procurement
- Lead times: How fast are the products needed
- Number of potential suppliers
- Donor requirements
- National policies
- Patent issues

Storage and Distribution
- Assessment of capacity and capability
- Conditions of storage and transport
- Is a separate storage and distribution system needed?

Push and Pull
- Push system - Health authorities determine what and how much a health facility will receive
- Pull system - Health facility prepares requisition often based on consumption data
- Advantages and Disadvantages
- Continuing presence of the right quantities
- Rational selection
- Flexibility
- Waste, overstocking, undersupply
- Capacity building

Conclusions
- The procurement of ARVs has very specific components that differ from the procurement of other drugs
- The strategy and planning of procurement of ARVs can only be short term and flexible due to rapidly changing treatment protocols and market situation
- The procurement of ARVs must be a long term commitment

Activity 7: Supply chain management
Types of Supply
- Full Supply – Commitment and financing available to purchase enough of the commodity to cover all the demand or need.
- Limited Supply – Are those products for which the demand far exceeds the programme or system's capacity to supply them.

Importance of type of supply to Supply Chain Management
- Full Supply – Forecasting can be done for full supply products
- Limited Supply – Short-term quantification
- Using Pull Vs. Push Systems - relating to full and limited supply
- Integrated Systems Vs. Vertical Systems
- These are critical issues to consider – for special programme commodities such as those for HIV/AIDS, TB or malaria, do you integrate (or not) into existing systems?
- The decision you make will determine different strategies for inventory management, storage and distribution.

Storage
- Purpose of Storage
  - Protect the quality of the product and its packaging throughout the supply chain.
  - Make product available for distribution.
- Key Issues To Consider For Storage
  - Type of product - (cold chain/temperature)

- Type of facility
- Equipment - racking, material handling equipment, etc.
- Distribution

Constraints for Storage of HIV/AIDS Commodities

➢ General Constraints:
- Inadequate space
- Inadequate security (locking shelves)
- Temperature/cold chain requirements)
- Lack of storage equipment
- Operating according to FEFO (first-to-expire, first-out)
- Disposal of expired products
- Short shelf lives

➢ Shelf Life - Constraints For HIV/AIDS Commodities
- For HIV test kits – shelf life can range from 6 months to 18 months
- For ARVs – average shelf life ranges from 12 months to 18 months

➢ Cold Chain - Constraints for HIV/AIDS Commodities
- temperature of 2-27^0 C – does not necessarily need refrigeration, but temperatures in many facilities may reach well into the 30's
- HIV/AIDS commodities that require cold chains are not necessarily different from other commodities that require cold chains
- HIV/AIDS commodities that require cold chain (some HIV test kits, such as Unigold and some ARVs such as Kaletra)
- Unigold – which has a storage Example: Kaletra
  - Capsules are stable and potent for 2 months when stored at 25ºC
  - One day at being stored at 45ºC > capsules become soft, sticky and break apart when separated from each other.
  - Abbott recommendation: do not dispense more than 30 days supply when in hot climates.

➢ Storage - Determine HIV Test Kits
- Determine is a rapid HIV test that is commonly used in the testing algorithm of resource limited countries.
- Two key issues for its storage are:
  - Storage temperature is between 2 & 300 C
  - Shelf life for the chase buffer (11-13 months) is different from the shelf life for the test (12-18 months).

➢ Security Constraints - HIV/AIDS Commodities Security Management is important for all products, but RVs have special security considerations. This is because the value of ARVs in terms of cost as well as life-saving potential can create an incentive for mismanagement and pilferage.

➢ Storage
- Both at the Central Level and Facility Level
- Equipment Needs – Central level may need extensive shelving systems, pallets, forklifts, material handling equipment, etc.
- Facility Level – Security or adequacy of space may be an issue

Interventions for Storage

- Buying needed equipment, such as pallets, shelves, racking, locking shelves, refrigerators
- Integrating appropriate HIV/AIDS products (e.g. Long ELISAs, Kaletra, etc.) with other cold chain supply chains
- Developing and implementing a policy for what to do with expired products
- Facility level: constructing a lockable/impenetrable room; developing security procedures around access to ARVs or valuable commodities
- Knowing Storage Constraints Can…..
  - Influence the design of the logistics system
  - If there is a lack of storage space, you could have shorter review periods and increase the frequency of the shipments, which would lower the levels of required stock at one time. This can also prevent expiries and pilferage.

Storage Resources/Tools

- Storage guidelines – some of these guidelines do not always require the input of policy-makers or large amounts of money, while others may.
- Some solutions may be expensive and require structural changes, etc.
- Other solutions are within the storekeeper's ability, are low or at no cost and can help in prolonging the shelf life commodities.

Summary of Storage Session

- Storage conditions vary in each of the countries represented in this workshop and the guidelines reviewed in this session have been developed for use in most situations.
- Adapting for local needs is acceptable, but the basic purpose of storage guidelines is the same: to protect the quality and integrity of commodities while at the same time making them available to users.

LMIS for HIV/AIDS Commodities

- A well-functioning LMIS provides decision makers throughout the supply chain with accurate, timely, and appropriate logistics data.
- Logistics managers use these data to make key decisions, such as how much of each product to order or re-supply, identify potential supply problems at facilities, forecasting demand and planning procurements.
- LMIS is to improve management decisions that govern the logistics system.
- Information in logistics systems tends to be more time sensitive than other forms of health information. HMIS may collect, summarize and report data on an annual basis, but logistics data needs to be reported more frequently to avoid system failures.
- Types of analyses required in logistics systems are different from those in HMIS.
- Adapting one information system – HMIS or LMIS – to achieve full integration of all data requirements is unworkable, becomes unwieldy and tends to present information that is not necessary at certain locations.
- How is a LMIS for HIV/AIDS products different for LMIS for other commodities?
  - Scaling up treatment programmes means unpredictable trends in consumption
  - Need for specific patient data
  - HIV/AIDS programmes are often managed outside established systems

Key decisions in LMIS

- What data to collect

- What format the LMIS should be
- Essential Data Items are:
  - Stock on Hand – quantities of USUABLE stock available at all levels of the system at a point in time
  - Rate of Consumption – the average quantity of commodities DISPENSED TO USERS during a particular time period
  - Losses/Adjustments – losses are the quantity of health commodities removed from the distribution system for any reason OTHER THAN consumption by clients (e.g., losses, expiry, and damage). Adjustments may include receipt or issue of supplies to/from one facility to another at the same level (e.g., transfer, or a correction for an error in counting). L/A may therefore be a negative or positive number.
- Situation Without All Three Essential Data Items
  - Would not be able to predict how long their stock would last
  - Clinic would order too much, too soon, which is expensive for the programme if every clinic in the country is doing this or wait until they stock out, and that would be dangerous to the patient.

