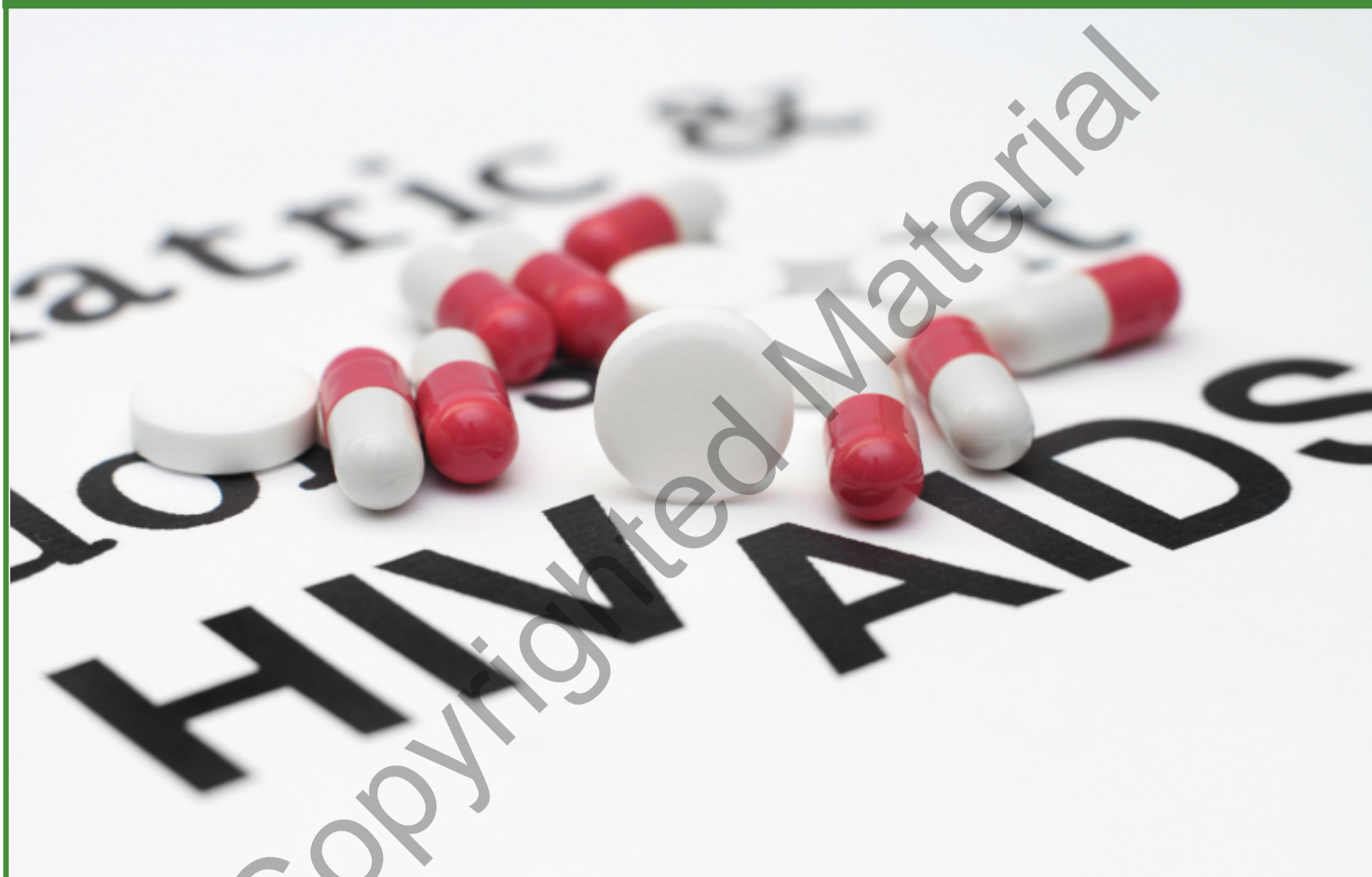


CLINICAL PHARMACY TRAINING MANUAL FOR HIV MEDICINE



AIDS Prevention Initiative in Nigeria



A P I N
Improving health, changing lives

January 2014



AIDS Prevention Initiative in Nigeria (APIN)

in collaboration with Northwestern University Center for Global Health

CLINICAL PHARMACY TRAINING MANUAL FOR HIV MEDICINE

January 2014

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PREFACE

Over 34 million adults and children are living with HIV worldwide, and Nigeria bears approximately ten percent of this global burden. Fortunately, life-saving antiretroviral drugs have changed the face of the HIV epidemic. With access to effective therapy, HIV-infected persons are now able to live long, active, healthy and productive lives. However, use of these drugs does not come without challenges, including adverse effects, drug-drug or drug-food interactions, as well as the need for near perfect adherence. A multidisciplinary approach to care for HIV-infected persons is optimal and has become the standard of care in HIV treatment programs throughout the world; pharmacists are an integral part of this multidisciplinary team. Clinical pharmacists who specialize in HIV therapy management have unique knowledge and skills related to antiretrovirals, including clinical pharmacology of the medications and adherence counseling, as well as adverse event and drug-interaction monitoring and management. These skills are linked to improved patient outcomes, which improves confidence within the healthcare team, knowing the pharmacist is effectively identifying, communicating, and managing unique antiretroviral considerations.

Realizing the importance of the pharmacist in providing optimal HIV treatment and care services, the AIDS Prevention Initiative in Nigeria (APIN), previously part of the Harvard School of Public Health's PEPFAR (President's Emergency Plan for AIDS Relief) program, places a high priority on clinical pharmacy training programs for Nigerian pharmacists caring for HIV-infected adults and children. To-date, APIN has sponsored ten centralized training programs in either basic or advanced topics of clinical HIV pharmacotherapy or pharmacovigilance, benefitting over 500 pharmacists throughout the country. In order to expand specialized learning opportunities in HIV therapy to even more pharmacists, APIN, in collaboration with Northwestern University Center for Global Health, is proud to release the Clinical Pharmacy Training Manual for HIV Medicine. The manual includes self-learning chapters, which are intended to provide introductory through advanced level learning opportunities for pharmacists providing care for HIV-infected patients. The beginning chapters form the framework for HIV medication management by providing an overview of HIV infection and course of disease, a review of key pharmacokinetic and pharmacodynamic considerations as they pertain to antiretroviral therapy, a review of important clinical pharmacy topics for each antiretroviral drug class, and a primer on the importance of antiretroviral adherence. The later chapters focus on special HIV-infected patient populations, antiretroviral drug interactions, common HIV co-morbidities and pre- and post-exposure prophylaxis.

Along with the expansion of access to antiretroviral care and treatment programs, we hope that the Clinical Pharmacy Training Manual for HIV Medicine will reach the hands of countless pharmacists across Nigeria, thus contributing to their role in providing pharmaceutical care and improving health outcomes for millions of people affected by HIV.

Kristin M. Darin, PharmD, BCPS (AQ-ID)
Oluremi O. Olaitan, BPharm, MSc, Cert in Pepi & Pvig
Kimberly K. Scarsi, PharmD, MSc., BCPS (AQ-ID)

FOREWORD

Over the past decade there has been tremendous progress in the provision of HIV prevention, care and treatment to populations with the highest burden. As the most populated nation in sub-Saharan Africa, the HIV prevalence in Nigeria coupled with its immense population has meant that the burden of disease is only second to South Africa worldwide. In early 2000, it was estimated that several million Nigerians were in need of antiretroviral therapy (ART). That year, the government of Nigeria purchased the first ART drugs to treat 10,000 adult patients in need. In 2004, the President's Emergency Plan For AIDS Relief (PEPFAR) funded the Harvard School of Public Health to support comprehensive prevention, care and treatment in Nigeria, in partnership with the AIDS Prevention Initiative in Nigeria (APIN) and the Northwestern University Center for Global Health. Transition of the program to APIN Ltd. occurred in 2012, now with 22 supported hospitals and clinics and over 160,000 patients having benefited from the program by receiving ART.

In order for the APIN program to provide the highest quality HIV care and treatment, the development of a robust capacity development and training program was required. This involved a continual targeted training program that was informed by site visits and assessments. As a result, the physical infrastructure development of clinics, labs and pharmacies was coupled with an equally strong educational program for the relevant health care workforce. As a result of these significant investments in human resources, we believe that the continued success and progress of the Nigerian response to HIV will be assured.

I am honored to introduce the Clinical Pharmacy Training Manual for HIV Medicine. This important reference manual has been written, by both Nigerian and US pharmacists and clinicians in collaboration; in its creation, it demonstrates the benefit of long-term partnership that has served as the cornerstone to the APIN program. I am confident that this manual will not only serve as an important training tool for our many dedicated pharmacists throughout the country, but also inform the national policy for pharmacy training in HIV medicine.

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Principal Investigator, Harvard/APIN PEPFAR program
Professor of Immunology and Infectious Disease
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FOREWORD

The HIV/AIDS treatment program of the Nigerian National Response was launched in 2000, when the former President Olusegun Obasanjo directed that 10,000 adults and 5,000 pediatric AIDS patients be initiated on Antiretroviral Therapy (ART). This was at a time when most health workers did not have much training or experience with the clinical use, important side effects, or patient education required for these important medications.

The AIDS Prevention Initiative in Nigeria (APIN) supported the Federal Ministry of Health in this endeavor at the very early stages through a grant from the Gates Foundation to the Nigerian Institute of Medical Research (NIMR) to develop the first sets of ART modules for the training of health workers in Nigeria. At that time, these same modules were used to train all cadres of health workers, though the modules were more suited for the training of physicians. After a few years, and as services were scaled up, it became necessary to design more specific modules that addressed the capacity gaps of other health care providers. APIN in collaboration with Northwestern University and the Harvard School of Public Health assembled a team of national and international experts to produce ART modules for the training of clinical pharmacists.

This training manual has been field tested at our many training sessions and we commend it to other stakeholders as a veritable training tool for clinical pharmacists who provide important services in HIV treatment programs. It is my hope that the adoption of this tool as a national training manual for pharmacists in Nigeria will help to ultimately improve the quality of care that AIDS patients receive from treatment facilities throughout Nigeria.

*Prosper Okonkwo, MD, FWACP
Chief Executive Officer
AIDS Prevention Initiative in Nigeria*

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Our thanks also go to the Northwestern University team for their technical support and collaboration in the development of this manual. We specially acknowledge the remarkable support and personal commitments of the program’s pharmacologists, and so to Drs. Kim Scarsi and Kristin Darin, we say thank you. To Professor Rob Murphy, we say a big thank you for your support, encouragement, and long-standing commitment to clinical training in the APIN program. To Drs. Chad Achenbach and Babafemi Taiwo, many thanks to each of you for your written contributions to this manual. Additionally, we would like to thank Adela Mizrachi for the design elements and finishing touches that she brought to this manual.

There were other contributors from the Northwestern Medicine community and beyond who helped to write the chapters within this manual and to each of you, we are thankful. This includes Dr. Ramona Bhatia and pharmacists (Drs.) Katie Allen, Jim Rhodes, Elise Wozniak, Jordan Ambrose, Angela Loo, and Sharon Seifert (University of Colorado).

We would also like to thank our many colleagues within the Harvard School of Public Health for their years of commitment to the growth and development of the APIN program. Specially, to Dr. Holly Rawizza, we say thank you for all the clinical training support you have given, as well as your contributions to this manual.

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We also wish to acknowledge the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), through which the APIN program is funded.

Last but not least, we want to thank you, the readers and users of this manual, for your commitment to continuing education and improving the lives of those affected by HIV/AIDS.

*Oluremi O. Olaitan, BPharm, MSc, Cert in Pepi & Pvig,
On behalf of the APIN team*

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CHAPTER 2: OVERVIEW OF HIV/AIDS AND PRINCIPLES OF ANTIRETROVIRAL THERAPY (ART)

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Purpose

The overall purpose of this chapter is to provide an introduction to concepts regarding infection with the human immunodeficiency virus (HIV), such as the viral structure, life cycle, and routes of transmission, as well as the mechanism of antiretroviral (ARV) drugs used to treat HIV and principles of antiretroviral therapy (ART).

