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TREATMENT AND CARE OF HIV DISEASE

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The treatment and care of HIV-infected people requires comprehensive integration of patient-centered medical and social services. Essential elements of this approach include the provision of clinical care, nursing care, nutritional care and support, psychological support, health information and counseling, legal protection, and economic sufficiency. Notable components of successful clinical care include early diagnosis, access to care, antiretroviral therapy, symptom control, prophylaxis against opportunistic infections, treatment of opportunistic infections and malignancies, and end-of-life care. The achievement of these objectives requires multisectoral and multidisciplinary teams that are cross-linked to provide a continuum of care that involves patients, their families, health-care providers, governmental and nongovernmental organizations, and society at large.

Prevention of new infections should be integrated into HIV/AIDS treatment and care programs as HIV infection remains incurable despite advances in antiretroviral treatment. Toward this end, “social immunization” — such as through community mobilization, widespread education, counseling and testing, sexual abstinence until marriage, monogamy, condom use, and female empowerment — must be strengthened, as we await the perfection of vaginal microbicides, HIV vaccines, and other currently investigational prevention strategies. Even if HIV transmission were to cease

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completely in Nigeria and other resource-limited countries, the existing burden of HIV/AIDS would continue to task all stakeholders into the foreseeable future.

THE CASE FOR ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS

Antiretroviral therapy (ART) has significantly reduced morbidity and mortality, prolonged life expectancy, and improved quality of life among people with HIV infection (1). ART has also been effective in the prevention of mother-to-child transmission of HIV (PMTCT) (2). The increasing availability of ART has created a major incentive to participate in voluntary counseling and testing (3), and has broadened and enhanced prevention efforts by reducing stigma and increasing uptake of behavior change communication messages. Effective ART may reduce overall transmission at the population level. Comprehensive care—including antiretrovirals (ARVs), treatment of opportunistic infections, and the use of prophylactic agents—benefits the individual, the community, and the country.

The provision of affordable, accessible, and good quality treatment and care on a global scale for people living with HIV is essential for tackling the epidemic, improving lives, and protecting the significant development gains of the past 20 years. Addressing the care and treatment needs of HIV-infected people is also a critical component of achieving the millennium development goals of the next decade. Until 2005, only 5% of the six million people who required ARVs in resource-limited countries could access these drugs. Between 2003 and the end of 2005, however, these numbers rose three-fold (4), mainly from the massive scaling up of programs supported by the 3 by 5 Initiative of the World Health Organization (WHO); the Global Fund to Fight AIDS, Tuberculosis, and Malaria; the World Bank; and the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR). Nigeria, with a national seroprevalence of 5% (5) and an estimated four to six million people living with HIV, has at least 800,000 people in urgent need of ART. Only about 5% of those in need are currently receiving ART, but this number is expected to rise sharply with the 2005 presidential directive to treat 250,000 individuals by the end of 2006.

It should be noted that ART has many risks and limitations. First, early and delayed adverse effects—such as metabolic disorders, mitochondrial toxicities, and numerous organ-specific adverse reactions—are continual concerns. The scope of these adverse effects is rather broad, and our understanding of their pathogenesis and clinical presentations continues to evolve. Second, many HIV clinicians and researchers now view the late 1990s as a period of irrational optimism about the possibility of a cure for HIV. During that era, mathematical models suggested HIV infection in an individual could be eradicated by many years of continuously suppressive ART (6). It has since become clear, however, that such a feat is unachievable because of the complexity of the regimens, the difficulties of maintaining long-term adherence, viral mutation, and toxicity. Even in the absence of systemic replication, latently infected resting CD4+ T cell populations persist in lymph nodes and other organs. Prolonged ART appears to impair the development of HIV-1-specific immune responses because it reduces systemic HIV that

would otherwise serve as the antigenic stimulant of such responses. Therefore, plasma viremia inevitably rebounds whenever treatment is stopped.

ARVs do not cure HIV infection and therefore must be taken for life. They can result in major toxicities and drug interactions, and drug resistance can develop if adherence is poor. The cost of ARVs and laboratory monitoring pose major financial challenges, particularly in resource-poor countries. The lack of an adequate health infrastructure and insufficient human resources create serious obstacles to providing ART in an effective, durable, and sustainable manner. Furthermore, increased commitment to treatment and care may lead to the neglect of prevention efforts and programs aimed at reducing the social and economic impact of HIV.

NATURAL HISTORY AND CLASSIFICATION OF DISEASE

The natural history of untreated HIV infection can be divided into six stages: initial infection; acute retroviral syndrome, or primary HIV illness; recovery and seroconversion; asymptomatic chronic HIV infection; symptomatic HIV infection; and AIDS.

Acute retroviral syndrome develops two to six weeks after the initial infection and is characterized by an acute flu-like illness. The clinical features include fever, headache, malaise, joint pains, pain and tenderness in the muscles (myalgia), diarrhea, maculopapular rash, and generalized swollen lymph glands (lymphadenopathy). These symptoms may be accompanied by various self-limiting neurologic manifestations, such as atypical aseptic meningitis and acute encephalitis. Acute retroviral syndrome