Format of LMIS

- LMIS consists of data and the format that the data is recorded and reported
- Format –
  - How many items should be collected
  - How they are organized on the data collection form
  - What kinds of reports to use
  - How many levels there are and how the data gets presented and shared
  - Is the LMIS manual or automated or both

Records and Reports

- Types of Records – (1) storekeeping, (2) transaction, and (3) consumption records
- Reports – using the above record data, and to make data useful, it must be made available to managers in a form suitable for decision making
- Frequency of reporting as it relates to HIV/AIDS should also be determined at the central level

Interventions to Address Some of the Challenges in Designing LMIS

- Assessment of LMIS
- Design LMIS
- Determining the data to collect
- Selecting automation as a solution to immediate data requirements
- Participatory approach

Inventory Control

- Purpose of an inventory control system – is to maintain an appropriate stock level of all products, avoiding shortages and oversupply
- Key questions about inventory control – who places the order, when are orders placed, how are orders made, what commodities are ordered?

Type of Inventory Control Systems

- Maximum-Minimum is a common inventory control system (recommended for programmes with full supply availability)
- Max-Min systems are appropriate for managing any type of product
- Min is set at a level high enough to ensure that the facility never runs out of stock
- Max is set low enough to ensure that all of the stock fits in the storeroom, and it doesn't sit there long enough to expire before being used

Key Concepts in Mix/Man

- Max/Min is discussed in terms of months of supply.
- Example – an SDP may have a 3-month maximum stock level and 1-month minimum, while a central warehouse may have a 9-month maximum stock level and a 5-month minimum level of stock
- Factors in Setting Max/Min
  - The order interval (the longer the order interval, the higher the max)
  - Lead time – how long does it take to make an order and receive the supplies
  - Buffer against uncertainty. This includes things like reliability of the supplier, spikes in demand, wastage/pilferage/loss factors, etc.
  - Increasing your maximum levels increases the length of your pipeline

How Do You Shorten the Pipeline?

- Shorten the min/max stock levels at each facility by shortening the order interval, increasing dependability of transportation
- You can also eliminate levels in the system, for example, bypassing the regional and district levels and distributing straight from the central level to facilities
- Advantages of Having a Shorter Pipeline
  - Fewer points at which ARV drugs and HIV test kits will be stored, thereby decreasing the number of sites to be monitored, facilitating timely submission of reports and training staff in the management of these commodities
  - Fewer locations needing increased or reinforced security for ARV drugs
  - Reduced need for buffer stock throughout the system, thus maximizing the use of available resources for treatment

Other Types of Inventory Control Systems

- "Just in Time" (JIT)
- Top Up

Interventions for Inventory Control

- Assessment of inventory control system
- Design of appropriate max/min inventory control systems
- Dedicated distribution specifically for ARVs
- Shortening the pipeline
- Keeping stocks at facilities on an as needed basis only (e.g., 2nd line ARV drugs)

Activity 8: Logistic system for ART

The purpose of a logistics system is to fulfil the six rights:

- the right good
- in the right quantity
- of the right quality
- delivered to the right place
- at the right time
- at the right cost

Ensuring Quality

- System design
- Frequent orders (quarterly for most products, more frequently for some, like ARVs), help ensure that the product is fresh and has been properly stored
- Storage system
- Routine visual inspection
- Look for crumbling tablets, bad smelling tablets/solutions, suspensions that will not re-suspend if settled
- Check expiration dates and remove expired products from the shelves

Getting Orders to the Right Place

- Eliminating steps and bureaucracy
- For the ARV programme, hospitals take original order forms to the central store at Oshodi and collect supplies which is delivered to the hospital store
- The system can be improved by ensuring hospitals take orders to the Central store in Oshodi (or e-mail, phone, fax, or complete on-line) and the store delivering to the hospital, when original order forms can be picked up
- Facilities may be able to receive their orders directly from the MSD Zonal store the same day, eliminating the need for a separate delivery

Getting the right timing

- Facility orders will be sent directly to Central Stores, Oshodi in a pull (or indent) system, rather than sending orders to MOH programme managers, eliminating the time delay in reviewing orders (MOH will receive the data after the order has been received)
- Facilities will need to order by the deadlines that are set
- Facilities will need to order on a routine, rather than an ad hoc basis

Keeping costs down

- Routine ordering helps eliminate extra, costly deliveries
- ARVs, while provided for no cost to facilities, have a very high cost, so minimizing the quantities in the facilities reduces the potential loss due to diversion or expiration, and maintains high storage standards

Product ordering systems

- Variety of systems:
- Indent system using Combined Requisition and Issue Notes (CRIN) sent to Central Stores Oshodi, paired with the Central Stores Oshodi Sales Invoice
  - For ordering most drugs, especially for OIs
  - For ordering lab and diagnostic items
  - For ordering preventive items (e.g., gloves)

- Vertical programmes
  - Family planning (esp. condoms for prevention)
  - STI programme
  - PMTCT programme
  - TB programme
- Variety of timing: ad hoc, monthly, quarterly
- Variety of reporting: some with no data, others with more data reported

ARV Order Formula

- Formula is similar to the one previously discussed under "max-min"
- Because the report will be monthly, the quantity reported actually dispensed is used for the average
- In a system where ordering is done monthly, keeping a maximum of 3 months allows a facility to:
  - keep 1 month of stock to use during the quarter
  - keep 1 months of stock to use while ordering and waiting for the order to arrive (the lead time stock)
  - keep 1 months of stock as buffer stock, in case the lead time is extended and to allow the programme to expand
  - The quantity requested is to be rounded up (or down) to the nearest unit of issue

Ordering other Products

- Products such as drugs for treating OIs, other lab supplies, and stationary, should be ordered as all other products, using the Combined Requisition and Issue Note (CRIN)
- Although the ordering formula is not printed on the form, for product ordered quarterly, a good formula would be the same as for STI:
- Ordering for TB/L
- TB/L drugs are an important component of a comprehensive ARV programme given the incidence of TB among HIV-infected patients
- TB/L drugs will continue to be ordered as they are currently

Reviewing Orders

- Supervisors should look for:
  - Beginning balance for the current report should matching the ending balance from the previous report
  - Math errors
  - Logic in the quantities ordered
  - Ending balances of zero, indicating a stockout at the end of the current period

Ordering All Products

- All orders should be submitted to either the Hospital Therapeutics Committee for review
- Approved orders should be taken directly to the central stores Oshodi
- There store presently does not accept orders made by letters, faxes, phone calls, e-mail, or on-line ordering but systems are being developed to facilitate delivery
- The original form should be given to MSD on collection of drugs