Learning Objectives

The content of this chapter will enable the reader to:

- Know the burden of HIV disease globally and nationally
- Describe the basic structure of HIV and the steps of the HIV life cycle
- Discuss the possible modes of transmission of HIV
- Know the available classes of antiretroviral drugs and their target sites of action
- Summarize the principles for selection of combination ART
- Define virologic, immunologic and clinical treatment failure
- Recognize common ART regimens for first-, second- and third-line treatment

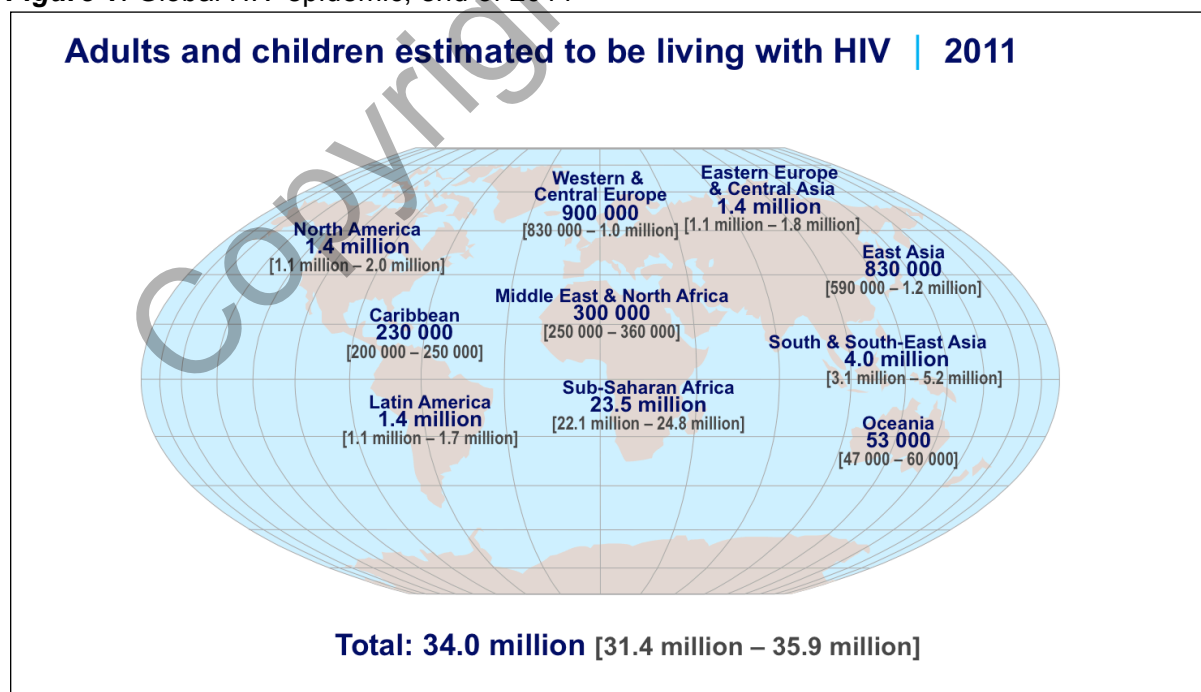
Introduction

Public awareness of the acquired immune deficiency syndrome (AIDS) started in 1981 when the United States (U.S.) Centers for Disease Control and Prevention (CDC) published a report about the occurrence of *Pneumocystis carinii* pneumonia (PCP) among men who have sex with men in major U.S. cities.¹ In 1983, a virus isolated at the Institut Pasteur in France was later confirmed in laboratories of the U.S National Institutes of Health (NIH) to be the causative agent for AIDS and the virus was named the human immunodeficiency virus (HIV). The first two cases of HIV/AIDS in Nigeria were identified in Lagos in 1985 and first reported in 1986 at the International AIDS Conference. In 1987 the first antiretroviral drug, zidovudine, was approved by the U.S. Food and Drug Administration, and the use of combination antiretroviral therapy (ART) became widespread in the U.S. and Europe a decade later. However, it was not until 2001 that ART became available in Nigeria as part of the National ART Program. By 2003, the scarce access to ART in developing countries prompted the World Health Organization (WHO) to declare HIV/AIDS a global health emergency. Since that time, global aid programs, such as the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) have provided support for ART scale-up programs benefiting millions of HIV-infected adults and children.

Epidemiology

The 2012 report on the global AIDS epidemic, published by the Joint United Nations Programme on AIDS (UNAIDS), estimates that 34 million adults and children were living with HIV by the end of 2011.² Sub-Saharan Africa bears 69% of the global burden with 23.5 million adults and children estimated to be living with HIV (Figure 1).

Figure 1: Global HIV epidemic, end of 2011



Source: UNAIDS November 2012 Core Epidemiology Slides^{2,3}

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HIV Transmission

Transmission of HIV can occur through three major routes:

- Sexual transmission
- Vertical transmission (mother-to-child)
- Parenteral transmission

Sexual Transmission

Sexual transmission of HIV is the major route of transmission worldwide. In Nigeria and other African countries, transmission is mostly through heterosexual vaginal intercourse. The risk of sexual transmission depends on many factors, such as:

- Probability that sexual partner is infected
- Type of sexual practice (Table 1); receptive anal intercourse carries the highest risk (Table 1)
- Number of sexual exposures
- Number of sexual partners
- Amount of virus present in the blood or body fluids of the infected partner
- Presence of other sexually transmitted diseases, in particular genital ulcer disease

Table 1: Risk of HIV transmission after a single event of sexual activity

Exposure Type	Risk of Infection
Receptive anal intercourse ⁷	1.4%
Receptive vaginal intercourse ⁸	0.08%
Insertive anal intercourse ^{9,10}	0.06% - 0.62% ^a
Insertive vaginal intercourse ^{11,12}	0.05%
Receptive oral sex with male partner ^{9,13}	Low, but not zero

^a Within this exposure type, the highest risk rate was reported in uncircumcised men¹⁰

Vertical Transmission

Vertical transmission, or transmission of HIV from mother to child can occur during intrauterine gestation, labour and delivery (approximately 50% of vertical transmission) and post-partum through breast-feeding. The transmission rates are greatest among mothers with a high viral load or advanced HIV disease, instrument assisted vaginal delivery, greater length of breast-feeding

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interrupted and doing so can lead to disease progression and further immunologic damage.²⁰ The benefits of ART include improved survival, reduced AIDS-related morbidity and decreased risk of HIV transmission.^{18,20,21} At this time, there is no cure for HIV.

Goals of ART

The primary goals of ART are to provide the following.^{22,23}

Goal 1: Potent, durable virologic suppression

The amount of HIV RNA in the plasma is an objective measure of ART efficacy. Therefore, the first goal of ART is to reduce the amount of HIV RNA (viral load) in the plasma to below the limit of assay detection (“undetectable”) *within 6 months of initiating ART* and to maintain the viral load below this level for as long as possible. Through viral suppression, the emergence of antiretroviral-resistant strains of HIV strains is also prevented or minimized.

Goal 2: Robust, prolonged immune recovery

As a result of viral suppression, the host immune system gains the chance of recovery. Therefore, another goal of ART is improvement in CD4+ cell counts to as high as possible, thus restoring and preserving immunologic function.

Goal 3: Reduction in HIV-associated morbidity and mortality

Through virologic suppression and immunologic recovery, additional benefit of ART includes a reduction in HIV-associated clinical events, such as opportunistic infections, as well as prolonged duration of life.

Goal 4: Improved quality of life

With the use of effective ART, persons infected with HIV are now living longer, healthier lives. The absence of symptomatic HIV and HIV-related illness contributes to a much-improved quality of life for those infected.

Goal 5: Prevent HIV transmission

By reducing the viral load to undetectable levels in plasma, effective ART has been shown to also be an effective means by which to prevent transmission of HIV. Thus, widespread access to effective ART provides public health benefit by reducing transmission of HIV in the community.

Several strategies can be followed to optimize ART to help ensure these goals are met. One such strategy is selection of individualized ART regimens to ensure a low pill burden, convenient dosing times, minimal adverse effects, and avoidance of drug-drug interactions based on each patient's lifestyle, preferences and co-morbidities. Additionally, ongoing patient counselling to convey the importance of adherence is also vital to achieving these goals. Refer to *Chapter 8: Adherence to ART*.

When to Start ART

The indications for initiation of ART are dynamic and may vary between different organizations and countries. At this time, most developing countries, Nigeria included, currently follow the 2010 WHO recommendations on when to start ART.²⁴ These recommendations are summarized in Table 2.

Table 2: When to start antiretroviral therapy^{23,24}

Patient Population	2010 WHO and Nigerian Recommendation
HIV+ adults	CD4+ $\leq$ 350 cells/mm ³ (regardless of symptoms, even if asymptomatic or WHO clinical stage 3 or 4 (Annex A) at any CD4+ cell count
HIV+ pregnant women	Same as above for HIV+ adults
HIV/TB co-infection	Presence of active TB disease at any CD4+ cell count
HIV/HBV co-infection	Individuals who require treatment for their HBV infection (ie. active chronic HBV) at any CD4+ cell count

TB: tuberculosis, HBV: hepatitis B virus

What to Start

In addition to country-specific guidelines, where possible, additional consideration should be given to patient-specific factors in order to select an individualized ART regimen. Some factors to consider include:²²

- Comorbid conditions (eg. liver disease, renal disease, cardiovascular disease, psychiatric disease, or TB)
- Potential adverse drug effects;
- Potential drug interactions with other medications;
- Pregnancy or pregnancy potential;
- Gender and pre-treatment CD4 count, if considering nevirapine;
- Patient adherence potential; and
- Convenience* (eg. pill burden, dosing frequency, and food considerations)

* When available and feasible based on other factors (eg. renal function), the use of fixed-dose combination (FDC) tablets is preferred.

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Update: 2013 WHO Recommendations

On June 30 2013, the WHO released new recommendations on the use of ARVs for treating and preventing HIV infection.²⁵ Some of the key recommendations include:

When to start:

- ART should be initiated in individuals with CD4 count ≤ 500 cell/mm³ regardless of WHO clinical stage, as well as individuals with HIV and tuberculosis or hepatitis B virus co-infection, and partners with HIV in serodiscordant couples
- All pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk, or lifelong, if possible (based on programmatic guidance).
- ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count.

What to start:

- The preferred first-line ART regimen for all adults (including pregnant or breastfeeding women) is the once daily FDC (TDF + 3TC (or FTC) + EFV).

Monitoring response to ART:

- Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure.

At the time this manual was going to print, many of these 2013 WHO recommendations had not been fully implemented into Nigerian HIV treatment guidelines. However, it is important to be aware of these new recommendations, as they are likely to be the way of the future.

Summary

Over the past 30 years significant scientific advances have allowed for improved understanding of HIV, including its structure, modes of transmission, and replication life cycles. Simultaneously, the introduction and evolution of potent and durable ART has occurred, which has been demonstrated to improve infected persons' quality of life and reduced HIV-related mortality. Understanding the basic concepts of the HIV life cycle, classes of antiretroviral agents, and guiding principles for selecting and monitoring the efficacy of antiretroviral therapy is important for providing optimal pharmaceutical care to HIV-infected patients. Choice of ART, as well as when to start ART, is a dynamic field, as is evident by the recent 2013 WHO recommendations;²⁵ therefore, consultation with an up-to-date resource, including WHO or US treatment guidelines that are updated frequently, is strongly recommended.