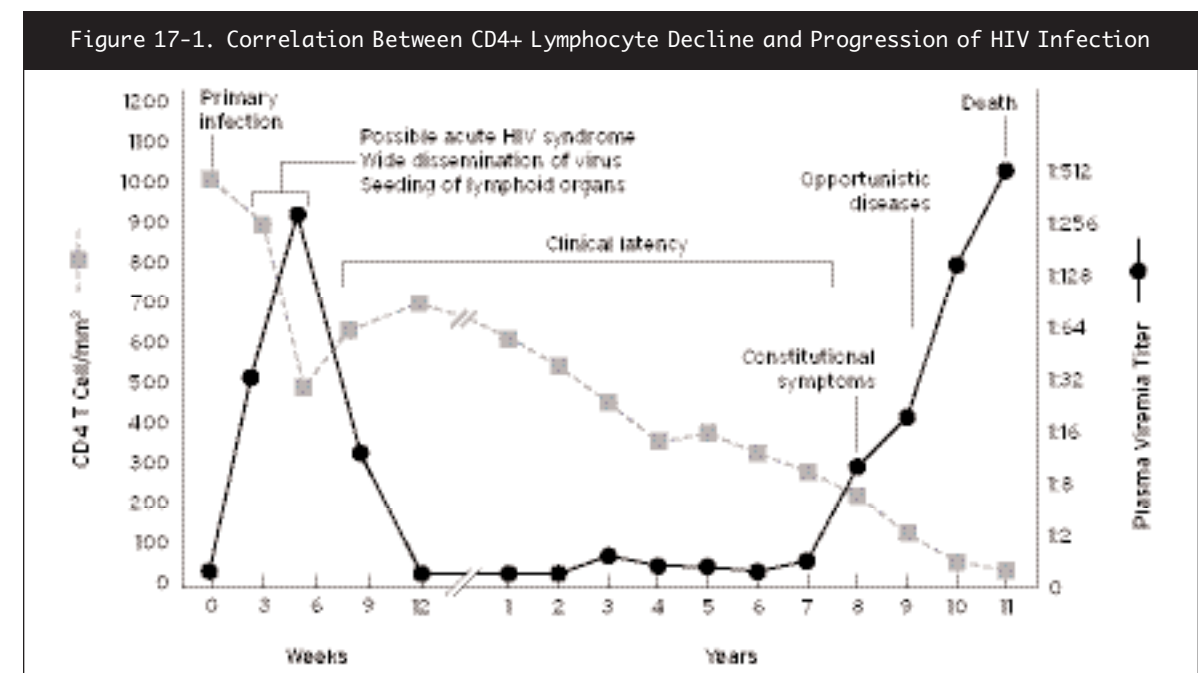


Figure 17-1. Correlation Between CD4+ Lymphocyte Decline and Progression of HIV Infection. Natural history of HIV infection with initial infection, acute retroviral infection, recovery and seroconversion, asymptomatic (latent) chronic HIV infection, and the eventual development of AIDS. Source: Fauci AS, Pantaleo G, Stanley S, Weissman D. Immunopathogenic mechanisms of HIV infection. *Ann Intern Med*, 1996;124:654-663.

CD4+ Cell categories	Clinical Classification		
	Asymptomatic	Symptomatic	AIDS related disease
> 500/mm ³	A1	B1	C1
200 - 499/mm ³	A2	B2	C2
< 200/mm ³	A3	B3	C3

Candidiasis–esophageal
Cervical cancer–invasive
Cryptococcosis–extrapulmonary
Cryptosporidiosis with diarrhea > 1 month
Cytomegalovirus: any organ except spleen, liver, or lymph nodes
Herpes simplex with mucocutaneous ulcer > 1 month or with bronchitis, pneumonia, or esophagitis
Histoplasmosis–extrapulmonary
HIV-associated dementia
HIV-associated wasting with involuntary loss of > 10% body weight + chronic (> 30 days) diarrhea, fatigue, or fever
Isosporosis with diarrhea > 1 month
Kaposi’s sarcoma
Lymphoma of brain
Lymphoma–non-Hodgkin’s
<i>Mycobacterium avium</i> or <i>Mycobacterium kansasii</i> disseminated
<i>Mycobacterium tuberculosis</i> –disseminated or pulmonary
Nocardia
<i>Pneumocystis carinii</i> pneumonia
Pneumonia, recurrent
Progressive multifocal encephalopathy
Salmonella septicaemia
Strongyloides extraintestinal
Toxoplasmosis of internal organ

during acute retroviral syndrome include: thrombocytopenia, lymphopenia, anemia, monocytosis, low-level atypical lymphocytosis, thrombocytosis, bandemia, and abnormal liver function tests.

The infected individual is most infectious during acute retroviral syndrome because of the high viral replication level. Reports from Malawi have shown that in areas of high HIV prevalence, up to 3% of individuals in high-risk populations, such as those with sexually transmitted infections (STIs), may have acute HIV infection and are potential sources of HIV transmission even though they have negative serology for HIV (9). This type of situation poses a major public health challenge in resource-limited countries where high-risk individuals may form a significant proportion of blood donors. This problem

goes unrecognized in many individuals perhaps because of a lack of suspicion or perhaps because it is difficult to distinguish these features from a host of other common tropical illnesses, such as malaria, typhoid fever, the common cold, and glandular fever. Acute retroviral syndrome is characterized by high plasma viremia and depressed CD4+ cell numbers and function (Figure 17-1). Acute retroviral syndrome has also been described in chronically HIV-infected patients who are reinfected with another strain of HIV, and a similar clinical syndrome occurs in some patients as a result of virologic rebound following withdrawal of suppressive ART (7).

During acute retroviral syndrome, tests that directly detect HIV—HIV RNA by polymerase chain reaction (RNA PCR), DNA PCR, and p24 antigen—are usually positive, but HIV antibody tests are negative. The sensitivity of RNA PCR for diagnosing acute retroviral syndrome approaches 100%, but the specificity is slightly lower (about 98%). HIV RNA level during this syndrome is usually greater than 100,000 copies/ml. The sensitivity of p24 antigen is lower compared to HIV RNA, but p24 is the most specific test (8).

Other possible laboratory abnormalities

is compounded in such environments by the lack of screening tools that directly detect HIV.

Following seroconversion, infected individuals become HIV antibody positive and remain asymptomatic for five to ten years before developing clinical illness. During this asymptomatic period, some balance is established between the virus and the immune system, allowing the rate of HIV replication to remain relatively stable in the absence of treatment. The plasma viral load at which this relative equilibrium occurs has been termed “viral set-point.” It is influenced by the pathogenicity of the infecting strain and the host immunologic repertoire; hence, it varies from one person to the next. However, continuous destruction of the immune system usually occurs, ultimately leading to an immunologic collapse with two major clinical consequences: the occurrence of opportunistic infections caused by microorganisms that the body’s immune system normally holds in check, and the development of certain cancers. Symptomatic disease usually begins with minor opportunistic infections, progressing later to life-threatening disease—AIDS. This late stage disease is characterized by CD4+ counts of less than 200 cells/mm³, AIDS-defining opportunistic infections and cancers, wasting syndrome, and neurologic complications (10). Less than 5% of HIV-infected people are long-term non-progressors, who escape this eventual immunologic and clinical collapse.