Activity 9: Pharmaceutical systems

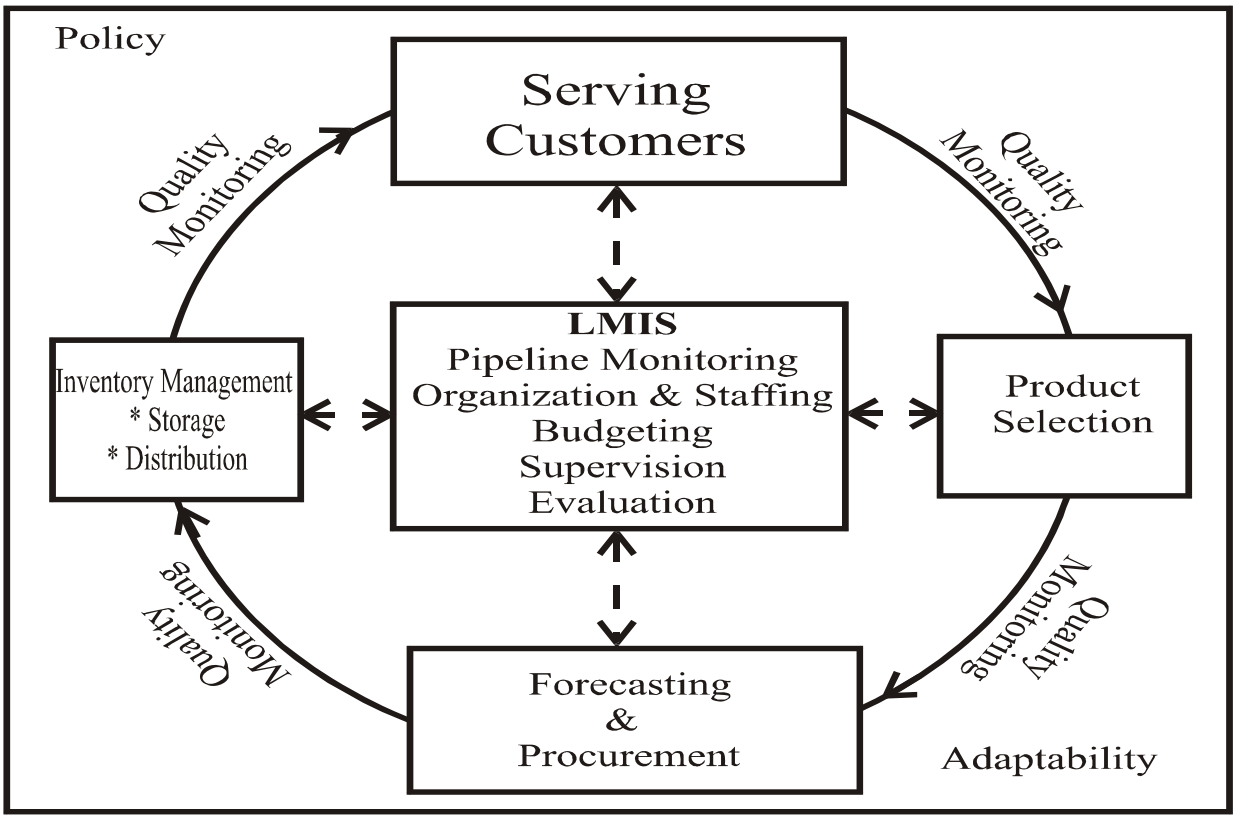
Importance of Pharmaceutical Systems

- Drugs are specialised health commodities
- Pharmaceuticals are the second highest public health budget expenditure in most countries
- Drug expenditure accounts for 50-90% of non-personnel health system costs
- Access to affordable high quality health commodities is central to health care systems
- Drug availability promotes confidence in health systems
- Management of pharmaceutical systems is complex

Role of pharmaceutical systems

- Uninterrupted availability of pharmaceuticals
- Affordability of pharmaceuticals
- Ensuring that safe and efficacious drugs are available in the correct form and condition for the correct indication and at an affordable cost whenever client needs them

Logistics Cycle



- The framework through which pharmaceutical systems function
- Ultimate goal is to meet customer needs
- All the components of the cycle should be carefully planned, implemented and monitored
- Emphasis must be placed on creating an enabling environment for effective pharmaceutical management

Determinants of Access to Pharmaceuticals

- Availability
  - Research & Development
  - International Trade Agreements
  - National Regulatory Systems
  - Procurement mechanisms
- Affordability
  - Pricing policies
  - Government public health expenditures
  - Family income
- Use
- Inventory management
- Rational drug use
- Pharmaceutical System Failure
  - Stock out of essential drugs is a clear sign of pharmaceutical system failure
  - Government Failure
  - Market Failure
  - Income gap
- Government Failure
  - Low health expenditure
    - Public drug expenditure <US$2 per capita in 38 developing countries
    - Public health expenditure US$57 billion short of minimum for basic care (WHO, 2002)
  - Inadequate regulatory capacity - 10-20% drugs fail quality control tests in developing countries
  - Inefficient use of resources
  - Corruption
- Market Failure
  - Developing countries are a small market to global pharmaceutical market (20% sales, 80% global population)
  - Little spent on R&D for tropical diseases
  - Global AIDS drug gap
  - Significant barriers to domestic manufacture
- Corruption defined as "..behaviour on the part of officials in the public and private sectors, in which they improperly and unlawfully enrich themselves and/or those close to them, or induce others to do so, by misusing the position in which they are placed."
- Pharmaceutical Industry
  - Big Pharma
    - research based, patented, "branded" medicines (GSK, Pfizer, BMS, Merck, Abbott)
    - compete on exclusivity (patents)
  - Generic manufacturers
    - copies of patented or off-patent drugs
    - Big Pharma also make generics
    - compete on price

How the drug industry works

- Drugs expensive to manufacture but easy to copy
- R&D very expensive ($800 m/drug)

- To do R&D, companies need incentive
- IP: Patents for 20 years - "market exclusivity"
- but what happens in:
  - Markets where public has no purchasing power
  - Diseases that have no profits (malaria)
  - 10% of R&D spending on diseases that cause 90% of global disease burden

The Pharmaceutical Controversy
- Drug companies want to maximize profits
- Public Health aims to maximize impact
- Big Pharma argues no profit, no R&D (except publicly funded e.g. vaccines)

So how do you reconcile profits and access?
- TRIPS and Doha Declaration
- Public Health/Pharmaceutical Scale
- Are rights to IP >, = or < Right to Health?