Self-Assessment Questions

1. What is the approximate seroprevalance and number of persons infected with HIV living in Nigeria?
 - a. 8% and 3.4 million individuals
 - b. 8% and 10 millions individuals
 - c. 4.1% and 3.4 million individuals
 - d. 4.1% and 10 million individuals
2. Which type of sexual activity carries the highest risk of HIV transmission?
 - a. Receptive anal intercourse
 - b. Receptive vaginal intercourse
 - c. Insertive vaginal intercourse
 - d. Receptive oral intercourse
3. Which of the following best describes the mechanism of action of efavirenz (EFV)?
 - a. As a nucleoside analogue, it blocks the active site of reverse transcriptase enzyme and terminates the elongating HIV DNA strand.
 - b. It binds near the active site of reverse transcriptase enzyme to alter the protein and block the transcription of HIV single-stranded RNA to double-stranded DNA.
 - c. It blocks binding and fusion of the HIV particle with the human CD4+ cell membrane
 - d. It binds to the protease enzyme and blocks the production of HIV proteins required for proper virus assembly
4. Which of the following is an indication to start ART?
 - a. Asymptomatic patient with CD4+ cell count ≤ 350 cells/ μ l
 - b. HIV and active pulmonary TB co-infected patient with CD4+ cell count of 425 cells/ μ l
 - c. HIV and active HBV co-infected patient with CD4+ cell count of 450 cells/ μ l
 - d. All of the above
5. Which of the following is a preferred initial ART regimen (first-line)?
 - a. AZT + ddI + EFV
 - b. FDC (d4T + 3TC + NVP)
 - c. AZT + TDF + EFV
 - d. FDC (TDF + 3TC + EFV)
6. A 35 year-old HIV-infected woman initiated FDC (TDF + 3TC) + NVP three years ago. At time of initiation, her CD4+ cell count was 85 cells/ μ l. One year later, her HIV RNA was undetectable (< 200 copies/mL) and CD4+ cell count was 367 cells/ μ l. Today she presents with shortness of breath and cough. Her chest X-ray suggests *Pneumocystis carinii* pneumonia. An HIV RNA obtained last week is 60,000 copies/mL and CD4+ cell count is 145 cells/ μ l. The patient reports excellent adherence for the past 12 months. The patients meets which of the following criteria for first-line ART treatment failure?
 - a. Virologic failure
 - b. Immunologic failure
 - c. Clinical failure
 - d. All of the above

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CHAPTER 3: NUCLEOS(T)IDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

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Purpose

The overall purpose of this chapter is to provide an overview of the nucleoside reverse transcriptase inhibitor (NRTI) class of antiretrovirals by describing their mechanism of action, clinical pharmacology, drug interaction potential, adverse effects and resistance principles.

Learning Objectives

Upon completion of the chapter, the participant should be able to:

- Explain the mechanism of action of NRTIs
- Describe the role of the dual NRTI therapy as the backbone of combination antiretroviral therapy (ART)
- Describe dosing and administration considerations of each NRTI
- Identify common and/or serious adverse effects associated with the NRTIs
- Understand considerations for NRTI use among special patient populations
- Describe basic principles related to resistance within the NRTI class

Introduction

The nucleos(t)ide reverse transcriptase inhibitors (NRTIs) were the first class of antiretroviral drugs available for the treatment of HIV infection. The U.S. Food and Drug Administration (FDA) approved the first NRTI, zidovudine (AZT or ZDV), for monotherapy against HIV infection in 1987.¹ Although it provided potent inhibition of viral replication, within a few years HIV developed resistance to zidovudine when it was given as monotherapy. Today, there are seven NRTIs commercially available. In addition to zidovudine, this includes lamivudine (3TC), emtricitabine (FTC), abacavir (ABC), didanosine (ddI), stavudine (d4T), and tenofovir (TDF).

Current World Health Organization (WHO) antiretroviral treatment guidelines recommend the use of two NRTIs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) as initial antiretroviral therapy (ART) for HIV-1-infected patients.² The two NRTIs are often referred to as the “backbone” of the ART regimen. Specifically, current Nigerian recommendations suggest the use of tenofovir plus lamivudine or emtricitabine or zidovudine plus lamivudine as the “preferred” NRTI backbones for first-line ART. This is based on evidence supporting their efficacy and safety, as well as considerations of cost and availability in resource-limited settings.

Mechanism of Action³

During the HIV life cycle, the virus enters the human lymphocyte releasing viral RNA and viral proteins such as reverse transcriptase (RT) into the cytoplasm. Reverse transcriptase then acts by transcribing the viral RNA into DNA, which then becomes integrated into the host cell DNA.

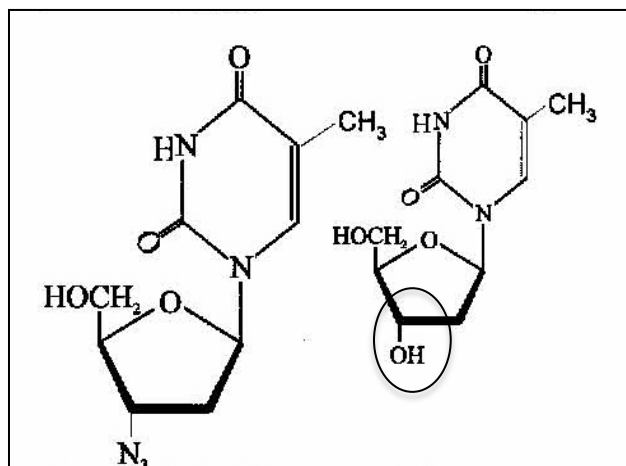
The NRTIs act by mimicking the natural deoxynucleoside triphosphate that the reverse transcriptase utilizes to create the viral DNA (Table 1). The administered form of the NRTI is phosphorylated intracellularly to its active triphosphate form and then added to the growing viral DNA strand. The NRTIs inhibit viral replication by competing with endogenous nucleotides for binding at the catalytic site on reverse transcriptase. Once incorporated, because the NRTIs lack the 3' hydroxyl group found on the natural deoxynucleoside triphosphate, additional nucleotides cannot be added to the growing chain and so DNA polymerization is halted, resulting in the termination of viral DNA (Figure 1).

Table 1: NRTI – nucleoside pairs

	NRTI	Nucleoside
Pyrimidine	Stavudine	Thymidine
	Zidovudine	Thymidine
	Emtricitabine	Cytosine
	Lamivudine	Cytosine
Purine	Abacavir	Guanosine
	Didanosine	Adenosine
	Tenofovir	Adenosine

Each of the nucleoside RTIs requires the addition of *three* phosphate moieties; whereas, tenofovir, the only nucleotide RTI, requires *two* additional phosphorylations. There does not appear to be any clinical advantage of NtRTIs versus the NRTIs. Therefore, for simplicity, the NRTI abbreviation will be used to also refer to the NtRTI from this point forward.

Figure 1: Structural similarity between thymidine and zidovudine



Source: Clinical Care Options

Zidovudine (left) lacks a 3' hydroxyl group (circled), which is present on the naturally occurring deoxynucleoside triphosphate, thymidine (right), thus resulting in DNA chain elongation termination.

Pharmacology

The NRTIs are all readily absorbed following oral administration with variable bioavailability ranging from 25% with tenofovir (fasting) to 93% with emtricitabine.^{3,4} In general, NRTIs can be administered without regard to food. An exception to this is didanosine, which should be taken on an empty stomach in adults. Refer to the drug-specific sections, below, and *Chapter 13: Antiretroviral Drug-Drug and Drug-Food Interactions* for additional information on how food effects NRTI pharmacology.

The NRTIs are not affected by nor impact the cytochrome P450 enzyme system. Rather, most of the NRTIs are primarily eliminated by renal excretion and require dose adjustment in patients with renal impairment. The recommended NRTI renal dose adjustments are based on patients' glomerular filtration rate or creatinine clearance estimated using the Cockcroft-Gault equation (*see Dosing*). Abacavir is the only NRTI that does not require any dosage adjustment in patients with renal impairment, as it is primarily eliminated by alcohol dehydrogenase metabolism. Recommended adult doses are provided below (*see Dosing*).

Dosing

Table 2 provides recommended doses for adult patients with normal and impaired renal function. When NRTIs are used as part of a fixed-dose combination (FDC) tablet, refer to the recommended dose by individual drug. In most cases, use of the FDC tablets cannot be accommodated in patients with renal impairment because the proper dosage adjustments cannot be made; therefore, use of single-line NRTI formulations is preferred.

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polymerase gamma, an enzyme responsible for repair of oxidative damage to mitochondrial DNA, which may result in toxicity to tissues that have high metabolic activity. Mitochondrial toxicity can manifest clinically as peripheral neuropathy, myopathy, lactic acidosis, hepatic steatosis, pancreatitis, and lipodystrophy. Mitochondrial toxicities are more commonly seen with NRTIs that are potent inhibitors of the human mitochondrial DNA polymerase gamma such as stavudine and didanosine as compared to other NRTIs, such as abacavir or tenofovir.¹¹

Lactic Acidosis

Lactic acidosis is one of the best-characterized serious adverse events resulting from NRTI-associated mitochondrial toxicity. Incidence rates have been described as 0.1 to 0.4% in developed countries to approximately 1.5 to 2% in developing countries.^{12,13} Onset may be gradual and early symptoms often include gastrointestinal disturbances, weight loss and fatigue. In severe cases, a rapid progression of disease including respiratory distress, tachycardia, and multi-organ failure may follow. Mortality has been reported in 7-30% of cases in HIV-infected patients.¹⁴ Identified risk factors include female gender, advanced HIV disease, age above 40 years, and use of didanosine and/or stavudine.¹⁵ This higher rate in developing countries may be due to the higher use of stavudine in those settings. In patients who have experienced lactic acidosis on one of these NRTIs, substitution with an NRTI less likely to cause lactic acidosis, such as tenofovir or abacavir, or to a non-standard antiretroviral regimen excluding the NRTI class, may be warranted.

Hepatotoxicity and Hepatic Steatosis

Varying degrees of hepatotoxicity have been reported in HIV-infected patients receiving NRTI-containing ART. Asymptomatic elevation in liver function tests occurs in approximately 1-5% of patients; hepatomegaly and fatal hepatic failure have also been reported on rare occasion. Lactic acidosis is a common co-morbidity and use of stavudine and/or didanosine are reported risk factors.

Also a result of mitochondrial toxicity, non-alcoholic fatty liver disease, is another serious complication reported with the use of NRTI therapy that may progress to hepatic steatosis and cirrhosis. Many patients presenting with hepatic steatosis also have lactic acidosis and lipodystrophy. It has been reported that approximately 30-40% of HIV-infected patients may have some degree of hepatic steatosis, which is slightly higher than estimates for the general population. In addition to HIV itself, some potential risk factors include obesity, hepatitis co-infection, and use of certain NRTIs, including stavudine, didanosine, and zidovudine.¹⁶

Lipodystrophy

Lipodystrophy is the redistribution of fat including both lipoatrophy (fat wasting of arms, legs, face, buttocks) and hyperadiposity or lipohypertrophy (fat accumulation in the belly, breasts, back of the neck). The thymidine analogues (stavudine and zidovudine) are the NRTIs most commonly implicated with development of lipodystrophy. Long-term use of NRTIs in combination with PIs increases the risk for lipodystrophy. In two African studies, the prevalence of moderate to severe

lipodystrophy was reported between 31-34% among patients receiving stavudine or in some cases zidovudine as part of the ART regimen.¹⁴

Drug interactions

Because NRTIs do not undergo metabolism via the CYP450 pathway, fewer drug-drug interactions are expected with their use as compared to PIs and NNRTIs. However, there are still some notable drug-drug interactions that are common within this class, including pharmacodynamic interactions that occur between various NRTIs. The NRTI pairs to avoid are mentioned below in Table 3. These and additional drugs of concern are detailed in the drug-specific sections that follow.