The staging of HIV and AIDS disease has important implications for clinical decision making and priority setting for treatment because patients with AIDS, symptomatic disease, and low CD4+ counts usually have more severe disease and therefore require more

<p>Clinical Stage I: Asymptomatic</p> <ol style="list-style-type: none"> Asymptomatic Persistent generalized lymphadenopathy And/or performance scale 1: asymptomatic, normal activity
<p>Clinical Stage II: Early (Mild) Disease</p> <ol style="list-style-type: none"> Weight loss < 10% of body weight Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis) Herpes zoster within the last five years Recurrent upper respiratory tract infections (e.g., bacterial sinusitis) And/or performance scale 2: symptomatic, normal activity
<p>Clinical Stage III: Intermediate (Moderate) Disease</p> <ol style="list-style-type: none"> Weight loss, > 10% of body weight Unexplained chronic diarrhea > 1 month Unexplained prolonged fever (intermittent or constant) > 1 month Oral candidiasis (thrush) Oral hairy leukoplakia Pulmonary tuberculosis within the past year Severe bacterial infections (e.g., pneumonia, pyomyositis) And/or performance scale 3: bedridden < 50% of the day during the past month
<p>Clinical Stage IV:</p> <ol style="list-style-type: none"> HIV wasting syndrome <i>Pneumocystis carinii</i> pneumonia Toxoplasmosis of the brain Cryptosporidiosis with diarrhea > 1 month Cryptococcosis, extrapulmonary Cytomegalovirus disease of an organ other than liver, spleen or lymph node (e.g., retinitis) Herpes simplex virus infection, mucocutaneous (> 1 month) or visceral Progressive multifocal leukoencephalopathy Any disseminated endemic mycosis Candidiasis of the esophagus, trachea, bronchi, or lungs Atypical mycobacteriosis, disseminated Non-typhoid salmonella septicemia Extrapulmonary tuberculosis Lymphoma Kaposi’s sarcoma HIV encephalopathy And/or performance scale 4: bedridden > 50% of the day during the past month

Table 17-4. WHO Staging System for HIV in Children	
Clinical Stage I:	
1. Asymptomatic	
2. Generalized lymphadenopathy	
Clinical Stage II:	
1. Chronic diarrhea > 30 days duration in absence of known etiology	
2. Severe persistent or recurrent candidiasis outside the neonatal period	
3. Weight loss or failure to thrive in the absence of known etiology	
4. Persistent fever > 30 days duration in the absence of known etiology	
5. Recurrent severe bacterial infections other than septicemia or meningitis (e.g., osteomyelitis, bacterial (non-TB) pneumonia, abscesses)	
Clinical Stage III:	
1. AIDS-defining opportunistic infections	
2. Severe failure to thrive in the absence of known etiology	
3. Progressive encephalopathy	
4. Malignancy	
5. Recurrent septicemia or meningitis	

Table 17-5. CDC AIDS Case Surveillance Definition for Infants and Children						
Immune Category	< 12 months		1-5 years		6-12 years	
	CD4+/mm	%	CD4+/mm	%	CD4+/mm	%
Category 1: No suppression	≥ 1,500	≥ 25	≥ 1,000	≥ 25	≥ 500	≥ 25
Category 2: Moderate suppression	750-1,499	15-24	500-999	15-24	200-499	15-24
Category 3: Severe suppression	< 750	< 15	< 500	< 15	< 200	< 15

GOALS OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

The goals of HIV therapy are to provide optimal and individualized treatment for HIV-infected people at all stages of disease. ART for HIV became available in 1987 with the approval of AZT, a reverse transcriptase inhibitor and nucleoside analogue now known as zidovudine (11). While zidovudine monotherapy prolonged life, its beneficial effects were short-lived and within months the disease would again progress. Combination therapy with two nucleoside analogues offered some improvement. However, the benefits were again time-limited regardless of the specific combination (12). It was not until new classes of ARVs—the non-nucleoside reverse transcriptase and protease inhibitors—became available and were used in

urgent attention. The U.S. Centers for Disease Control and Prevention (CDC) classification (Table 17-1) employs a set of AIDS- and non-AIDS-related diseases, as well as CD4+ count, to determine disease severity. All patients in categories A3, B3, and C1–C3 are defined as having AIDS based on the presence of an AIDS-defining illness and/or a CD4+ count of less than 200/mm³.

The WHO has developed a clinical definition of AIDS for surveillance, whereby adults with a positive HIV antibody test and one or more of the conditions listed in Table 17-2 are considered to have AIDS. The WHO has also developed an improved clinical staging system with four categories of clinical conditions believed to have prognostic significance (Table 17-3). A performance scale has also been incorporated into the system. Table 17-4 shows the WHO staging system for HIV infection and disease in children, while Table 17-5 shows the CDC AIDS case surveillance definition for infants and children.

combination with two nucleosides that sustained results were achieved. The use of three ARVs from two drug classes has been termed triple-combination therapy or “highly active antiretroviral therapy” (HAART). HAART use is associated with sustained suppression of plasma HIV RNA (viral load) as measured by PCR, and significant improvement in immune status as measured by absolute and percentage CD4+ counts (13). These results have led to increased survival, reduced morbidity (14), and decreased vertical (15) and sexual transmission (16). HAART may also be used to prevent infection following inadvertent exposure to HIV (17).

Although HAART has produced dramatic benefits by increasing healthy survival, eradication of the virus in any individual has been elusive. The apparent invincibility of HIV, even in the face of HAART, has been aided by complex viral and cellular kinetics that allow it to persist in long-lived cells such as latently infected CD4+ T lymphocytes and tissue-bound macrophages. In addition, there are potential “sanctuary” sites such as the brain, testes (18), and retina (19), where the presence of blood-tissue barriers limits entry of otherwise potent ARVs.

Therapy must often be tailored to fit the needs of individual patients; however, the goals of ART remain the same:

- **Clinical:** Prevent progression of disease, prolong life, and improve the quality of life.
- **Virologic:** Maximally suppress plasma HIV RNA (viral load).
- **Immunologic:** Reconstitute the immune system with an increase in the quantity and quality of CD4+ cells.
- **Therapeutic:** Provide the most convenient HAART regimen with a low pill burden, few food requirements or limitations, and an infrequent dosing schedule, and enhance adherence.
- **Toxicity:** Select a regimen with the fewest acute and chronic adverse effects.
- **Pharmacokinetic:** Choose regimens with favorable pharmacokinetic properties and a high threshold for development of resistance.
- **Public health:** Reduce infectiousness in the population.

HAART has become the standard of care for treatment of HIV infection. The key to successful HAART in a resource-limited country such as Nigeria is the concept of durability. A durable regimen is one in which the potency of the drug—defined by its ability to suppress virus below levels of detection (< 50 or < 400 HIV RNA copies per ml, depending on the assays used—is maintained over a long period of time. A durable regimen can prevent the emergence of resistance, promote health, reduce the complexities of care, and ensure health cost savings. Current knowledge of the mechanisms of action, toxicity, drug resistance, and pharmacokinetic profile of available ARVs should inform the development of a durable regimen. Other key issues that will influence the development of durable regimens in resource-limited countries include knowledge of the effectiveness of available regimens, patterns of resistance, and the presence of comorbidities, such as tuberculosis and hepatitis B or C. Monitoring and evaluating ART programs to ensure they produce the desirable outcomes is also important for enhancing durability.