Equity Pricing
- Drug pricing to equity according to ability to pay
- Criteria include economic indicators (wealth, income) and disease burden
- Forms of equity pricing
  - Preferential pricing
  - Market segmentation
  - Differential pricing
- Problems with Equity Pricing
  - Some consumers pay MORE than others
  - Reference Pricing – middle tier countries demanding African prices for ARVs
  - Diversion/Leakage – difficult to keep markets separate

Marginal Cost Pricing
- Marginal cost: Direct cost of producing one additional unit, assuming fixed costs (R&D, factory, equipment, testing etc.) are already covered
- For ARVs fixed costs are very high (hundreds of millions) but marginal costs may be cents
- Marginal cost pricing: charging marginal cost per production unit
- Low marginal costs = opportunities for equity pricing

Key Considerations for ART Pharmaceutical Systems
- Policy framework
- Selection
- Forecasting and quantification
- Procurement
- Storage and Distribution
- Use
- LMIS
- Commodity security

Policy Framework
- National ART plan

- Vertical or integrated supply chain system
- Sources levels of funding
- Detailed SOPS including guidance on patient selection criteria
- Drug regulatory policy
- Patent laws
- Pricing policy to patients

Product Selection
- Drug selection committees
- National Treatment Guidelines
- Other treatment guidelines

Drug Regulatory Agency registration
- WHO prequalification
- FDA approval
- Patent status of proposed drugs
- Cost considerations
- FDC and single drug formulations
- Remember to plan for children

Forecasting and Quantification
- This must be done prior to commencing an ART programme
- Always consider newness of ART programmes
- lack of accurate data
- Use available data e.g. other programmes, demographic, morbidity
- Careful monitoring of consumption and programme performance
- Need for flexibility as data is gathered from the programme

Procurement
- Design and understand the ARV pipeline
- Detailed procurement plan must be developed
- Procurement strategy
  - Single source – direct contracting
  - Limited source – limited international bidding
  - Multi source – international competitive bidding
- Procurement contract flexibilities
- Monitoring of the procurement plan
- Computerised systems – software

Inventory Management and Use
- Storage
  - Security
  - Storage space
  - Cold chain
- Dedicated distribution system
- Rational use of ARV drugs
- Training of health care workers (prescribers)
- Knowledge of PLWHA – treatment literacy

- Adherence strategies

Logistics Management Information System (LMIS)
- The need for an information system to manage the supply chain is not an option
- ARV LMIS should be developed prior to starting an ART programme
- Training of healthcare workers

Commodity Security
- Generally ARV drugs are not in full supply
- However the pharmaceutical system must ensure uninterrupted supply for ALL patients started on ART
- The system must also have the capacity to accommodate any planned programme scale-up
- Sustainability of ART programmes is directly related to the pharmaceutical system capacity

Role of Pharmaceutical Systems in ART Programmes
- Access
- Durability
- Scalability
- Sustainability

Conclusions
- Pharmaceutical policies reach beyond health and touch on areas of trade and industrial policies
- The global drug gap is due to market and government failures and limited budgets and income in developing countries
- Governments can turn to outside support for technical assistance when desired
- Domestic drug production can be a solution to solving the drug gap
- Policies and practices should be in place to ensure well-functioning pharmaceutical systems

Activity 10: National guideline on ART procurement & management
- Orders to the Central Medical Stores should be made as stipulated to allow supplies to reach the facilities in time.
- Reserved and marked stocks should be set aside for continued treatment of existing therapy recipients.
- Procurement of Antiretroviral drugs will be done by Medical Stores Department which will then distribute the medicines to all the accredited facilities across the country. Requisition of antiretrovirals from the facilities will follow the normal way procedures but a separate requisition form will be used.
- On the receipt of the drugs at the facility the individual responsible for the pharmacy should check on the ARVs brought by Central Medical Stores and sign the delivery note
- Adequate safety stock must be kept at all times to avoid stock outs.
- These levels must be closely monitored, especially at the beginning of the programme.

Quantification
- The pharmacist should work together with clinicians to get an accurate estimate of the number of people to be enrolled on therapy.
- He/She should forecast demand for short term and long term.

Methods to determine the right quantity

- Look at general population data (demographics) and make assumptions about disease patterns
- Look at the number of people or services and make assumptions about what they received
- Look at the quantities actually issued (logistics data)—this is the preferred method

Using logistics data to determine the right quantity

- Based on a simple formula, actual dispensing data can be used to determine the right quantity of ARVs to order

Beginning Balance (A)	Received This Period (B)	Actual Dispensed (C)	Lost/ Adjusted (D)	Ending Balance [E=A+B-C±D] (E)	Quantity Needed [F=(Cx3)-E] (F)

- The formula is: Quantity to Order = Quantity Dispensed X 3 - Stock on Hand
- What is the importance of 3? (hint: for ARVs, you order them monthly)

Understanding Max-Min

- The formula for ordering is based on maximum-minimum inventory control
- In max-min, the goal is to not keep too much stock or too little stock
- In a system where ordering is done monthly, keeping a maximum of 3 months allows a facility to:
  - keep 1 month of stock to use during the month
  - keep 1 month of stock to use while ordering and waiting for the order to arrive (the lead time stock)
  - keep 1 month of stock as buffer stock, in case the lead time is extended and to allow the programme to expand
  - The buffer stock of 1 month in a monthly ordering system ensures that the programme can grow by double during each period

Warehousing Requirements

Ensure proper control and security of storage facility. The following procedures will be used to ensure this:

- **At facility pharmacy**
  - Stock must be kept in secure, high risk storage area, in a cage or cupboard with a single pharmacist/pharmaceutical technician (at any one time) responsible for receipt and issue.
  - Normal stock records will be kept for all receipts and issues. Bin cards must be maintained for each item. A running balance must be kept.
  - At the end of each month, the pharmacy in charge must check the physical stock against the stock records.
  - Stock must be stored in a temperature controlled environment.
  - For drugs like Kaletra (Lopinavir/Ritonavir) they must be stored in a refrigerator.
  - The pharmacist/any responsible person for the pharmacy must make sure that all times there is adequate stock as well as buffer stock for new patients for all required medications (first line, second line, adults, paediatrics)
- **Ensuring control**
  - Records of all the medicines dispensed should be kept in a register book.

- There should be a separate manual register at the pharmacy for Antiretrovirals only, until the time when in integrated system is installed at the facility.
- Patients or appointed adherence assistant should have the cards which will be presented to the dispenser whenever collecting their medicines, this form should be signed by both patients and dispenser when medicines are dispensed.

➢ **Register at the Pharmacy**

- The personnel responsible at the pharmacy must record all the ARV which is dispensed at the register book located in the dispensing unit at the pharmacy.
- The dispenser upon giving the medicines must make sure that the patient signs on the register while receiving the medicines and the dispenser should also sign on the same book upon issuing the medicines.
- Patients' medication cards are to be issued.
- The cards are to be issued upon presentation of the prescription to the dispenser who will then record all the medications being dispensed on this card.
- On each follow up visit, a patient is supposed to bring this card to the dispenser who will then sign on the card upon issuing of the medication.
- In the case where the patient cannot collect the medicines due to the condition of patient worsening, the appointed adherence assistant of the patient can also sign on behalf of the patient on the same card upon receiving the medicines.
- Statistics and reports on the consumption of drugs should be sent to the Ministry of Health through the DMO for national collation of uptake and usage data, which is crucial to plan in advance drug orders so as to avoid stock outs at all the necessary levels of the distribution system.