Table 3: NRTI pairs to avoid^{2,5}

NRTI Pairs to Avoid	Rationale
Zidovudine + Stavudine	Antagonistic
Lamivudine + Emtricitabine	Therapeutic duplication, no additive benefit
Stavudine + Didanosine	Increased risk for peripheral neuropathy, lactic acidosis, and pancreatitis
Tenofovir + Didanosine	High rate of early virologic failure and inferior immunologic outcomes

Special Patient Populations

Co-infection with HIV and Hepatitis B Virus

Three NRTIs have potent activity against hepatitis B virus – tenofovir, lamivudine and emtricitabine. In patients co-infected with HIV and hepatitis B, at least two NRTIs active against both viruses should be included in the ART regimen. As such, HIV/hepatitis B co-infected patients should receive an ART regimen that includes an NRTI backbone of tenofovir plus either lamivudine or emtricitabine.^{2,5} Furthermore, it is important to remember that the NRTIs are not only contributing to HIV suppression, but are also suppressing replication of hepatitis B virus. As such, in co-infected patients, frequent monitoring of liver function is required if NRTIs are discontinued for any reason, as cases of severe exacerbation of hepatitis have been reported.

Pregnancy^{17,18}

The use of NRTIs in HIV-infected pregnant women will be covered in more detail in *Chapter 11: Key Principles in PMTCT of HIV*. Though briefly, NRTIs are widely used in HIV-infected pregnant women, both as treatment for the mother as well as PMTCT. Unique among the NRTI class (as

compared to NNRTIs and PIs) is their excellent placental transfer, providing antiviral protection to the fetus in-utero. Given its extensive use in pregnant women, zidovudine, often in combination with lamivudine, has historically been the preferred NRTI backbone for pregnant women. However, other dual NRTI combinations may be used in pregnant women, particularly if the woman is already virologically controlled on an alternate regimen (eg. tenofovir plus lamivudine). One notable dual NRTI backbone to avoid in this patient population is stavudine plus didanosine as fatal cases of lactic acidosis and pancreatitis have been reported in HIV-infected pregnant women receiving both of these agents.

Paediatrics

The use of NRTIs in HIV-infected, paediatric patients, as well as in HIV-exposed infants as part of PMTCT, will be addressed fully in *Chapter 12: Key Principles for HIV Care and Treatment in Infants and Children*.

Resistance

Resistance to NRTIs occurs via two mechanisms: (1) the virus prevents the NRTI from being incorporated into the growing DNA chain, or (2) the virus removes the NRTI from the DNA chain allowing DNA transcription to continue.¹⁹ Mutations that allow the virus to block the NRTI from joining the growing DNA chain include the M184V and K65R mutations among many others. As a single point mutation, the presence of the M184V substitution confers high-level resistance to lamivudine and emtricitabine. This mutation can appear rapidly when either drug is given as monotherapy. These mutant strains replicate more slowly than wild-type strains, that is they are “less fit”, and may also improve susceptibility to zidovudine and tenofovir.²⁰ Because of this potential benefit of M184V, lamivudine or emtricitabine are sometimes maintained as part of an ART regimen even when the virus is known to be resistant to these drugs.⁵ K65R, the signature tenofovir-associated mutation, can confer resistance to all NRTIs except zidovudine. In addition to tenofovir, K65R is often selected by exposure to abacavir and didanosine.

A group of mutations termed the thymidine analogue mutations (TAMs) are responsible for allowing the virus to remove the NRTI from the DNA strain to allow DNA replication to resume. These mutations occur slowly and can also confer resistance to all NRTIs but are most common with regimens that include zidovudine and stavudine.

Given the lack of ready access to genotypic resistance testing in resource-limited settings, current WHO recommendations for which NRTIs to include in second-line ART are largely based on basic principles of NRTI resistance, including which NRTI(s) are most likely to have retained activity following first-line virologic failure. For example, if a thymidine analogue (zidovudine or stavudine) is used in first-line ART, then a purine analogue (eg. tenofovir) should be used as part of second-line ART and vice-versa.²

NRTI-Specific Considerations

Zidovudine (AZT, ZDV)¹

A. Pharmacology

Zidovudine is rapidly absorbed following oral administration and has an oral bioavailability of 64%. Administration with food does not alter zidovudine pharmacokinetics, so it can be taken without regards to meals. Zidovudine has a very short plasma half-life (approximately 0.5-1 hours), as well as a short intracellular half-life (approximately 3 hours); therefore, the oral formulation must be taken twice daily. An intravenous formulation of zidovudine is available and used in some pregnant women during labor and delivery; however, its availability is limited to developed countries. Zidovudine is metabolized by glucuronidation and its major metabolite of is then excreted renally.

B. Special Patient Populations

Renal Impairment: Because its major metabolite is excreted renally, there is a need for dosage adjustment in patients with end-stage renal disease (CrCl <15 ml/min) or those on dialysis (see *Dosing*).

Hepatic Impairment: Given its extensive hepatic metabolism, it is expected that zidovudine clearance would be reduced in patients with hepatic impairment; however, there are no recommendations for a reduced dose in such patients.

C. Adverse Effects

When initiating zidovudine therapy, adverse effects such as headache (63%), muscle aches ($\geq 5\%$), fatigue (53%), and mild gastrointestinal disturbances, such as nausea (51%) and vomiting (17%), commonly occur. The constellation of symptoms is often “flu-like” with or without fever. However, these effects are usually transient and resolve after a few weeks of therapy. Patient counseling at initiation of therapy is important so that patients know what to expect and have reassurance that many of the early-onset bothersome adverse effects will likely resolve within a few weeks.

Bone Marrow Suppression: Another common adverse effect associated with zidovudine is bone marrow suppression, typically macrocytic anemia or neutropenia. This can manifest clinically as persistent severe weakness and fatigue as early as 2-4 weeks after initiation of therapy or after long-term use. For some patients, anemia is treatment limiting and zidovudine must be substituted with another NRTI. This is generally recommended when hemoglobin is less than 7 g/dL and/or absolute neutrophil count is less than 750 cells/mm³.² In developed countries, the incidence rate of zidovudine-associated severe anemia (hemoglobin < 6.5 g/dL) is only 1% in adults; however, estimates in resource-limited settings are higher, approximately 7%.¹⁴ The difference is likely attributable to the lower baseline hemoglobin levels in patients in developing countries, due to other infections that may suppress bone marrow (eg. hookworm, tuberculosis, malaria). These and other common causes of anemia should also be considered (eg. iron or folic acid deficiencies) and treated as appropriate.

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Self-Assessment Questions

1. Which of the following adverse effects have been associated with zidovudine use?
 - a. Anaemia
 - b. Myopathy
 - c. Lipoatrophy
 - d. Fingernail discoloration
 - e. All of the above
2. Which of the following NRTI drugs are active against hepatitis B virus?
 - a. Abacavir, Emtricitabine, and Lamivudine
 - b. Emtricitabine, Lamivudine, and Tenofovir
 - c. Lamivudine, Tenofovir, and Zidovudine
 - d. Emtricitabine, Tenofovir, and Stavudine
 - e. Abacavir, Lamivudine, and Zidovudine
3. Which of the following NRTI pairs is NOT recommended as part of antiretroviral therapy?
 - a. Zidovudine + Lamivudine
 - b. Zidovudine + Stavudine
 - c. Tenofovir + Lamivudine
 - d. Tenofovir + Emtricitabine
 - e. Abacavir + Lamivudine
4. Which of the following statements is true?
 - a. Didanosine and stavudine can be safely co-administered as part of ART
 - b. Tenofovir has been associated with renal impairment; important dosage adjustments are required in patients with CrCl < 50 ml/min.
 - c. Lamivudine use can commonly result in development of lipoatrophy
 - d. Abacavir frequently causes treatment-limiting anaemia.
 - e. Zidovudine has been associated with a hypersensitivity reaction, most common in patients with an HLA-B*5701 allele.
5. Which of the following NRTIs does not require dosage adjustment in patients with renal impairment?
 - a. Didanosine
 - b. Emtricitabine
 - c. Abacavir
 - d. Stavudine
 - e. Tenofovir

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CHAPTER 9: PHARMACEUTICAL CARE FOR PERSONS LIVING WITH HIV

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Purpose

The purpose of this chapter is to enable the pharmacist to understand patient-centered pharmaceutical care and how it applies to the management of persons living with HIV. At the end of the chapter, the reader should be able to identify the steps needed to develop a patient-centered care plan for HIV-infected patients receiving antiretroviral therapy.

Learning Objectives

The content of this chapter will enable the reader to:

- Describe the key elements of a pharmaceutical care plan
- Understand the major functions of pharmaceutical care
- Define the phrase “drug therapy problem”
- Recognize categories of drug therapy problems that relate to medication indication, safety, efficacy and adherence and provide examples of each, as they relate to pharmaceutical care for an HIV-infected patient
- List the main steps of the pharmaceutical care process and describe each step
- Describe expanded functions of the pharmacist who provides care for patients infected with HIV

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time, the *pharmaceutical care* model is most recognizable on an international level, so will remain the focus on this chapter.

Key Elements of a Pharmaceutical Care Model²

As defined by ASHP,² “the principle elements of pharmaceutical care are that it is *medication related*; it is *care* that is *directly provided* to the *patient*; it is provided to produce *definite outcomes*; these outcomes are intended to improve the patient’s *quality of life*; and the provider accepts personal *responsibility* for the outcomes.” Each of these key elements will be further discussed below.

Medication Related

Pharmaceutical care relates to medication provision and medication *use* for individual patients. Thought should be paid as to whether medication therapy is appropriate or inappropriate, based on indication or co-morbid conditions, as well as based on dosage, route of administration, duration of therapy. Also considered by this principle element are provision of medication information to the patient and patient counseling.

Patient-Centered Care

The second principle element of pharmaceutical care is that is patient-centered care. In order to help a patient with his or her medication-related issues, it is first necessary to understand *what the patient wants and needs*, which therefore requires the pharmacist to understand *how the patient thinks about his illness and his medications*.¹⁰ During this process, the patient and pharmacist engage in what has been termed a *therapeutic relationship*, or a partnership or alliance with the patient, formed in order to help optimize the patient’s medication experience and clinical outcomes.¹¹

Definite Outcomes

Through provision of pharmaceutical care, the pharmacist aims to improve certain therapeutic outcomes, including disease cure, halting, slowing, or prevention; and/or symptom relief or elimination. In their *Statement on Pharmaceutical Care*, ASHP cites three major functions of pharmaceutical care that must be performed in order to achieve such outcomes:^{1,2}

- (1) *Identifying potential and actual medication-related problems*
- (2) *Resolving actual medication-related problems, and*
- (3) *Preventing potential medication-related problems*

Categories and components of medication-related problems (or drug therapy problems) will be further described below (see *Drug Therapy Problems* section).

Quality of Life

Various tools now exist to aid in assessment of quality of life and researchers are continually evaluating the pharmacist’s role in improving quality of life.¹²⁻¹⁵ As part of the pharmaceutical care plan, pharmacists should assess objective and subjective measures related to the drug therapy problem at baseline and then, with the pharmacist’s assistance, establish reasonable quality of life goals for the drug therapy interventions.

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Table 5: Common causes of drug therapy problems related to **adherence**

Category	Cause	Description
Adherence	<i>Does not understand instructions</i>	The patient does not understand how to properly take or use the drug product and dosage regimen.
	<i>Cannot afford drug product</i>	The patient cannot afford the drug therapy recommended or prescribed.
	<i>Patient prefers not to take</i>	The patient prefers not to take the drug therapy as instructed.
	<i>Patient forgets to take</i>	The patient does not remember to take sufficient doses of the medication.
	<i>Drug product not available</i>	Sufficient supply of the drug product is not available to the patient.
	<i>Cannot swallow or administer drug</i>	The patient is not able to swallow or administer the drug therapy as intended.