NRTIs	NtRTIs	Nucleotide/NRTI	PIs	NNRTIs	Fusion Inhibitors
Zidovudine	Tenofovir	Truvada®	Saquinavir	Nevirapine	
Didanosine			Ritonavir	Delavirdine	Enfuvirtide
Didanosine EC			Indinavir	Efavirenz	
Stavudine			Nelfinavir		
Stavudine XR			Ampranavir		
Abacavir			Lopinavir/ritonavir		
Lamivudine			Atazanavir		
Combivir®			Fosamprenavir		
Trizivir®			Tipranavir		
Epzicom®					
Emtricitabine					

Abbreviations: NRTIs: nucleoside reverse transcriptase inhibitors; NtRTI: nucleotide reverse transcriptase inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors; PIs: protease inhibitors

Notes: Combivir®=zidovudine + lamivudine; Trizivir®=zidovudine + lamivudine + abacavir; Epzicom®=abacavir + lamivudine; Truvada®=tenofovir + emtricitabine; lopinavir/ritonavir=Keletra®

Actions required to achieve durable ART include:

- Maximize adherence to the ARV regimen;
- Select sequential ARVs in a rational manner, starting with the most potent, locally proved combinations;
- Preserve future treatment options;
- Select drug combinations with high mutational thresholds;
- Use resistance testing in selected clinical settings;
- Select drugs with similar pharmacokinetic profiles;
- Limit the use of drug combinations with high toxicity;
- Use combinations with low pill burden, food requirements, and refrigeration storage needs; and
- Avoid adding single agents to a failing drug regimen.

CLASSES OF ANTIRETROVIRALS AND MODES OF ACTION

The major classes of ARVs are: nucleoside reverse transcriptase inhibitors (NRTIs); nucleotide reverse transcriptase inhibitors (NtRTIs); non-nucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PIs); and fusion inhibitors (Table 17-6). The drugs in each of these classes interfere with specific steps in the HIV replication cycle.

NRTIs are synthetic nucleoside analogues that are inactive until taken up by infected cells and converted to the triphosphate compound through the action of cellular enzymes. The active triphosphate forms

inhibit HIV-1 replication by incorporating into the viral DNA chain and competing with deoxynucleotide triphosphate (dNTP), which is the natural substrate for HIV reverse transcriptase (RT). This terminates the growing DNA strand, leading to incomplete replication of the virus.

The only NtRTI that is used for HIV treatment is tenofovir disoproxil fumarate (tenofovir DF). Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir. Tenofovir is then taken up by cells and is phosphorylated to tenofovir diphosphate, which competes with the natural substrate (deoxyadenosine 5-triphosphate) for incorporation into viral DNA. This causes premature DNA chain termination and incomplete replication of the virus.

NNRTIs do not require intracellular phosphorylation to be active. Instead, these agents bind to a hydrophobic pocket of RT that is distinct, but close to the dNTP binding site. Thus, they do not compete with template or nucleoside triphosphates, but rather exert non-competitive inhibition of RT. These agents are active against HIV-1, but not HIV-2.

Normal HIV replication involves the action of two groups of proteases. First, there are cellular proteases that cleave envelope precursor polyprotein, leading to the formation of the glycoprotein spikes that are on the surface of the virus. Viral proteases are responsible for cleaving Gag and Gag-pol precursor polyproteins with formation of the remaining viral proteins, including RT, protease, and integrase. PIs act by inhibiting HIV protease, making the enzyme incapable of processing the Gag and Gag-pol polyproteins and resulting in the production of immature non-infectious HIV particles.

The only fusion inhibitor in use at this time is enfuvirtide (T-20). This agent inhibits the fusion between HIV and cellular membranes by binding to the gp41 portion of the HIV glycoprotein envelope, preventing the conformational changes that are necessary for the fusion of HIV to cellular membranes.

Currently investigational ARV drug classes include coreceptor antagonists and maturation inhibitors. CCR5 and CXCR4 are coreceptors for the binding of HIV to target cells; thus, agents that antagonize them have the potential to interfere with this critical step in the lifecycle of the virus. However, one potential limitation of CCR5 antagonists is that they are only likely to be effective against CCR5-tropic HIV, while CXCR4 antagonists are expected to be effective only against CXCR4-tropic virus. It is uncertain whether the use of CCR5 antagonists will cause selection of CXCR4-tropic virus, or conversely, whether selection of CCR5-tropic virus will occur with the use of CXCR4 antagonists.

CHOICE OF ANTIRETROVIRAL REGIMENS

While there are many effective HAART regimens that are used to treat HIV infection, the initial strategy must be based on specific drug and patient factors such as proven potency, ease of administration,

Patient-Related Factors	Drug-Related Factors
<ul style="list-style-type: none"> • HIV RNA levels (viral load) • Baseline CD4+ cell count • Comorbidities (viral hepatitis, TB) • Lifestyle • Preference • Childbearing potential 	<ul style="list-style-type: none"> • Potency • Convenience • Tolerability • Adverse events (toxicity) • Resistance profile • Cost • Refrigeration

potential drug toxicities, pharmacokinetics, resistance threshold, expense, and availability (Table 17-7). The current Nigerian ART guidelines recommend starting with an initial HAART regimen that includes two NRTIs plus one NNRTI or a PI (20). The preferred first-line regimen is zidovudine or stavudine, plus lamivudine; or emtricitabine, plus nevirapine or efavirenz. Three alternative first-line regimens are also recommended: tenofovir, plus lamivudine or emtricitabine, plus nevirapine or efavirenz; abacavir, plus lamivudine or emtricitabine, plus nevirapine or efavirenz; or zidovudine or stavudine, plus lamivudine or emtricitabine, plus tenofovir or abacavir.

Previous reports have shown that the potency of NNRTI-containing regimens was equivalent to that of PI-containing regimens (21). As an initial strategy, if a PI-containing regimen is chosen, most PIs can be combined with ritonavir for pharmacokinetic enhancement. Although enhancement of a PI-based regimen with ritonavir is likely to be more effective than using another PI alone, it may cause more side effects (22). A review of several clinical trials indicates that the most potent HAART regimens include efavirenz or lopinavir/ritonavir in combination with two NRTIs (23).