➢ **Reports and audit**

- Relevant data on the consumption of the antiretroviral medicines must be kept and sent to the Ministry of Health every month, according to the MSD indent format.
- Procurement, storage, distribution and dispensing procedures and records as well as stock on hand will be subject to the usual internal and external audit procedures

Activity 11: Group Activities/Discussions

Case Study

In your small groups, review the case study which you have already read. As a group, identify critical issues raised by this case study. Use the guided discovery questions to prompt discussion.

Case Discussion Question

➢ How should the government of Fatakia prioritize elements of Good Manufacturing Practices, given the unique situation it faces in procurement, storage, and distribution of anti-retroviral? What if Fatakia does not have the capacity to pre-qualify suppliers?

➢ Given the unique factors of the drug distribution system in Fatakia, what particular issues related to stability must be considered? How can the drug distribution be modified to optimize pharmaceutical stability?

➢ In evaluating claims and documents made by different manufacturers of the same drug, what principles must be weighed to ensure optimal health outcomes?

➢ How would you advise the government of Fatakia to develop an evaluation scheme for multiple, competing providers of the same medicine?

Key Issues

- Health System Infrastructure (e.g. laboratory testing facilities, medics, etc.)
- Drug Distribution System (e.g. transport/storage logistics, deterioration in quality of products, drug diversion issues)
- Financial Pressures (e.g. use of generic products)

Group Exercise 2

Is the Procurement of ARVs something special?
As a group, discuss those issues that make the procurement of ARVs different from the procurement of the essential commodities we routinely procure for our programmes

List the 3 most important considerations that affect procurement of ARVs
Be prepared to explain to the meeting why you have listed them as priority considerations

Group Exercise 3

As a group, briefly share how the procurement of **HIV COMMODITIES** is organised in your centre, using the following points as guides:
•Current MOH Procurement agencies involved
•The Bidding process
•Pre-qualification of suppliers, quality control
•Bid evaluation, contract awards and management
•Warehousing, storage and distribution
•Capacity to support programme(s) going to scale

- Is the capacity in the procurement agency sufficient to conduct this procurement?
- List the 3 most important deficiencies that need to be addressed for you to be a 'BEST PRACTICE EXAMPLE' in the region.
- If you were to issue a bid for a third party procurement agency to conduct procurement on your behalf, what are the three most important considerations to take into account

Module 9
VCCT and Home Based Care

Objectives

1. Have acquired the necessary knowledge and skill to offer VCCT in the community
2. Provide appropriate psychosocial and medical referrals for prevention of HIV/AIDS and OIs in the community
3. Provide VCCT service in the community

Content

- Overview of voluntary counselling and testing
- Home based care
- Bereavement counselling
- Caring for the carers

Materials required

- Overhead projector
- Data/Multimedia projector
- Transparencies
- Flipcharts and flipchart stand
- Markers
- Masking tape
- Laptop
- Diskettes/Other media storage devices

Time: 180 minutes

Activity 1: Voluntary counselling and confidential testing

The session would focus on highlighting the key issues relating to voluntary counselling and testing. Emphasis would be laid on the need for confidentiality

Time: 20 minutes

Activity 2: VCCT as entry point to prevention, care, treatment and support services

The session would discuss the role and importance of VCCT to the entire HIV/AIDS programming It would highlight the central role of VCCT to a successful prevention, care and treatment programme.

Time: 10 minutes

Activity 3: Home Based Care

Participants will recognize the importance of HBC in response to the impact of HIV/AIDS on individuals, their families and communities and would have information on key elements of home base care.

Time: 30 minutes

Activity 4: Caring for the carers

Participants would be aware of the need for carers and how to address these various needs.

Time: 20 minutes

Activity 5: Psychosocial support

Participants would learn about the various ways of providing psychological support for PLWHA and the importance of such support services.

Time: 20 minutes

Activity 6: Special counselling sessions

There are various counselling services that are needed to address peculiar issues. Participants would get to identify the various peculiar circumstances and how to counsel clients appropriately.

Time: 40 minutes

Activity 7: Counselling in Loss and Bereavement

In Africa, the culture of silence over death makes it difficult for many people to deal with losses especially with respect to HIV/AIDS. Participants would learn how to counsel clients and help these individuals to handle crisis and bereavement.

Time: 30 minutes

Lecture/Facilitator's notes

Introduction

Voluntary counselling and confidential testing is regarded as the gateway for identifying clients who are seropositive and would need care and support. In addition, clients who are seronegative can also receive a one-on-one education about HIV infection which is more effective in ensuring behaviour change. For seroconverters, there is room for management of clients in the home. This has its advantages and disadvantages. The session would be focusing on VCCT, its importance and its link with respect to managing clients on ARV therapy.

Time: 5 minutes

Activity 1: Voluntary counselling and confidential testing

- Voluntary counselling and testing (VCCT) has been shown to be a cost-effective approach to reducing HIV-related risk behaviours.
- Stigma is an important issue to be considered for this intervention.
- Sensitivity counselling, community education, and involvement of partners in the VCCT process may help alleviate the stresses caused by the stigma of HIV.
- The following lessons have been learnt from VCCT programmes:
  - Systems should be in place to ensure confidentiality of VCCT services.
  - Men and communities need to be sensitized about VCCT.
  - Health workers must be properly trained in VCCT.
  - Counselling programmes should be offered to support HIV-infected women and men.
  - Peer counsellors, service providers, and social workers must be properly trained.
  - Prevention messages should be included with VCCT, especially in the context of
  - MTCT: because newly infected women are twice as likely to transmit the virus to their infants.
- During the pre-test VCCT, health workers should carry out knowledge assessments and encourage women to involve their partners.
- At the post-test VCCT, counselling on HIV prevention and infant feeding should begin for pregnant women. For other PLWHA, nutrition counselling should be carried our.
- Experience show that people requests the same health workers at each meeting for reasons of confidentiality and a relationship that is often developed.
- In addition to counselling, other health education sessions and group meetings should offer information on VCCT.

For more information please refer to the National Voluntary and Confidential Testing Manual.

Activity 2: VCCT as entry point to prevention, care and support services

- Voluntary counselling and confidential testing is not an end point in itself but an essential link and an entry point to prevention, care and support services.
- .
- If this link is well established and the services provided meaningful, then VCCT services can be a powerful catalyst towards increased prevention, care and support and vice versa.
- People who test positive can gain prompt access to medical care, health information and on-going psychosocial support services.