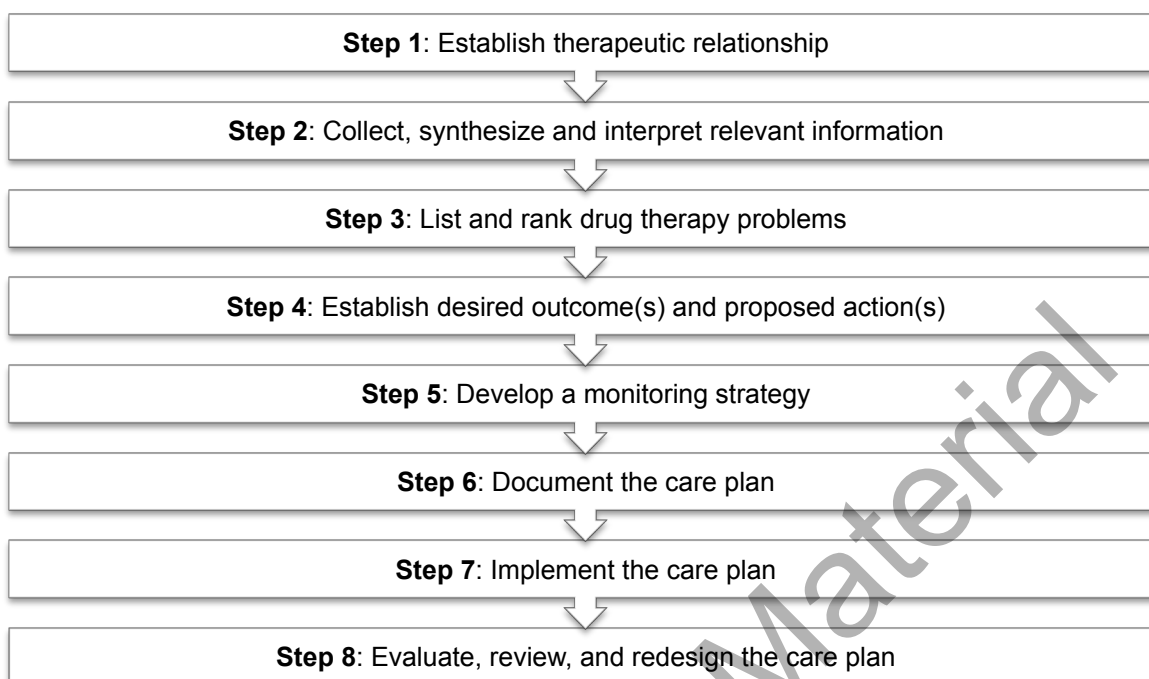
Source: Cipolle RJ et al. 2012¹⁰

Examples of HIV drug therapy problems related to **adherence** include:

- Several HIV-infected children at a rural clinic miss three days of ART due to a local stock-out of their regimen, zidovudine/lamivudine/nevirapine pediatric fixed dose tablets. (*Adherence > Drug product not available*)
- During a religious holiday, a patient decides to not take her morning dose of antiretroviral drugs because she is fasting and the medication is to be taken with food. (*Adherence > Patient prefers not to take*)
- After experiencing a stroke, an older gentleman can no longer swallow his ART regimen, consisting of tenofovir/emtricitabine/efavirenz. (*Adherence > Cannot swallow drug*)

Steps of a Pharmaceutical Care Plan

There are various methods for the provision of pharmaceutical care. The recommendations and steps for designing a pharmaceutical care plan also have evolved with time. However, ASHP provides guidance on a standard method for pharmaceutical care, from which the following eight steps have largely been adapted (Figure 1).¹⁸

Figure 1: Steps of a pharmaceutical care plan¹⁸

These steps may be adapted to any pharmacy practice setting (eg. clinic, hospital, retail), and will aid the pharmacist in achieving the goals of pharmaceutical care. Each step will now be discussed in further detail.

Step 1. Establish therapeutic relationship

To provide pharmaceutical care the pharmacist must see the patient, explain the proposed relationship, obtain information and seek cooperation, trust and permission. The initial encounter occurs when the pharmacist interviews the patient personally upon admission or presentation of prescription. The therapeutic relationship needs to be maintained throughout the care process, so contact with the patient should occur regularly.

In some instances, for example, when the patient is comatose, legally under age or mentally incompetent, the pharmacist may need to establish a surrogate relationship with the patient's family or caregiver. In other instances, the pharmacist may need to rely solely on the physician, nurse, another pharmacist, or another healthcare provider to relay information pertinent to the care plan on the patient's behalf.¹⁹

The primary resources required to establish the therapeutic relationship are:²⁰

- Access to the patient
- A clear and articulate definition of the purpose for pharmaceutical care
- Ability to communicate with the patient

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Illustrative case study, step 3

RB is a 54 year-old male recently diagnosed with HIV and tuberculosis (TB). RB is a known alcoholic. CD4+ cell count = 125 cell/mm³, HIV RNA (viral load, VL) > 750,000 copies/mL, Hb = 12 g/dL, ALT = 30 units/L, SCr = 95 mmol/L, weight = 59 kg. Standard 4-drug anti-tuberculous therapy (rifampin, isoniazid, pyrazinamide, ethambutol, RHZE) was initiated 4 weeks prior.

The patient is presenting to the clinic for initiation of ART. You recommend that RB initiate efavirenz (EFV) 600 mg daily at bedtime plus zidovudine/lamivudine (AZT/3TC) 300/150 mg fixed-dose combination (FDC) twice daily. One week later, RB returns to clinic with complaints of dizziness and trouble sleeping. He is worried that the drugs are poisoning his body and mind.

Question: Identify drug therapy problems for this patient. Indicate whether they are actual or potential problems. Rank the drug therapy problems in order of priority.

Answer:

Drug therapy problem	Description	Actual or Potential	Priority Rank
Unnecessary drug therapy	Chronic alcohol is an unnecessary drug, which is a risk factor for drug non-adherence	Potential	3
Adverse drug reaction	Complaints of dizziness and trouble sleeping, both which are known side effects associated with efavirenz use	Actual	1
Needs additional therapy	Cotrimoxazole is indicated for preventative therapy in HIV-infected patients with CD4+ cell counts below 350 cells/mm ³	Actual	2
Dosage too low	Rifampicin may reduce efavirenz plasma concentrations when given concomitantly. Consider increasing the dose of efavirenz to 800 mg daily (weight=59 kg) and/or monitor patient closely for virologic efficacy.	Potential	4
Adherence	Although patient does not report missing any doses, adherence should be reinforced at each visit. Given the adverse effects, risk of non-adherence is high.	Potential	5

Hb = haemoglobin, ALT = alanine aminotransferase, SCr = serum creatinine

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among care providers. Although many electronic medical records are not specifically designed to integrate the pharmaceutical care plan with other providers' plans, the electronic system regardless provides many useful features, including a reliable, consistent structure within which pharmaceutical care plans can be documented and data retrieved for future patient care or program evaluation purposes.

Step 7. Implement the care plan

The pharmaceutical care plan is implemented with the agreement of the patient and, where possible within the context of the overall care of the patient, in cooperation with other members of the health care team. It is critically important to the success of the care plan that the patient is properly educated, is in agreement and actively participates along with other care givers in the implementation of the care plan.

Step 8. Evaluate, review, and (if needed) redesign the care plan.

Actual outcomes are evaluated in relation to the therapeutic objectives to determine whether drug therapy problems have been resolved. If outcomes are not achieved, the care plan should be reviewed. The actual outcomes may then be accepted as being the best achievable for the patient, or an alternative plan may be necessary. The plan should develop as original drug therapy problems resolve and new drug therapy problems appear, which require resolution.³

Providing Pharmaceutical Care to HIV-Infected Patients

Since 1996, when the use of highly active antiretroviral therapy (ART) was shown to significantly reduce mortality, HIV has become a manageable, chronic, lifelong illness.²⁷ Many persons have been living with HIV for over 30 years and new evidence-based knowledge of the pathophysiology, immunology, and treatment of the disease continues to evolve as scientists continue the pursuit of a cure. However, management of HIV is not without challenges and complications. Use of a multidisciplinary healthcare team, not limited to physicians, pharmacists, nurses, social workers, and counselors, is recommended to best manage HIV-infected patients' multiple medical, social, and psychiatric needs.²⁸

Benefits among HIV-infected Patients

Pharmacists have played a key role in the management of HIV-infected patients for over twenty years. The number of FDA-approved antiretroviral drugs has increased to over 30, with eight new approvals occurring within the past seven years and several investigational products in late phases of development. This rapid evolving field introduces numerous challenges for optimal pharmaceutical care, as regimen appropriateness, adherence, and drug interactions, to name a few, must routinely be evaluated for each patient on ART.

In addition to improving ART adherence, pharmacist involvement in HIV care has also been shown improve other clinical outcomes, including increasing CD4+ T-cell counts, decreasing HIV viral load, and reducing the occurrence of ART-related adverse events.²⁹ Additionally, active

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Table 10: Expanded functions of the HIV-specialized pharmacist

1.	Monitoring efficacy of the regimen by tracking CD4+ counts and viral load, when appropriate, and providing input about patients' response to therapy to other members of the health care team.
2.	Providing individualized health promotion recommendations and disease prevention advice and activities, such as HIV, tuberculosis or malaria prevention practices (eg. ensuring appropriate patients are receiving cotrimoxazole or isoniazid for prevention).
3.	Referring patients to other health care or social service providers, such as counselors, social service groups (eg. alcohol or narcotic dependency support groups) or other peer support groups, in conjunction with the patient's primary care provides.
4.	Educating the community about modes of HIV transmission and effective techniques for prevention of transmission.
5.	Performing research related to antiretroviral therapy (eg. adherence, quality of life, and pharmacokinetics).
6.	Monitoring adherence to antiretroviral therapy and working with patients and other care providers to address barriers to adherence, including identifying and following up on patients who miss appointments for antiretroviral refills.
7.	Working with providers and patients to identify and appropriately manage antiretroviral-related adverse drug reactions, as well as report such reactions to local and national drug authorities for surveillance purposes.
8.	Working with providers and patients to identify and appropriately manage antiretroviral-related drug-drug or drug-food interactions.

Adapted from ASHP Statement on the Pharmacist's Role in the Care of Patients with HIV Infections, 2003²⁴

Summary

Pharmaceutical care is a prospective patient-centered practice with a focus on identifying, resolving and preventing drug therapy problems. The objectives of pharmaceutical care are achieved through a patient centered process comprising of four major steps: assess the patient drug therapy needs, develop a care plan to meet those needs, implement the care plan and evaluate and review the care plan.²¹ Pharmacists who provide patient-centered care to HIV-infected patients are responsible for having a good knowledge of standard antiretroviral treatment guidelines, principles of antiretroviral therapy, and knowledge of antiretroviral pharmacology and antiretroviral-related side effects and drug interactions, as well as clinical skills required to deliver pharmaceutical care. Together with an interdisciplinary healthcare team, pharmacists play a key role in improving clinical outcomes among HIV-infected patients.

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CHAPTER 13: ANTIRETROVIRAL DRUG-DRUG AND DRUG-FOOD INTERACTIONS

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Purpose

The overall purpose of this module is to provide an overview of drug-drug interaction mechanisms and common antiretroviral (ARV) drug-drug and drug-food interactions encountered in clinical practice. Additionally, some useful resources for finding ARV drug-drug interaction information will be provided.

Learning Objectives

The content of this chapter will enable the reader to:

- Know the difference between a pharmacokinetic and pharmacodynamic drug-drug interaction.
- Understand common mechanisms for pharmacokinetic drug-drug interactions.
- Be familiar with the CYP enzymes responsible for metabolism of and inhibited and/or induced by commonly used ARVs.
- Know the difference between enzyme or transporter inhibition and induction and the potential effect on a co-administered substrate drug's pharmacokinetics.
- Know the direction of interaction between commonly used ARVs and statins, hormone contraceptives, azole antifungals, anticonvulsants, and corticosteroids and understand the clinical relevance of the observed or expected interactions.
- Recognize medications that should never be given concomitantly with certain ARVs.
- Describe the effect of food on the pharmacokinetics of commonly used ARVs and provide clinical recommendations for managing food-ARV interactions.
- Know key resources for obtaining reliable, up-to-date information on ARV drug-drug interactions and practice retrieving data from those sites.

Introduction

Treatment of HIV requires the use of three or more unique antiretroviral (ARV) medications. Comorbidities, many of which also require complex drug therapy, are common among HIV-infected patients, such as opportunistic infections, hepatitis, erectile dysfunction, malignancies, neuropsychiatric disease, and cardiovascular disease. Given the high likelihood of polypharmacy among this patient population, the scope and extent of drug interactions in clinical practice is great.