Based on a review of data from a number of studies, the preferred initial HAART combinations for adults are: efavirenz in combination with lamivudine and either zidovudine, stavudine, or tenofovir; or lopinavir/ritonavir in combination with lamivudine and either zidovudine or stavudine (24). A number of alternative regimens are less preferred because of the increased pill burden, potential adverse events, or limited efficacy data. Clinicians try to avoid stavudine as a first-line therapy because of its long-term, cumulative toxic effects.

NRTI Backbones

Multiple options are now available for the initial choice of dual NRTIs, the “NRTI backbone” (Table 17-8). The Nigerian guidelines recommend four of them: stavudine plus lamivudine, zidovudine plus lamivudine, tenofovir plus lamivudine/emtricitabine, or abacavir plus lamivudine (20). All of the backbone combinations are effective when combined with an NNRTI or PI, but their side effect profiles are different. Didanosine, although a very effective drug, should be avoided as an initial therapy because of the potential for developing neuropathy and pancreatitis, which can be fatal.

The NRTI, tenofovir, plus either lamivudine or emtricitabine, has been shown to be well tolerated and as effective as stavudine plus lamivudine (24). To date, it appears that effects of long-term toxicity such as lipoatrophy and hypertriglyceridemia occur less frequently with tenofovir than with stavudine-based treatment (25). The coformulation of a tenofovir/emtricitabine (Truvada[®]) tablet means that this combination can be taken once daily with efavirenz with only two pills. Compared to Combivir[®], the coformulation Truvada, when given in combination with efavirenz, had a superior virologic effect, less toxicity, and no tenofovir resistance. The Truvada/efavirenz combination is now widely used in Western countries because of its high virologic success and low toxicity rates (26).

Stavudine plus lamivudine is well tolerated in the short term; however, over time, some patients develop peripheral neuropathy and/or peripheral and facial lipoatrophy. Zidovudine plus lamivudine is associated with gastrointestinal side effects, anemia, and neutropenia; however, it is not associated with

Table 17-8. 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); lactic acidosis (rare)
Tenofovir + lamivudine or emtricitabine (an alternative recommendation)	Acutely well tolerated; fewer long-term complications	Fewer long-term complications; expensive; limited availability; drug interactions more likely with tenofovir (i.e., atazanavir); tenofovir must be taken with food
Stavudine + didanosine (an alternative, not recommended initially)	Effective; inexpensive	Peripheral neuropathy; pancreatitis; lactic acidosis (rare); lipoatrophy; hypertriglyceridemia; didanosine must be taken without food
Zidovudine + didanosine (an alternative, not recommended initially)	Effective; inexpensive	Side effect profile not optimal: gastrointestinal effects; anemia; neutropenia; peripheral neuropathy; pancreatitis; lactic acidosis (rare); lipoatrophy
Abacavir + lamivudine	Effective and well tolerated	Abacavir hypersensitivity reaction
Zidovudine + stavudine (contraindicated)	None; should never be used	Antagonistic interaction; should never be used together

Abbreviations: HAART: highly active antiretroviral therapy; NRTI: nucleoside reverse transcriptase inhibitor

peripheral neuropathy and is associated with less peripheral and facial lipoatrophy than stavudine-containing regimens. Because of the high prevalence of anemia in Nigeria, the hemoglobin of all patients commencing treatment with zidovudine must be checked; zidovudine is contraindicated if the hemoglobin is less than 8 gm/dl.

The combination of abacavir and lamivudine is well tolerated, is usually not associated with mitochondrial toxicity, and can be dosed once or twice daily. A coformulation of the two drugs (Epzicom[®]) has been used successfully in a number of clinical trials (27). One major limitation of the widespread use of abacavir, however, is the occurrence of hypersensitivity reaction (HSR) in 5% to 10% of patients, which may occur in the first few weeks of therapy. Thus, physicians need to be trained to distinguish abacavir hypersensitivity rash from nevirapine-associated rash. Moreover, subsequent rechallenge after initial hypersensitivity can lead to death. HLA haplotype B-5701 has been associated with abacavir HSR, but the magnitude of the association is uncertain since many patients with the HSR lack HLA B-5701 (28). It has also been suggested that heat shock proteins (Hsp 70) represent an early component of the abacavir-specific immune response, which is sensitive to inhibition of type 1 alcohol dehydrogenase and influences interferon-gamma expression (29). It appears that African ethnicity, male gender, and CDC class C disease are associated with reduced risk (30). A preliminary report suggested that the incidence of severe HSR may be higher with once daily dosing compared to twice daily dosing (31).

Coformulated NRTI Combinations

There are currently three coformulated dual NRTI combinations: zidovudine/lamivudine (Combivir), abacavir/lamivudine (Epzicom), and tenofovir/emtricitabine (Truvada). When combined with an

Table 17-9. Antiretroviral Drugs Added to Dual Nucleoside Combinations in HAART

Third 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); unfavorable 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-limited); rash (usually mild to moderate); potential fetal abnormalities—cannot be used in pregnancy
Lopinavir/ritonavir (Kaletra®) (an alternative choice)	Potent; relatively well tolerated	Gastrointestinal; hyperlipidemia; abdominal and truncal fat accumulation; expensive; requires refrigeration
Indinavir with or without ritonavir (an alternative choice)	Inexpensive relative to protease inhibitors	Without ritonavir, 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; a low-pill burden; 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 favorable safety data available in pregnant women; low potency	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; must be used with ritonavir rather than alone; abdominal and truncal fat accumulation

Abbreviation: HAART: highly active antiretroviral therapy

NNRTI or a PI, these formulations offer reduced pill burden, improved adherence, and preserved potency. A notable disadvantage is the lack of flexibility in dosing: if changes are needed, the patient must revert to the individual drugs. Unlike the traditional thymidine NRTI backbones, failures with the abacavir/lamivudine and tenofovir/emtricitabine backbones are associated with M184V mutations with or without the L74 or K65, which leaves some plausible sequencing options (32). Interestingly, individuals developing the K65R mutation who experience virologic failure are still able to maintain a mean viral load decrease of 0.9 log from baseline as observed in the Gilead 903 study (24). In this study, using both virtual phenotype and true phenotype, patients with K65R mutation were hypersensitive to zidovudine and stavudine and had full or partial susceptibility to abacavir, and in many cases, based on the results of testing resistance alone, remained sensitive to tenofovir and didanosine. This occurred in the absence or presence of the M184V mutation, which is known in vitro to hypersensitize the virus to tenofovir. Therefore, patients experiencing failure with a K65R mutation may have virologic success with a second regimen, including one containing tenofovir.