- Those who test negative can continue to receive services that enhance their ability to stay negative.
- VCCT therefore facilitates early and prompt access to effective referrals which helps to prevent infection and enhance the quality of life of persons who test positive
- Such services include; health information that promotes and facilitates behaviour change; PMTCT services: access to medical management of opportunistic infections and ARVs, access to support services; as well as services that helps individuals plan for the future (will, orphan care).
- In addition, VCCT is an indirect tool for addressing stigma and discrimination in the community.
- It is therefore important that each VCCT centre
  - Network with other service providers.
  - Counsellors need to be able to make holistic assessment of client's need and draw up an individualised care plan to address this. The care plan outlines the client's daily living activities, specific needs and means of addressing them.
  - Counsellor should be able to communicate the need for on-going counselling for all clients as well as the need for accessing medical and social services promptly
  - VCCT service centres should be accessible and should access both infected and affected persons.

Activity 3: Home based care

What is home based care for PLWHA and why home based care?

- Home based care is any form of care given to those affected and infected by HIV in their own homes.
- It is a form of care given for chronic disease conditions, which enables patients spend as much time as possible out of the clinical setting.
- It would include things that individuals do to take care of themselves and care given to them by family or health care provider in their home.
- It is the range of care spanning from physical to psychosocial and spiritual care and support.
- It is holistic in nature.
- It is an inevitable element of comprehensive care for PLWHA especially when counselling has reached the extent of co-opting family, community and other significant people in the care.

The goals of home base care are to:

- Improve the quality of life for PLWHA and to provide quality clients care
- Reduce the stigma experienced by PLWHA and members of their family in public healthy institution.
- Reduce the expenditures and economic impact of HIV on the family.
- Strengthen care givers capacity in the aspect of prevention, care, counselling community mobilization and support.
- Provide health care providers with the information they need to help families gain confidence about the ability to care.

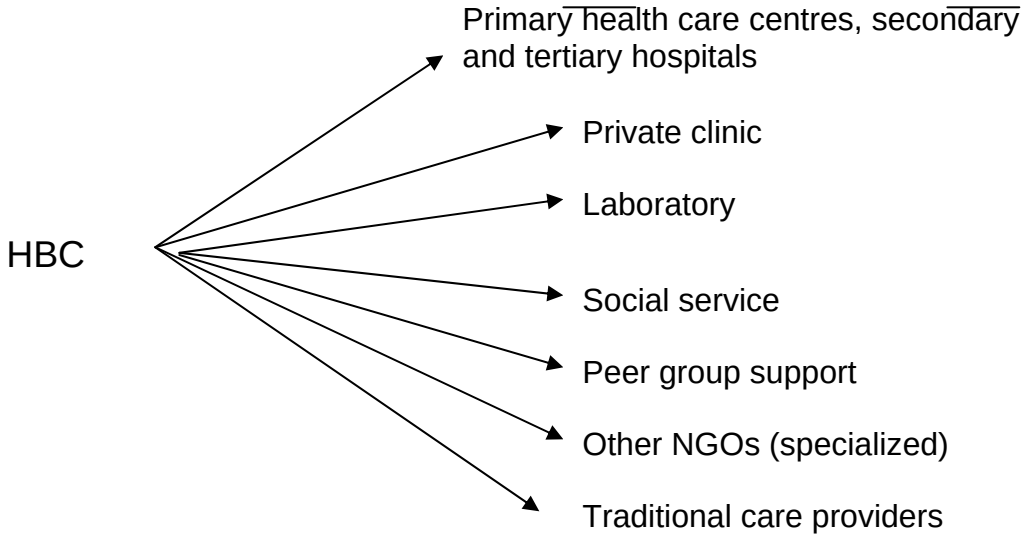
Why home based care?

It is important to appreciate the reasons why home care is appropriate. This includes:

- The home is the primary source of care for the members of the family.

- The extended family is still strong in many places and is willing to provide care once the condition of the patient is explained.
- Hospital care is not readily accessible for many people (cost and otherwise).
- Hospital care is not always desirable for people with chronic and terminal illness owing to overcrowding and understaffing which results in poor standards of care.
- Home based care provides health workers access to the immediate family and community, allowing opportunity for education as well as support. This leads to acceptance of the disease and helps promote prevention.

HBC is linked to other forms of services a PLWHA can access. This is to ensure a network of service provision for PLWHA can be facilitated by carers thereby assuring PLWHA comprehensive care. After this the facilitator presents the diagram below and explains the feasibility of ensuring a referral system linking HBC to other essential facilities for the PLWHA.



Benefits of home based care for PLWHA

- Cheaper for the client
- Brings help closer to the client and strengthen family bonds
- Encourages family education about HIV/AIDS
- Reduces the stress on carers
- Allows for alternative support for the client
- It can help compliment the efforts of patients' clinical management during ARV therapy.
  - Adherence of patients to drug therapy can be increased
  - Prompt management of opportunistic infections can be effected
  - Care-givers can assess social constraints limiting patients' clinical management
- How can clinical management of patients be linked with home-based care services?
  - The hospital can establish home base care services that can provide home based care to patients diagnosed with HIV infection
  - The hospital can link up with organizations that provide home base care services and refer all patients to that service for effective monitoring
  - The hospital can work with volunteers who can make regular home visits and monitor the patients Identify organizations that can do this.

Setbacks of home based care for PLWHA

- Problem of shared confidentiality
- Problem of dependency on care provider
- Stressful for carers especially when clients are many

Activity 4: Caring for the carers

Causes of Stress

- HIV/AIDS is a disease which:
- Is incurable
- Causes terrible suffering
- Kills many young people
- Is highly stigmatized
- Workload
- Shortage of staff
- Personal identification with suffering

Forms of Psychological Support for carers

- Counselling clinics
- Refresher courses
- In-service education
- Shared confidentiality
- Policies reinforcing prevention and control
- Praise for work done
- Ward rotations

Primary Care-givers

- Involve care-givers in decision-making
- Pre-discharge planning
- Assessment of home and family prior to discharge
- Counselling of patient and family on HIV/AIDS care and social support
- Care and Support at Home
  - Meeting basic needs of client
  - Providing appropriate and safe care
  - Controlling symptoms
  - Infection control
  - Financial support
- Community Involvement
  - HIV/AIDS prevention and care
  - Empowerment and education of people living with HIV and AIDS
  - Individual and group counselling
  - Support of care-givers
  - Training of community educators

Activity 5: Psychosocial Support

- As HIV infection advances, PLWHA have increasing needs for medical care and psychosocial services. This often leads to a lot of strain on the family, community and health care services.
- Psychosocial support services could be provided through organized systems to help reduce the stress individuals and families bear in taking care of PLWHA. Services to be provided include:
- Provision of emotional support which empathises with concern and fears
- Promotion of peer support
- Ensuring access of PLWHA to essential care and support services like home based care, orphan care, legal services etc.
- Facilitating spiritual counselling when clients have need for this.
- Enhancing access to replacement feeding for HIV infected women.
- Ensuring children and orphan care and support.
- Caring for the primary carers who are often children and grandparents.
- Handling bereavements and crisis with families.