One study in Kenya evaluated the frequency of and predictors for clinically significant drug interactions among 996 HIV-infected patients.¹ After 15 months of person follow-up, risk of 432 clinically significant drug interactions were identified among 334 patients (33.5%), of which over one-third may have resulted in a significant decrease in ARV plasma concentration. This high rate of potential drug interaction was similar to reports from developed countries in which the reported prevalence of clinically significant drug interactions has ranged from approximately 20-40%.²⁻⁶ Commonly reported drug interactions with ARVs included medications used to treat co-infections, such as tuberculosis or malaria, as well as antifungals, anticonvulsants, lipid lowering agents and cardiovascular medications.

Protease inhibitors (PIs) have consistently been identified as a risk factor for drug-drug interactions.^{1,6} The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are also frequently implicated, but interactions are much less common with the nucleos(t)ide reverse transcriptase inhibitors (NRTIs). These differences are largely attributable to the role of cytochrome P450 (CYP) oxidative enzymes on PI and NNRTI metabolism, as well as the effect of the PIs and NNRTIs on CYP enzymes; whereas, the NRTIs do not have CYP involvement. Other identified risk factors for significant drug interactions with ARVs include advanced disease (World Health Organization (WHO) clinical stage 3 or 4), as well as low CD4+ cell count and possibly low baseline weight and female gender.¹ A recent study among 914 HIV-infected patients with a median age of 49 years identified increasing age as a significant risk factor for potential ARV drug-drug interactions, after adjusting for other factors including gender, race and number and class of ARVs.⁷

Given the extent and significance of drug-drug interactions related to HIV therapy, challenges in clinical management often arise. Pharmacists play a key role in optimizing HIV therapy outcomes by recognizing and providing guidance for optimal management of such interactions. In addition to reviewing common mechanisms or pathways for drug-drug interactions, this chapter will also address some common ARV drug-drug and drug-food interactions encountered in clinical practice, as well as provide information on key drug-drug interaction resources available to healthcare providers.

Drug-Drug Interaction Mechanisms

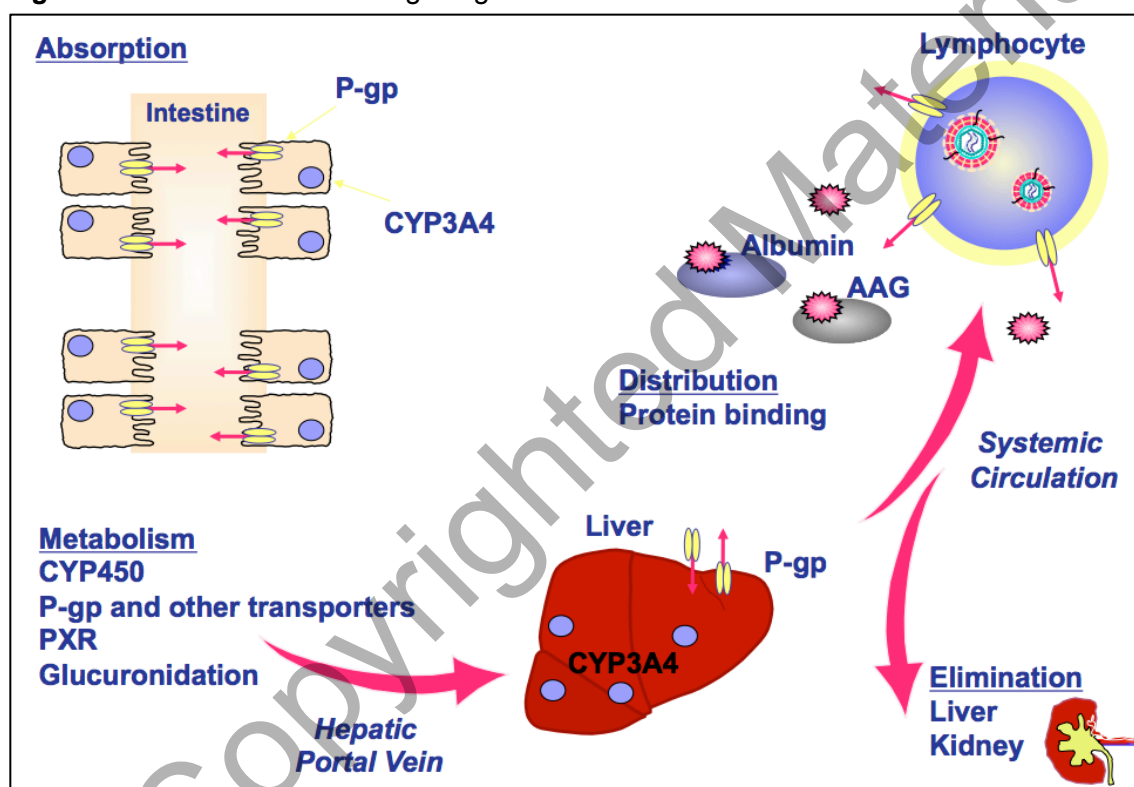
Drug-drug interactions occur when the pharmacokinetic or pharmacodynamic properties of one drug are altered as a result of a co-administered drug. Simply stated, *pharmacokinetics* refers to what the body does to the drug, in other words, how the drug is absorbed, distributed, metabolized and eliminated following its administration; whereas, *pharmacodynamics* refers to

what the drug does to the body, or the drug's efficacy or toxicity. Most commonly, drug-drug interactions are pharmacokinetic in nature and occur as a result of altered drug metabolism, causing either an increase in a drug's plasma concentration, which may increase the risk of toxicity; or a decrease in a drug's plasma concentration, which may increase the risk of suboptimal efficacy.

Pharmacokinetic

Pharmacokinetic interactions can occur at the point of drug absorption, distribution, hepatic metabolism and transport, and renal elimination (Figure 1). Specific examples of each of these mechanisms of interactions are described in the following sections.

Figure 1: Pharmacokinetic drug-drug interaction mechanisms⁸



Source: figure courtesy of Marta Boffito, MD, PhD

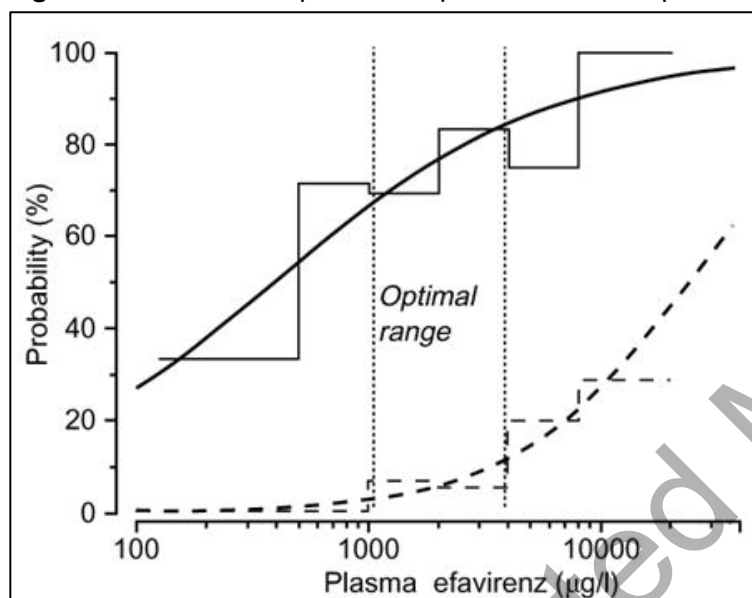
A. Absorption

Interactions that impair a drug's rate and/or extent (bioavailability) of absorption can occur through various mechanisms. For example, changes in gastrointestinal acidity may enhance or impair dissolution and/or absorption of a co-administered drug. Other potential mechanisms include changes in gastrointestinal motility (or gastric emptying time) or changes in intestinal enzyme or transporter activity (induction or inhibition). Also, direct interactions may occur through processes such as chelation or direct binding to another drug. Food may also enhance or impair the rate and extent of absorption through similar mechanisms such as

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Specifically, the highest rates of virologic failure were observed in patients with EFV plasma concentrations below 1000 µg/L and the highest rates of central nervous system-related adverse effects were noted in those with EFV plasma concentrations exceeding 4000 µg/L.²³ Thus, one could predict that if a drug-drug interaction involving EFV resulted in its plasma concentrations falling outside of this therapeutic window (less than 1000 µg/L or greater than 4000 µg/L), then the interaction would likely have clinical significance.

Figure 4: Efavirenz exposure-response relationship



Source: Marzolini C, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS*. 2001; 15(1):71-75.

Given this complexity, it is helpful to consult a reliable drug interaction resource to assess the clinical implications of, and suggested clinical management for, pharmacokinetic and pharmacodynamics drug interactions. Refer to the “Drug Interaction Resources” section below.

Common Antiretroviral Drug-Drug Interactions

Although not inclusive of all known ARV interactions, the following section is meant to provide an overview of some interactions commonly encountered in clinical practice.

Pharmacokinetic Boosting

The strategy known as “boosting” results is a well-known, *favorable* drug-drug interaction. Historically, “boosting” has involved the use of ritonavir and another PI, in which ritonavir is administered at a low dose (commonly, 100 mg once or twice daily) for the purpose of increasing (or “boosting”) the plasma exposure of the co-administered PI. The mechanism of this interaction is improved bioavailability (i.e. an increase in maximum plasma concentration and exposure, Figure 5A) and/or reduced clearance (i.e. an increase in the half-life, Figure 5B), mediated by

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Given the potential serious maternal and child consequences of unintended pregnancy among HIV-infected women, family planning, including access to safe and effective forms of hormone contraception is essential. If hormonal contraception is used, a second form of contraception, e.g. condom, is highly advised. Long-acting reversible forms of contraception, such as implants, may be desirable (i.e. female-controlled, convenient, quick reversal of action upon removal) and their worldwide use is increasing; however, pharmacokinetic data are urgently needed to guide their safe and effective use in women on ART.

Antifungals

Fungal infections, such as oral or esophageal candidiasis, cryptococcal meningitis, as well as aspergillosis and endemic fungi (e.g. histoplasmosis), are not uncommon among HIV-infected individuals. As a result, concomitant antifungal and ARV therapies are often needed. There are four “azole” antifungal agents commonly used to treat or prevent various fungal infections – fluconazole, itraconazole, voriconazole, and posaconazole. A fifth azole, ketoconazole, is also available; however, safety concerns (liver toxicity, adrenal insufficiency, and potential for serious, significant drug-drug interaction) have driven the U.S. Food & Drug Administration and EMA to recommend limited⁴¹ or suspended⁴² use of oral ketoconazole. The azole antifungals are highly susceptible to drug-drug interactions given their involvement as substrates and inhibitors of various CYP enzymes or P-gp (Table 4).

Table 4: Involvement of CYP enzymes and P-gp with the azole antifungals^{43,44}

CYP2C9	CYP2C19	CYP3A4	P-gp
Substrate voriconazole	Substrate voriconazole	Substrate - itraconazole - ketoconazole - voriconazole	Substrate posaconazole
Inhibitor - fluconazole - itraconazole - voriconazole	Inhibitor - fluconazole - ketoconazole - voriconazole	Inhibitor - fluconazole - itraconazole - ketoconazole - posaconazole - voriconazole	Inhibitor - itraconazole - ketoconazole - posaconazole

CYP: cytochrome P450 enzyme; P-gp: P-glycoprotein

The extent to which each azole inhibits a specific enzyme differs by drug and CYP enzyme. For example, ketoconazole, followed by itraconazole, are the most potent CYP3A4 inhibitors of the class; whereas, fluconazole and voriconazole are both potent inhibitors of CYP2C9. The degree to which the CYP enzyme(s) is responsible for azole metabolism also differs across the class, in that itraconazole and ketoconazole are both predominantly metabolized by CYP3A4; whereas this isoenzyme is responsible for only approximately 11% of fluconazole’s metabolism.⁴³ These are some of the characteristics that provide the basis for the drug-drug interaction potential of the azoles and ARVs. The resultant interactions range from no clinical significance, to significant pharmacokinetic differences in ARV and/or antifungal that may impact drug toxicity and/or

efficacy. These findings, as well as the clinical recommendations for management of select azole antifungal-ARV interactions are summarized in Table 5 (with PIs) and Table 6 (with NNRTIs). In general, ketoconazole should be avoided for all patients; itraconazole should only be used if benefit outweighs the risk; fluconazole is generally safe and effective, though careful monitoring is recommended when given with NVP; and posaconazole and voriconazole should only be used when benefit outweighs the risk, with consideration given to the specific ARV.