Other NRTI Combinations

Alternative double nucleoside choices exist; however, their use is limited by availability constraints or potential toxicity. The combination of stavudine plus didanosine has been shown to be quite effective. However, toxicity from the combination is unacceptable with excessive rates of pancreatitis, lipoatro-

phy, peripheral neuropathy, and lactic acidosis. Tenofovir plus didanosine is generally inappropriate for initial regimens, and should be avoided in salvage regimens, if alternatives are available. When used together, didanosine dose should be reduced. Tenofovir plus abacavir should be avoided; this combination has been associated with an increased risk of virologic failure, especially in patients with a viral load of more than 100,000 copies/ml and a CD4+ count of fewer than 200 cells/mm³ (33). Even among some people who achieve viral suppression, a paradoxical decline in CD4+ count occurs, which is poorly understood. It is worth noting that inappropriate dosing of didanosine was a common finding in patients with adverse outcomes (34). Lamivudine plus didanosine has been demonstrated to be an effective NRTI backbone in many studies. However, potential problems with this regimen include pancreatitis and peripheral neuropathy due to didanosine and probably increased risk of some manifestations of mitochondrial toxicity. Thus, it is not used in initial regimens. Emtricitabine has also shown to be effective when combined with didanosine and efavirenz once daily in treatment-naive patients (35), but this combination is not used in initial regimens because of toxicity. Zidovudine plus didanosine is usually used in second-line regimens after failure of initial therapy. Table 17-8 outlines the advantages and disadvantages of different NRTI combinations.

Selecting the Third Drug

In addition to the NRTI backbone, the third drug of a HAART regimen is a critical choice and should be chosen based on potency, pharmacokinetics, adverse event profile, and availability (Table 17-9). The most common third drug added to a HAART regimen is a non-nucleoside, either nevirapine or efavirenz. Both drugs have favorable pharmacokinetic profiles, are dosed infrequently (typically once daily), and have been shown to be effective (36). Both drugs are inducers of the cytochrome P450 (CYP450) system and may lower the effective concentrations of hepatically metabolized drugs in the blood, although to different degrees (37). The largest study to date comparing efavirenz-containing and nevirapine-containing regimens (the 2NN trial) found that both had similar virologic and immunologic efficacy. The major difference between these drugs is their toxicity profiles. Efavirenz was better tolerated with lower incidence of severe hepatic and cutaneous toxicity (38). Delavirdine, a third approved non-nucleoside, is infrequently used because of a higher pill burden and a lack of central nervous system penetration. Delavirdine is an inhibitor of CYP450. Non-nucleoside drugs should not be used together and should only be used in combination with two other ARVs.

Nevirapine

Nevirapine, the first non-nucleoside to be approved, is associated with rash in approximately 17% of patients. One-half of the rashes are mild, characterized by intact skin and absence of blistering, skin desquamation, involvement of mucous membranes, angioedema, or systemic signs (body aches, arthralgias, myalgias, fevers, lymphadenopathy, or significantly elevated hepatic transaminases). It is usually self-limited and does not require discontinuation of the drug. Antihistamines may offer some symptomatic relief. In approximately 0.5% of patients, the rash can be serious and includes potentially fatal Stevens-

Johnson syndrome or toxic epidermal necrolysis. Following the recommended lead-in dosing reduces the likelihood of developing nevirapine-associated rash.

Mild asymptomatic liver enzyme elevations (LEE) are relatively common, often self-limited, and do not require treatment discontinuation. Liver enzymes should be checked regularly until they have returned to normal. Symptomatic elevations of ALT and hepatic failure also occur with nevirapine (39), particularly during the first six weeks of treatment. Reported symptoms, including nausea, vomiting, and abdominal pain, are similar to those that occur in patients with pancreatitis and lactic acidosis; therefore, these conditions should be excluded. About half of the patients with nevirapine-associated hepatotoxicity have rash with or without other manifestations of autoimmune disease, strengthening the theory that it is essentially a hypersensitivity phenomenon. Risk factors for this rash-associated hepatitis include female with CD4+ counts greater than 250 cells/mm³ and male with CD4+ counts greater than 400 cells/mm³ (40). Therapy should be discontinued in patients with symptomatic LEE (with or without manifestations of hypersensitivity), liver failure, or lactic acidosis. Therapy with ARVs that are less hepatotoxic may be cautiously restarted after resolution of the LEE. Required supportive therapy should be given. Fatal hepatic failure has been reported but is rare (41).

Although nevirapine is not absolutely contraindicated in patients coinfecting with HIV and hepatitis C virus (HCV), it should be used with caution because of preliminary reports that suggest an accelerated rate of hepatic fibrosis in such patients (42). Choosing another agent may be prudent to reduce the risk of necroinflammation and fibrosis in some patients. Also, the use of nevirapine in post-exposure prophylaxis (PEP) regimens is discouraged because of its propensity to cause hepatotoxicity in patients with intact immune systems (39). For HIV-infected patients who are coinfecting with hepatitis B virus (HBV) or HVC, it is usually difficult to distinguish liver enzyme abnormalities caused by ARV hepatotoxicity or hypersensitivity from those caused by a flare of HBV or HCV due to immune reconstitution. It is important to make this distinction correctly, however, since it directly impacts the decision to continue or interrupt HAART. A helpful strategy involves close monitoring of the patient's laboratory and clinical course: patients who remain asymptomatic and have improving liver enzymes while receiving the same ART regimen probably have immune reconstitution hepatitis flare, in which case therapy can be cautiously continued. Therapy should be interrupted in those who are symptomatic and those who experience progressive worsening laboratory results on ART, because they probably have hepatotoxicity or hypersensitivity. A distinct advantage of nevirapine is its lack of adverse effects on the fetus and newborn, hence its use for prevention of vertical transmission. A potential disadvantage is an interaction with rifampicin, which precludes the use of the two drugs together.

Efavirenz

Efavirenz also is associated with rash, but this is usually less severe than with nevirapine and only infrequently leads to drug discontinuation. The primary problems associated with efavirenz use are central nervous system side effects and potential fetal abnormalities, specifically neural tube defects. The neuro-

logic effects associated with efavirenz include mood alterations, sleep disorders, unusual dreams, hypomania, and anxiety. Usually these effects are self-limited and resolve after several days or weeks. Because of the potential adverse effects on the fetus, efavirenz should not be administered during pregnancy or in women contemplating pregnancy. The interaction with rifampicin is less than that of nevirapine. When the drugs are used together, the efavirenz dose is usually increased from 600 to 800 mg daily, although this may not be necessary in all patients. In one randomized, controlled study among Thai patients with tuberculosis and an average body weight below 60 kilograms, there was no significant difference in virologic and immunologic outcomes between patients who received 600 mg of rifampicin and those who received 800 mg in combination with an efavirenz-containing HAART regimen (43). In another study conducted in Durban, South Africa, serial trough efavirenz levels were followed in HIV-infected patients (mean weight 59.7 kilograms) with smear-positive tuberculosis. The patients received HAART regimens of efavirenz, didanosine, and lamivudine, while tuberculosis was treated with a rifampicin-containing regimen. Although there was wide variability in its plasma concentrations, efavirenz at a dose of 600 mg/day was found to be efficacious, with virologic success, immunologic success, and weight gain (44). The rifampicin dose did not require adjustment.