Role of support group organizations in the care of persons living with HIV

- Provide psychological support for peers
- Help to share experience with one another
- Share information relevant for use in coping with infection
- The psychological support helps individuals to cope with self and enacted stigma
- Increases ability of persons living with HIV and AIDS to advocate for their rights

What services do support groups provide for their members?

- Counselling
- Financial
- Legal
- Nutritional
- Medical
- Home visits
- Physical help

Support groups have been constituted in all states of the federation
If need for consultation, contact NEPWHAN in Abuja (nephwan@nepwhan.org)

Activity 6: Special Counselling Sessions

Counselling adolescents and Youths

- Adolescents are classified as children between the ages of 10 – 19 and youths as those between the ages of 15 – 24.
- It is a period of transition from childhood to adulthood.
- During this period, young people experience physical and psychological changes following puberty.
- Their reproductive health needs are many and include the need to improve their ability to informed decisions about their health, improving their skills to moderate environmental conditions that predispose individuals to indulge in risky behaviours, and establishing youth friendly centres that are easily accessible.

- Counselling services for adolescents and youths is basically the same as that of adults. However, there are a few points and issues that need to be modified during an adolescents or youth counselling session.
  - Confidentiality needs to be emphasised and maintained
  - Need to continually recognise and affirm the courageousness of the young for presenting to service
  - Encourage the individual when attempting to implement healthy practices
  - It is important to do a risk assessment and explore the individual's perception and factors relating to vulnerability
  - Explore existing support systems and help facilitate familiar and spousal support
  - Give ample opportunity for asking questions and sharing concerns
  - Give appropriate IEC materials.
  - It may be more appropriate to have a young person counsel an adolescent or youth.
  - Ensure facility is accessible by been friendly, having flexible hours. Cost should not be limiting factor.
- Anyone 18 years and above can give consent for VCCT. However adolescents between the age of 15 and 18 years can access VCCT if the counsellors determine that the individual is matured enough to understand the testing procedures and results.
- Young married individuals are considered as matured minors who can give consent for VCCT.
- Children under 14 years of age can be counselled but cannot be tested without parental consent. VCCT services should be offered to children who come to facility with parents only if there is clear benefit for the child and there are no potentials for abuse or neglect

Counselling for couples

- The only completely effective means of not transmitting HIV from the infected partner to the uninfected partner has been total abstinence—avoiding all sexual contact.
- While for some couples this has been an effective means of countering the risk, for many others, their desire to participate in sexual activity with each other has made it difficult to avoid the risk.
- Study show that people with a viral load of less than 1,500 copies per millilitre seemed never to transmit HIV to their partners; however, as viral loads increased, HIV was passed on through sexual relations. The lesson here seems to be that keeping the viral load low or undetectable levels is the key to keeping an uninfected partner healthy.
- The viral load of an HIV-positive partner is the most important factor affecting heterosexual transmission of the virus. Among 415 sero-discordant couples identified in a population-based study in Uganda, transmission rates increased with the number of copies of HIV ribonucleic acid (RNA) in the blood, from two sero-conversions per 100 person-years when the infected partner had fewer than 3,500 copies per millilitre to 23 per 100 person-years when the partner had at least 50,000 copies per millilitre. No sero-conversions occurred when the HIV positive partner's viral load was less than 1,500 copies per millilitre.
- One of the most frequently asked questions is: What is the effectiveness of condoms in preventing HIV transmission? The simple answer is that they are somewhat effective. Studies however show that the probability of HIV transmission when the infected partner's viral load is above 1,500 is between 11 and 20% during any twelve-month period, even with the use of a condom. Total compliance to a working HAART programme that keeps viral load to undetectable levels would decrease the risk.

- When counselling an HIV sero-discordant couple, the first thing you need to tell them is that HIV still has no cure. This disease will eventually result in death for the person who has it.
- Recent advances in medical intervention have almost rendered HIV chronic and manageable; however, there are still many side effects to the drugs that are used in the HAART therapy, and strict compliance with the dosing regimen is essential in order to maintain viral load reduction.
- Also, sero-discordant couples need to be counselled that there will always be some degree of risk attached to sexual activity and HIV. Condom failure, missed medicines, illness, and many other factors may increase the risk of obtaining HIV from an infected sexual partner. It is up to each couple to decide if that risk is at an acceptable level for both of them before they proceed with sexual activity.
- However, the future for sero-discordant couples is brighter than it has been in a long time. Currently, they are able to, in many cases, have children, enjoy each other's company, and have a certain level of sexual contact. Everyone who has access to the HAART drugs is having a longer life expectancy than ever before possible with HIV infection.
- The wise counsellor will educate the HIV sero-discordant couple just the same as they would regarding the options of abortion and adoption or carrying a baby to term. The counsellor should also stress to the HIV sero-discordant couple the need for fidelity and inform those who are HIV negative that the possibility of getting HIV increases proportionally with the number of sexual contacts.

What to do when one partner is HIV-positive and the other is HIV-negative

- There is still controversy over the best advice to give to sero-discordant couples.
- It is usually unwise for sero-discordant couples to have unsafe sex. Even when politely called a “conception attempt”, there is always a risk to the HIV-negative partner of contracting HIV.
- For an HIV-negative woman, for example, the chance of becoming HIV-positive from having unprotected sex will depend on many things, including the viral load in the semen of her male partner.
- An undetectable viral load result from a blood test does not mean that viral load is undetectable in seminal fluid.
- For an HIV-negative man, transmission risk depends on the level of viral load in the genital fluids of his female partner. Again, an undetectable viral load in blood does not always mean the same as in genital fluid.
- Other factors are also important. An uncircumcised man may be more at risk of contracting HIV because cells in the foreskin are more vulnerable to infection; and having sex with an uncircumcised HIV-positive man is of greater risk to an HIV-negative woman than sex with a circumcised man.
- Infections of the genital tract also increase the risk of sexual transmission of HIV. Regardless of the method of conception, both members of a sero-discordant couple should check for such infections. This should include screening and treatment for other sexually transmitted infections.
- The man should have a semen analysis. This can rule out any infection and also to ensure that his sperm count is fit and healthy.
- All these risk factors aside, HIV is actually quite a difficult virus to transmit. Statistically it is much harder to transmit HIV than to get pregnant. Therefore, limited conception attempts made during ovulation may carry a low risk if the positive partner has undetectable levels of viral load. But there is still a risk involved for both male and female

negative partners from any single unprotected exposure. After all, people can conceive from one attempt and also become HIV-positive from one exposure.