Table 5: Select azole antifungal and ritonavir-boosted PI interactions²⁰

Azole Antifungal	PI	Effect on PI or Azole	Clinical Management Recommendation
Fluconazole	ATV/r DRV/r LPV/r	No clinically significant effect observed or expected	No dosage adjustment necessary.
Itraconazole	ATV/r DRV/r LPV/r	itraconazole AUC ↑ expected	Itraconazole doses > 200 mg/day are not recommended; monitor itraconazole levels to guide dose adjustment.
Ketoconazole	PI/r	ketoconazole AUC ↑ 2 to 3-fold	Do not co-administer. FDA and EMA caution against the use of ketoconazole. ^{41,42}
Posaconazole	ATV/r	ATV AUC ↑ 146%	Monitor for ATV adverse effects.
Voriconazole	PI/r	With ritonavir 100 mg twice daily: voriconazole AUC ↓ 39%	Do not co-administer unless benefit outweighs the risk; monitor voriconazole levels to guide dose adjustment.

PI: protease inhibitor; ATV/r: atazanavir/ritonavir; DRV/r: darunavir/ritonavir; LPV/r: lopinavir/ritonavir; AUC: area under the curve; PI/r: ritonavir-boosted protease inhibitors; FDA: U.S. Food and Drug Administration; EMA: European Medicines Agency

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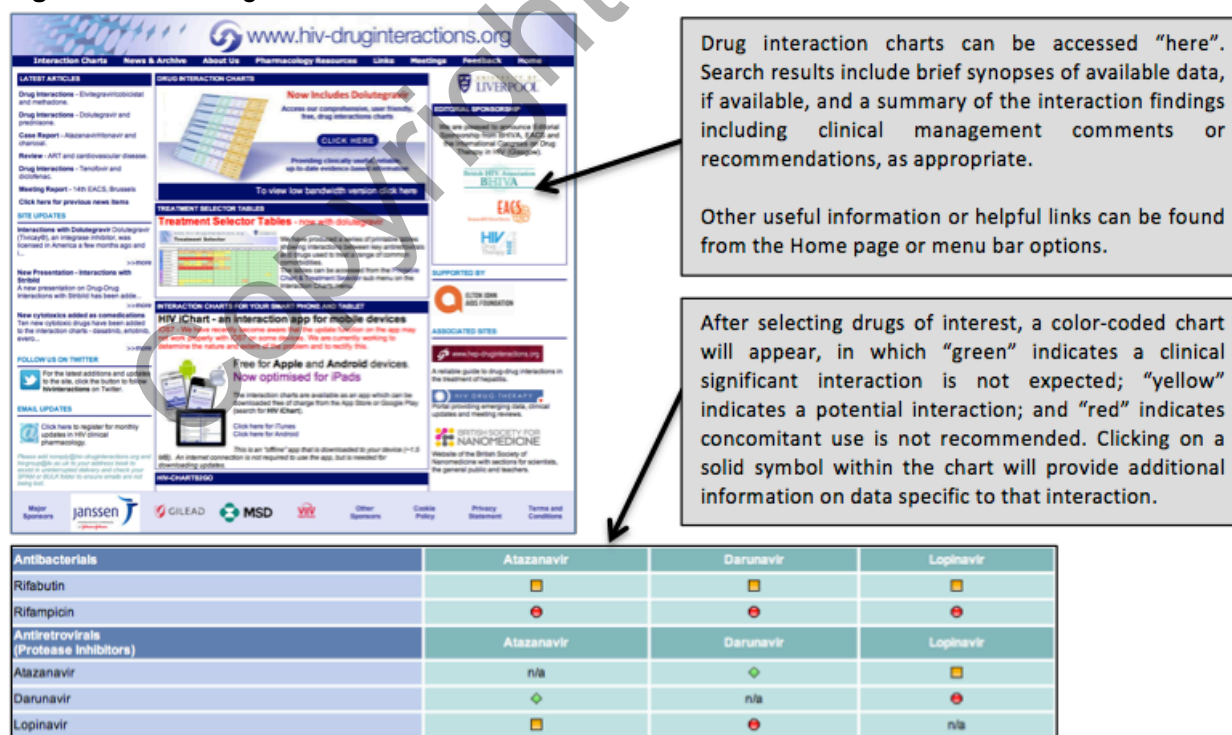
Drug-Drug Interaction Resources

The field of HIV therapy pharmacology continues to evolve, particularly information regarding ARV drug-drug interactions. Although providers of HIV care should be well versed in potential mechanisms for these interactions, as well as the most common and/or most serious interactions, it is not possible to know each and every possible interaction. Therefore, it becomes critically important for healthcare providers to know *where to look* to find up-to-date, reliable information on ARV drug-drug interactions. The following are some of the most useful Internet resources available for HIV therapy drug-drug interaction data.

www.hiv-druginteractions.org (main) or www.hiv-druginteractionslite.org (low graphics)

The HIV Drug Interactions website, based at the University of Liverpool, has been in operation since 1998. The Liverpool HIV Pharmacology Group and other experts provide oversight to the website, which provides up-to-date, clinically useful, evidence-based drug interaction data (Figure 7). In addition to the HIV drug interaction charts, the website includes other useful features, such as ARV fact sheets and drug interaction presentations under the “Pharmacology Resources” menu, recently published drug-drug interaction findings, under the “News & Archive” menu, and reports highlighting pharmacokinetic drug-drug interaction data presented at major HIV conferences, under the “Meetings” menu. The drug interaction charts can also be accessed from a low graphics version of the website (www.hiv-druginteractionslite.org), ideal in areas where Internet speeds are slow. A modified version of the HIV drug interaction charts is also available as an app that can be downloaded to mobile devices.

Figure 7: HIV Drug Interactions website⁷¹



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CHAPTER 16: OVERVIEW OF HIV AND MALARIA CO-INFECTION

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Purpose

The overall purpose of this chapter is to explore HIV and malaria co-infection in Nigeria with emphasis on pathogenesis, clinical manifestations, diagnosis, treatment, and drug-drug interactions in this unique patient population.

Learning Objectives

The content of this chapter will enable the reader to:

- Understand the epidemiology of HIV and malaria
- Understand the impact of HIV on malaria infection
- Understand the impact of malaria on HIV infection
- Describe the clinical manifestations of malaria in HIV-infected patients
- Describe the diagnosis of malaria in HIV-infected patients
- Describe the treatment of *Plasmodium falciparum* malaria in HIV-infected patients
- Describe potential drug-drug interactions between anti-malarial and antiretroviral agents
- Describe HIV and malaria co-infection in special cases
- Describe the pharmacist's role in managing HIV and malaria co-infection

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In vitro and animal studies

CD4+ T lymphocytes (CD4 cells), the main cellular targets for HIV, are necessary for an effective immune response to the malaria parasite through antibody and cytokine production and macrophage activation.^{16,17} CD4 cells (via effects on CD8+ T lymphocytes) also play a pivotal role in development of immunologic memory against *Plasmodium*.¹⁸ Thus, deficits in CD4 cells caused by HIV predispose an HIV-infected individual to malaria infection or more severe clinical manifestations, as discussed below.

In vivo studies

When compared to HIV-uninfected individuals, those with HIV infection are approximately twice as likely to present with malaria parasitemia or clinical malaria in endemic regions.¹³ These risks are higher with increased immune suppression as measured by decreased CD4 cell count.¹⁹ HIV and malaria co-infection is also associated with development of severe or complicated malaria,^{12,20-22} malaria-associated hospitalizations,²² and death,²² especially in those non-immune for malaria.¹² Epidemiologic modeling has revealed that in Nigeria, HIV may increase malaria incidence and death by 1.2% and 4.3%, respectively.²³ In addition, HIV-1 infection reduces the efficacy of anti-malarial agents.^{24,25} Potential drug-drug interactions between co-administered anti-malarials and antiretroviral therapy (ART) further complicate treatment of co-infected persons, as discussed later.

Impact of Malaria on HIV Infection***In vitro studies***

Malaria-associated disruptions in the immunologic milieu promote HIV replication. For example, blood cells stimulated with *Plasmodium*-derived antigens produce interleukin (IL)-6 and tumor necrosis factor (TNF)- α , the latter of which is associated with increased HIV-1 replication.²⁶ Activation of lymphocytes is also seen,²⁶ which may further enhance viral replication. Finally, malaria induces expression of CC chemokine receptor 5 (CCR5), an HIV co-receptor, on macrophages in human placental tissue, thereby enlarging the HIV viral reservoir.²⁷

In vivo studies

Consistent with *in vitro* observations, malaria affects HIV-related clinical parameters and contributes substantially to HIV morbidity.²⁸ Kublin *et al.* demonstrated that patients with malaria parasitemia had a nearly two-fold increase in HIV-1 viral load, which returned to pre-parasitemia levels after two months of follow-up in most patients.²⁹ Malaria-associated increases in HIV viremia may accelerate HIV disease progression and temporarily double the risk of HIV transmission.^{3,29} In addition, repeated malaria infections have been implicated in CD4 cell count decline of approximately 40.5 cells/ μ l/year.³⁰ This occurs in both HIV-infected^{30,31} and HIV-uninfected³¹ patients with malaria and is at least partially reversed after one month of successful anti-malarial therapy.³¹ Importantly, the transient increase in HIV viral load and decrease in CD4

cell count during malaria may result in misclassification of HIV disease status and premature initiation of ART or erroneous diagnosis of ART failure.³²

Clinical Manifestations of Malaria in HIV-infected patients

The clinical manifestations of malaria depend on the infecting *Plasmodium* species, host immunologic status (including presence or absence of HIV infection), and transmission pattern. Non-pregnant adults in Nigeria and other areas of stable transmission rates are relatively immune and often asymptomatic despite parasitemia. However, in areas of unstable transmission rates, immunity is less likely, and clinical malaria may develop with the symptoms described below.³³

Fever

Fever is the hallmark of malaria in both HIV-infected and –uninfected patients.³⁴ Among HIV-infected persons, febrile malaria events are more common in those with greater immune compromise. In one report, the incidence rate of febrile malaria was almost three times higher in those with CD4 cell counts <200/μl when compared to rates in patients with CD4 cell counts >500/ μl.³⁵ Other potential causes of fever in HIV-infected persons, such as immune reconstitution illness, tuberculosis, and opportunistic infection, often complicate diagnosis of malaria in the co-infected subgroup.

Anemia

Anemia is common in all patients with malaria, particularly children and those with HIV co-infection, and is often multifactorial in etiology.^{31,32} Potential contributors include malnutrition or zidovudine (AZT) use. In severe cases, blood transfusion may be necessary. This practice carries risk in settings that do not have blood screening practices in place, as blood transfusions given for anemia due to malaria may be contaminated with hepatitis B or C viruses or, less commonly, HIV.³⁶

Severe Malaria

Severe malaria is a catastrophic illness. It is defined as *Plasmodium* parasitemia with end organ involvement (including cerebral, pulmonary, or renal disease), acidosis, hypoglycemia, shock, severe anemia, and/or hyperparasitemia (density exceeding 5% of erythrocytes on peripheral smear).^{8,33} The absence of fever does not rule out severe malaria.⁸ Concomitant use of some antiretrovirals may also contribute to symptoms often seen with severe malaria. For example, observed mental status changes may be compounded by the use of home herbal remedies or efavirenz (EFV); lactic acidosis may be worsened by use of stavudine (d4T) or didanosine (ddI). These possibilities should be assessed for in the medication history.^{8,32}

Progression to severe malaria is associated with high parasite burden,^{12,33} splenectomy, lack of immunity,¹² and *P. falciparum* infection.³³ HIV co-infection also increases the risk of severe malaria by as much as 3-fold.¹² The prognosis of severe malaria is poor,³³ underscoring the need for rapid and accurate malaria diagnosis and treatment.