Protease Inhibitors

An effective alternative to the non-nucleoside approach is the addition of a PI as the third drug in a HAART regimen. The most effective and practical PIs to be considered for first-line therapy include lopinavir/ritonavir (Kaletra[®]), indinavir with or without ritonavir, and atazanavir with or without ritonavir. Nelfinavir is also an option, but it has been demonstrated to be less effective than lopinavir/ritonavir-based therapy (45). Pharmacokinetic enhancement of nelfinavir with ritonavir is less effective than with the other PIs and is associated with unacceptable gastrointestinal intolerance. Saquinavir hard gel (Invirase[®]) is an alternative only when co-administered with ritonavir. Amprenavir and its newer prodrug form, fosamprenavir, are not yet available in Nigeria.

Unfortunately, at their regular doses many PIs have trough levels close to the lowest concentration at which they exert antiviral activity, thus providing opportunities for viral replication and resistance. Ritonavir is a unique PI in that at very small doses, it alters the metabolism of other PIs by inhibiting gastrointestinal and hepatic CYP450 enzyme system. This improves pharmacokinetic parameters of co-administered PIs such as peak plasma concentration (C_{max}), half-life, and trough concentration (C_{min}). The area under the plasma concentration versus time curve (AUC), which determines the overall viral exposure to the PI, is also increased, often allowing a reduction in the dose needed for effective treatment. Also, the inhibitory quotient—the ratio of C_{min} to the concentration needed to inhibit viral replication by 50% (IC₅₀), which influences the likelihood of developing resistance mutations—is improved with ritonavir-boosted PIs. For these reasons, ritonavir-boosted PIs generally have improved potency and greater pharmacokinetic barriers to resistance.

In contrast to some unboosted PI regimens, failure of ritonavir-boosted, PI-based regimens in previously PI-naïve patients is unlikely to be due to development of resistance to the boosted PI. This was well

illustrated when lopinavir/ritonavir plus two NRTIs was compared to nelfinavir plus similar NRTIs (45). The “anti-resistance” characteristic, which has been demonstrated with other boosted PIs, including atazanavir/ritonavir and fosamprenavir/ritonavir (46), underlies some of the strongest arguments in favor of boosted PI regimens. Also, ritonavir-boosting can be used to overcome low-level resistance to PIs.

Triple Nucleoside Regimens

Triple nucleoside combinations also have been studied as first-line HAART. These combinations allow sparing of NNRTIs and PIs. Although these combinations are convenient and cause fewer drug interactions, the potency of the fixed combination of zidovudine/lamivudine/abacavir has been inferior to non-nucleoside- and PI-based regimens (47). Therefore, triple nucleoside combinations should only be used in circumstances in which NNRTIs and PIs are either not available or not tolerated. Conversely, the combinations of tenofovir/lamivudine/abacavir or tenofovir/lamivudine/didanosine should be avoided because they failed in two studies (48,49). Resistance testing in both studies showed the emergence of both M184 and K65R mutations in patients with evidence of virologic failure.

Preliminary reports from the DART study of the evaluation of tenofovir/lamivudine/zidovudine have shown promising results (50). The good response with this particular regimen appears directly related to the presence of zidovudine and tenofovir, a combination that has bidirectional protection against resistance. One concern with the use of the DART regimen in some resource-limited settings, however, is the apparently increased risk of anemia (51). Nonetheless, the DART regimen is particularly promising in settings with high rates of tuberculosis coinfection, because it does not contain NNRTIs or PIs that are responsible for the drug interactions that complicate the management of both infections. Some quadruple NRTI regimens that contain zidovudine and tenofovir also have shown some promise in preliminary trials, but there are lingering concerns about broad NRTI resistance and a clear role for the regimen remains undefined. It should be noted that the DART study has no comparative treatment arm, and results must be interpreted with caution at this time.

STEPS TO INITIATE ANTIRETROVIRAL THERAPY

Assessment of the Patient

Several patient-related factors may influence the choice and outcome of ART in resource-limited countries. In Nigeria, many patients may delay visiting a clinic until they present with advanced HIV disease (WHO stage III or IV) because of the prevailing stigma and the absence of widespread counseling and testing. Patients may present with coexisting morbidities such as anemia, malaria, tuberculosis, or hepatitis, which may affect the choice of the drug regimen due to potential drug interactions and toxicities. A 2001 sentinel survey conducted by the Federal Ministry of Health found 23% of tuberculosis patients to be HIV positive (52). Most patients are poor, and financial constraints can cause treatment interruptions.

A detailed clinical evaluation of the patient should be made at baseline and every three to six months subsequently. Each visit should include a review of current symptoms and concomitant ill-

nesses. Clinical features and diseases should be categorized as HIV-related or AIDS-defining. The patient should also be screened for the presence of coinfections, including malaria, tuberculosis, HBV, and STIs.

A detailed medical history, including a history of any high-risk sexual behavior and the number of sex partners, should be elicited from the patient. The history should also include the sexual and other relevant history of the patient's sexual partner or partners, as this information can be useful in determining the patient's relative risks for other infections, such as with the hepatitis B, hepatitis C, and human papilloma viruses. Other important information includes a history of any previous blood transfusions and, in women, the history of previous pregnancies, antenatal care, and deliveries. Many patients in Africa may be taking traditional medications for HIV-related disease. Identifying the remedies a patient may be taking is important, as these drugs may cause drug interactions or affect liver or kidney function, the ultimate pathways for the metabolism and excretion of most ARVs.

The initial physical examination of the patient should be detailed and should include: measuring weight, temperature, and vital signs; checking the skin for rashes, ulcers, and lesions; checking the oral cavity for thrush and sore throat; assessing mental and emotional status; and making appropriate assessments of the following organs or systems: lymph nodes, chest and cardiovascular, abdominal and gastrointestinal, genitourinary and rectal, gynecologic (women), neurologic, and ophthalmic.