- In one study of HIV-negative women and HIV-positive men, 4% of women became HIV-positive. Most would consider this an unacceptable risk.
- One additional point should be stressed. Although a low number of conception attempts can be relatively safe, some couples do not return to safer sex afterwards. This often results in the negative partner then becoming HIV-positive.
- It is important to highlight that HIV is still a disease that can affect the rest of your life. If a partner has stayed HIV-negative until now, one might not want to change this over a decision to have a baby.
- For those who wish to conceive, there are other options that involve almost no risk to the negative partner. These options are discussed overleaf.

- When the man is HIV-positive and the woman is HIV-negative you can use a process called sperm washing.
  - This involves the man giving a semen sample to the clinic. A special machine then spins this sample to separate the sperm cells from the seminal fluid.
  - Only the seminal fluid contains HIV-infected white blood cells. And these cells carry the risk of passing on HIV. Sperm cells themselves do not contain infectious HIV.
  - The washed sperm is then tested for HIV. Finally, a catheter is used to inject the sperm into the woman's uterus. In vitro fertilisation (IVF) may also be used. IVF is important if the man has a low sperm count.
  - An Italian doctor first developed this process. His clinic has used the process for over 3,000 samples of sperm washing.
  - There have been no cases of HIV transmission to women from sperm washing.
  - It has also led to the birth of over 600 HIV-negative babies. This is therefore the safest way for an HIV-negative woman to become pregnant from an HIV positive man.
  - Very few clinics offer sperm washing in the UK. The clinic with the most experience is the Chelsea and Westminster Hospital in London.
  - Cost is a barrier for many of these services and health authorities must address this issue
- When the woman is HIV-positive and the man is HIV-negative
  - The options are usually much simpler in this situation.
  - Do-it-yourself artificial insemination or "self insemination" using a plastic syringe carries no risk to the man. This is the safest way to protect the man from HIV.
  - Around the time of ovulation, one puts the sperm of the partner as high as possible into the vagina.
  - Different clinics may recommend different methods. One way is to have protected intercourse with a spermicidal-free condom. Another is for the partner to ejaculate into a container. In both cases, the sperm is inserted into the vagina with a syringe.
  - The clinic can provide the container and syringe and detailed instructions on how to do this, including advice on timing the process to coincide with your ovulation for couples interested in self insemination.

What to do when both partners are HIV-positive

- Many HIV-positive women become pregnant when they already know their HIV status. Many women are also already on therapy when they become pregnant.
- It is important that when an HIV positive woman plans to get pregnant, the healthcare provider should advise based on:
  - Consideration of her general health.

- Ensure she gets appropriate check ups.
- Treat any sexually transmitted infections.

- Appropriate care and treatment should also be given for HIV infection.
- Some discrimination still exists against HIV-positive people who decide to have children. To avoid any problems related to this sort of discrimination, the women should be referred to a PMTCT centre in the country or a maternity hospital that supports and respects the decision of a PLWHA to have a baby.
- When both partners are HIV-positive, safer sex is still recommended. This is to limit the possibility of re-infection with a different strain of HIV.
  - It is likely that this risk is very low, but it is possible. This risk of re-infection is even less likely if the couple only have unprotected sex a few times in order to conceive a baby.
  - Here are some other things to consider about the risk of re-infection:
  - The risk between HIV-positive couples is also likely to relate to viral load levels.
  - This risk is likely to be higher if one partner is doing well on treatment while the other partner is untreated and/or has a high viral load.
  - This is more serious if one partner is resistant to HIV treatment.
- Couples may be advised to limit unprotected sex to the fertile period for those practicing safer sex. They could also follow the advice for sero-discordant couples.
- For HIV-positive couples who do not practice safer sex now, continuing to do so to conceive a baby will carry no additional risk.
- All these options involve very personal decisions. Knowing and judging the level of risk is also very individual.
- All methods of becoming pregnant carry varying degrees of risk, cost and chance of success. These increases with every exposure.
- It is important that couples discuss about these options together. This way they can make decisions that both of them will be happy with.

Activity 7: Counselling in Loss and Bereavement

Bereavement/loss and dealing with catastrophe

- Although different, the feelings and ways of dealing with bereavement and catastrophe/trauma can have similar characteristics. Often, a trauma is associated with a sense of loss – not always a death – i.e., divorce, mugging, robbery, sexual assault, evacuation, losing a job unexpectedly, finding out you have an incurable disease.
- There are typical stages that most people go through when confronted by sudden, unexpected loss and tragedy. There are different models for this, but the following might be useful:
- Stages:
  - alarm/threat
  - impact of the news, event
  - searching/taking stock of the effects/ how does it affect others and me?
  - gaining a new identity/rescue and recovery/moving on
- Feelings:
  - shock
  - denial/guilt/anger
  - withdrawal/depression
  - sadness/ acceptance

- The important thing is to be able to accept the bereaved/upset person with all their ambivalences, contradictions and complexities. In accepting and understanding the stages of grief work, you can give reassurance that while each grief/tragedy experienced is personal and unique, the person experiencing it is not abnormal in the ways that they express themselves.
- If someone is angry, remember it is not you they are really angry at – try not to take it personally. Allow the person to be angry but without abusing you. If they are out of control, tell them you will call/come back in 10 minutes or get them to call/come back.
- Always give people as much information as possible, and if you don't have it tell them you'll find out and get back to them. Do not lie or make things up to make it easier at that moment in time. It will come back to haunt you!
- If you can, always tell people they can come back or call you back or you will call them. It is very reassuring to people to know that there is that concern and care (of course practically you may not have time for much of this, but it does sometimes lessen anxiety and therefore people's demands!).
- If things feel out of control and you are out of your depth – get help – don't feel you have to do it on your own.

Monitoring and quality assurance

- Monitoring of VCCT programmes helps to track the key elements of an ongoing programme over time (inputs, outputs, assessing service quality)
- Monitoring answers the questions:
  - To what extent are planned activities actually realized?
  - How well are these services provided?
- Monitoring assesses the extent to which the way a programme is undertaken is consistent with its design or implementation plan.
- Monitoring in the VCCT context includes day-to-day record-keeping, a built-in system of checks and balances, and reporting daily activities to ensure that activities are going as planned towards the achievement of identified programme goals and objectives
- Key elements of VCCT programme that needs to be monitored to ensure quality of programme include:
  - Stigma
  - Reporting requirements of host organisation
  - Confidentiality
  - Information giving- Is the right information being passed on to clients?
  - Personal and couple risk assessment
  - Informed consent for HIV testing
  - Explanation of the HIV test and test results
  - Development of a personal risk-reduction plan
  - Psychological/emotional support
  - Appropriate referral
  - Documentation of care
  - VCCT clients follow-up
- It is equally important to assess the testing quality assurance. This will include:
  - Type of tests used.
  - Sensitivity.
  - Specificity.