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Table 1: Recommended treatment of uncomplicated malaria in Nigeria^{4,8,33}

Medications	Dosage	Dosing Schedule		Comments and toxicities
Artemether plus lumefantrine	Co-formulated: 20 mg artemether with 120 mg lumefantrine	<i>Dosing:</i> Based on weight band (below), take the stated # of 20 mg artemether / 120 mg lumefantrine tablets twice daily for 3 days		The second dose should be administered 8-12 hours after the first dose. <i>Artemether toxicities:</i> Generally very well-tolerated. Mild gastrointestinal disturbances, dizziness, tinnitus, reticulocytopenia, neutropenia, and elevated liver function tests. <i>Lumefantrine toxicities:</i> Generally very well-tolerated. Mild nausea, abdominal discomfort, headache and dizziness have been reported (similar to malaria symptoms).
		Weight Band	# of Tablets	
		5 – 14 kg	1	
		15 – 24 kg	2	
		25 – 34 kg	3	
		≥ 35 kg	4	
Artesunate plus amodiaquine (AS/AQ)	Co-packaged: 50 mg AS with 153 mg base AQ	<i>Dosing:</i> Target dose = 4mg/kg/day of AS and 10mg/kg/day of AQ given once daily for 3 days		Co-formulated preparation preferred due to improved adherence. <i>Artesunate toxicities:</i> Generally very well tolerated. Mild gastrointestinal disturbances, dizziness, tinnitus, reticulocytopenia, neutropenia, and elevated liver function tests. <i>Artesunate toxicities:</i> agranulocytosis, hepatitis, and pruritus
		Weight Band (Age Range)	Dose (using co-formulated tablets)	
	Co-formulated as AS/AQ ratio: 25/67.5 mg 50/135 mg 100/270 mg	4.5 – 8.9 kg (2 – 11 months)	(one) 25/67.5 mg tab	
		9 – 17.9 kg (1 – 5 years)	(one) 50/135 mg tab	
		18 – 35.9 kg (6 – 13 years)	(one) 100/270 mg tab	
		≥ 36 kg (14 years and older)	(two) 100/270 mg tabs	

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Impact of HIV on Treatment Outcomes

Poor response to anti-malarial therapy is common in HIV-infected patients. In cases of uncomplicated *P. falciparum* malaria, HIV is associated with prolonged parasite clearance time (in those treated with artemisinin²⁴) and treatment failure/recurrence, which appears to be modulated by CD4 cell count (<200 cells/ μ l).²⁵ Though anti-malarial failure is not universally observed,^{38,39} other unfavorable treatment outcomes are seen with HIV co-infection, including slower hematologic recovery after parasite clearance.⁴⁰

Favorably, the use of co-trimoxazole prophylaxis in HIV-infected persons appears to be associated with improved treatment outcomes in those with uncomplicated malaria,³⁹ including a significant reduction in mortality.⁴¹ Also, the use of co-trimoxazole provides protection against malaria among HIV-infected persons, estimated at 99.5% protection based on pooled data.⁴²

Drug-Drug Interactions

HIV is a chronic condition requiring indefinite treatment with ART and/or prophylactic agents (i.e., co-trimoxazole), many of which have drug interactions with common anti-malarial agents. The drug interactions are often complex, with minimal research to describe the clinical impact of any drug-interaction, making treatment recommendations particularly challenging. This discussion will be limited to common 1st and 2nd-line ART regimens, and the antimalarials most often used in Nigeria, including artemether/lumefantrine, artesunate/amodiaquine, and quinine.

In general, the antimalarials discussed in this chapter are all metabolized to some extent by the cytochrome P450 (CYP) enzyme system (Table 3). This is the proposed mechanism by which many of the drug interactions between ART and antimalarials occur. However, there are other pathways and drug transporters that are still being defined that might impact the direction and/or extent of any interaction. Finally, not only are both antiretrovirals and antimalarials metabolized by the CYP enzyme system, but they can also induce or inhibit these same enzymes, making the potential for drug interactions even more complex.

Table 3: Known or suspected CYP pathways responsible for metabolism of, or affected by, common antimalarials⁴³

Medication	Metabolized by	Induces	Inhibits
Artemether	CYP3A4	CYP2C19, 3A4	---
Lumefantrine	CYP3A4	---	CYP2D6
Artesunate	CYP3A4, 2A6	---	---
Amodiaquine	CYP2C8	---	---
Quinine	CYP3A4, 2C19	---	CYP2D6, maybe 2C9 and 2C9

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asymptomatic hepatitis may have been due to excess exposure to amodiaquine. Thus, this combination is contraindicated.³³

D. Artesunate/Amodiaquine and Nevirapine

In a study conducted in Nigeria in HIV-infected subjects, co-administration of NVP-based ART with artesunate plus amodiaquine increased artesunate exposure by 45% and decreased amodiaquine exposure by 32%.^{47,50} Monitor patients on this combination for antimalarial efficacy.

E. Quinine and NNRTIs

No drug interaction studies have been done to evaluate the combination of quinine with either EFV or NVP. However, there is concern that quinine concentrations will be decreased when combined with either NNRTI, as both EFV and NVP induce the CYP3A4 enzyme, which is primarily responsible for quinine metabolism. Although the interaction is theoretical at this point, monitor patients on this combination for both excess toxicity and antimalarial efficacy.

Protease inhibitors and common antimalarials

Protease inhibitors (PIs) are essential to 2nd-line ART and are metabolized by, and either induce or inhibit, the CYP enzyme system. (Refer to *Chapter 5: PIs* for further detail.) To date, the only data available for the combination of antimalarials and PIs are with lopinavir/ritonavir. While the interaction potential may be different for other ritonavir-boosted PIs, such as atazanavir/ritonavir, until more data are generated, information may be cautiously extrapolated from lopinavir/ritonavir studies to other ritonavir-boosted PI regimens.

A. Artemether/Lumefantrine and Protease Inhibitors

The interaction between artemether/lumefantrine has been described with lopinavir-ritonavir based-ART in healthy volunteers⁵¹ and HIV-infected subjects.⁵² Lumefantrine exposure is significantly increased (2.3-fold and 386%, respectively), whereas artemether levels were decreased in healthy volunteers and HIV-infected patients receiving lopinavir/ritonavir (39% and 43%, respectively).^{51,52} Because lumefantrine does not have any known dose-related severe adverse events, it is believed that this combination can be used safely despite the expected higher lumefantrine concentrations. However, pharmacovigilance is important to ensure there are no excess adverse events related to this combination.

B. Artesunate/Amodiaquine and Protease Inhibitors

There are no drug interaction data to guide the use of this combination. However, because amodiaquine is metabolized via CYP2C8 and ritonavir may inhibit CYP2C8, there is a theoretical risk that the combination will result in increased amodiaquine exposure. One study evaluated artesunate/pyronaridine with lopinavir/ritonavir and found that artesunate and DHA concentrations were decreased (27% and 38%, respectively).⁵³ Monitor patients on this combination for excess toxicity and antimalarial efficacy.

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5 years of age with severe *P. falciparum* malaria.⁶² In all cases, a low threshold to evaluate and treat for concomitant invasive bacterial infection should be maintained given that up to 5% of children may also have bacteremia (commonly non-typhi *Salmonella* or *Streptococcus pneumoniae*), which independently predicts hospital mortality.^{63,64} HIV infection does not appear to predispose to bacterial co-infection.⁶⁵

Non-*Falciparum* Malaria

Though the vast majority of cases of malaria in Nigeria are due to *P. falciparum*, infections with *P. vivax*, *ovale*, and *malariae* can occur in travelers or immigrants from endemic countries. Only *P. vivax* and *ovale* are capable of forming hypnozoites, or liver parasites, that can cause relapsed infections. Thus, treatment must focus on eradicating both blood and liver reservoirs (i.e., “radical cure”). Of the non-*falciparum* organisms, *P. vivax* has the most well established guidelines. In general, chloroquine (when active) or ACT (with the exception of artesunate plus sulfadoxine-pyrimethamine) and two weeks of primaquine can be utilized to treat the blood and liver forms of uncomplicated *P. vivax* malaria, respectively. Severe non-*falciparum* malaria should be managed as severe *P. falciparum* malaria.

The Pharmacist’s Role in Managing HIV and Malaria Co-Infection

Recently, the WHO has prioritized the “T3” strategy for malaria control, comprised of scaling-up testing, treatment, and tracking of malaria cases.⁵ Pharmacists can contribute to this new initiative to optimize care for co-infected patients. For example, they can recognize symptoms suggestive of malaria and provide referral for further evaluation. If the diagnosis is confirmed, they are able to ensure that recommendations for first-line ACT treatment and treatment failure are followed. In sub-Saharan Africa, including Nigeria, a knowledge gap is apparent among retail pharmacists,⁶⁶ some of whom have been found to dispense suboptimal treatment such as artesunate monotherapy.⁶⁷ Even when ACT is administered, recent evidence points to widespread incorrect dosing.⁶⁸ These are critical areas for capacity improvement nationally.

Furthermore, pharmacists are positioned to provide up-to-date evidence-based data on drug-drug interactions with ART to physicians. Since non-adherence and incorrect timing of dosages are common obstacles to treatment success,⁶⁹ appropriate patient counseling by a knowledgeable pharmacist is essential. Finally, pharmacists can improve the poor uptake of IPTp by administering directly observed therapy.

Summary

Malaria and HIV synergistically contribute to substantial morbidity, mortality, and economic loss in Nigeria and other endemic areas. Prompt diagnosis and treatment are critical in the vulnerable co-infected population. As essential members of the health care team, pharmacists can ensure that best practice guidelines are followed in order to prevent new cases of malaria, as well as optimize outcome for those receiving treatment.

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APPENDIX A: ANSWERS TO SELF-ASSESSMENT QUESTIONS

Chapter 1: Pharmacokinetic and pharmacodynamic principles: a guide for HIV healthcare professionals

Self-Assessment Questions

1. True or false. The major goals in clinical pharmacology are to describe, quantitate and predict drug effects in humans

Answer: A. True.

2. Which of the following is not one of the processes that determine the time course of any drug in the body, and collectively define the pharmacokinetic profile of an agent?

Answer: D. Maximal effect (E_{max}).

Explanation: E_{max} is used to describe the pharmacodynamics of the drug, not pharmacokinetics, as it relates to the concentration-effect relationship.

3. Which of the following statements is true for a drug that obeys first-order elimination and has a terminal elimination half-life of 4 hours?

Answer: A. It will take 4 hours for concentrations to decrease from 100 mg/L to 50 mg/L, and another 4 hours to drop to 25 mg/L.

Explanation: First-order elimination means that the rate of elimination is proportional to the amount of the drug in the body and the half-life remains constant over time.

4. Which of the following statements is true regarding the relationship between area under the curve (AUC) and total body clearance for a drug that obeys linear pharmacokinetics?

Answer: B. If total body clearance decreases by half (50%) and dose stays the same, AUC doubles.

Explanation: Clearance and AUC are inversely related; therefore, as clearance decreases, AUC increases proportionally.

5. The relationship between drug concentrations in the body and the response produced (therapeutic effect) can be described with a maximal effect model (E_{max}) for most drugs. Which of the following is a characteristic of this model?

Answer: C. An increase in response with an increase in drug concentrations but only up to the maximal effect.

Explanation: E_{max} assumes that there is no effect when drug is not present and that the effect will only increase to a maximum effect, beyond which there is minimal additional drug effect.