Baseline laboratory investigations should include a chest X-ray for tuberculosis and pneumonia; microbiologic tests for tuberculosis, including a sputum smear and cultures; a full blood count; a fasting blood sugar; kidney and liver function tests; a lipid profile, including triglycerides and cholesterol; a pap smear for women; appropriate swabs for STIs; hepatitis B and C antibody tests; a syphilis test; a pregnancy test if indicated; a CD4+ count; and a HIV viral load if available.

After the initial work-up of the patient, the physician should have the information needed to determine the patient's stage of HIV disease and to assess other factors that will influence treatment decisions, such as the presence of HIV-related diseases and other concomitant illnesses, like hypertension or diabetes; the patient's weight profile; and concomitant medications, including any traditional medications. The decision of when to start ART and what regimen to choose in Nigeria is complicated by prevailing factors such as pregnancy, the presence of comorbidities (tuberculosis, HBV, or HCV), anemia, consideration of uninfected partners, and the availability and cost of the drugs. A successful HAART regimen should be tailored to the patient. For instance, in patients with a significant psychiatric history, efavirenz may not be the optimal choice because of its associated central nervous system effects. In women who are likely to get pregnant during treatment, efavirenz should be avoided because of the potential for fetal abnormality. Patients who are malnourished and anemic prior to treatment are not good candidates for therapy with zidovudine. Knowledge about the drugs and the full background of the patient is essential in designing the most acceptable and adhered to HAART regimen. The physician should see the patient at subsequent visits to discuss treatment options, including the risks and benefits of ART, and to choose the optimal ART regimen.

A treatment plan must be developed that the patient understands and to which he or she will be committed. Patient education and preparation are key to subsequent commitment and adherence to the administered regimen. There should be no rush to start patients on ART as this can lead to non-commitment, dropouts, and the generation of drug resistance. Clinicians should assess the patient's readiness for medication before initiation of therapy, potentially during multiple consultations. Patient education should include discussion of the goals of ART as well as the expected outcomes based on clinical, CD4+ cell, and viral load responses. It is critical for patients to understand that the first regimen has the best chance of long-term success. In addition, education and counseling should incorporate a detailed discussion of the need for adherence and possibly a detailed adherence plan, including the use of treatment partners. Adherence should be monitored and assessed at each clinic follow-up visit because there is evidence that adherence wanes over time (53).

Patients should be encouraged to join support groups as both peer education and support from members strengthen adherence among patients on ARVs. Furthermore, adherence goals should be built into all patients' treatment plans and interventions. Toxicities are the most common reasons for poor adherence to medications (54). When the treatment regimen is chosen, patients must be counseled on how to take the specific medications, what side effects could potentially occur, what to do in the event of an adverse effect, and where to go with any treatment or disease-related questions.

The criteria for commencement of ART according to the Nigerian guidelines (20) in both adults and adolescents are:

- WHO Stage IV disease (AIDS) irrespective of CD4+ count;
- WHO Stage III disease (symptomatic HIV) with CD4+ counts of less than 350/mm³; or
- WHO Stage I or II disease with CD4+ counts of less than or equal to 200/mm³.

Table 17-10. Suggested Monitoring Schedule for Patients Starting HAART

	Pre-Treatment	Week 2	Week 4	Week 8	Every 12 Weeks	Every 4-8 Weeks	Every 24 Weeks
Physical exam	X	X			X		
Adherence counseling	X	X	X	X	X	X	
HIV RNA (if available)	X				X**		X
CD4+ cell count	X				X**		X
Complete blood count	X						X
Chemistry*	X						X

* includes serum lipids
 ** at first 12-week visit only
 Abbreviation: HAART: highly active antiretroviral therapy

MONITORING ANTIRETROVIRAL THERAPY AND PATIENT FOLLOW-UP

Before initiating therapy, the clinician and patient must agree on a schedule for monitoring the progress and effects of therapy (Table 17-10). At a minimum, the physician should evaluate stable patients every three months and order laboratory assessments twice annually. At treatment initiation, at the time of any treatment change, or with concurrent illnesses, monitoring should take place more frequently.

The first return visit to the clinic should be scheduled two weeks after the patient starts HAART. At this time, it is wise to assess the patient's tolerance of and adherence to the medications, especially any side effects related to nevirapine or efavirenz use, which occur in the first few weeks of therapy. A brief physical exam should be performed and, if indicated, a complete blood count and chemistry should be done to assess any potential adverse effects on blood count and hepatic function in particular. If the patient on a nevirapine-containing regimen does not have a rash or any medication-related side effects, the dose of nevirapine should be increased from 200 mg/day to 200 mg twice daily. If a rash is present in any form, the 200 mg dose should be continued until resolution, at which time the dose can then be increased.

The patient should again return to the clinic every four weeks to pick up drugs. This schedule ensures supervision of drug therapy and provides opportunities for adherence counseling and contact tracing for patients who miss their appointments. A brief and targeted physical examination should be performed. In resource-poor settings like Nigeria, it is not practical to carry out plasma HIV RNA (viral load) at four weeks to assess early efficacy because of costs and the unavailability of the tests in most ART centers. However, CD4+ counts and plasma HIV RNA levels should be monitored 12 weeks after commencing therapy and subsequently every 24 weeks if patients are stable. Unstable patients may require more frequent monitoring. The standard of care in Nigeria for monitoring ART is CD4+ cell enumeration and plasma viral load quantification. Plasma viral load correlates with disease progression (55) and is a critical parameter for assessing virologic failure. In tertiary and referral centers that have the necessary infrastructure and trained personnel to perform this assay, viral load quantification will provide the physician and patient with critical information on virologic status during ART and will indicate when virologic failure has occurred. In points of care where this assay is not available, CD4+ cell enumeration and clinical monitoring can be substituted.

Targeted physical examinations should be done every 12 weeks and a detailed examination every 24 weeks. Comprehensive laboratory monitoring should be done every 24 weeks for stable patients (Table 17-10). This should include a complete blood count and blood chemistry including liver enzymes, renal function, serum lipids, a CD4+ count, and plasma HIV RNA (where available). Every attempt should be made to discuss the laboratory results at follow-up visits, as this is an important part of promoting adherence and commitment to therapy. As much as possible, these results should be used in making decisions about drug management, as patients are often encouraged by a decline in HIV RNA and lack of toxicity.

Patients should be instructed to return to the clinic at any time between scheduled appointments if they have treatment-related questions or problems. In the event they believe they are experiencing a

Table 17-11. Adherence Factors for Antiretroviral Therapy

Factors Associated with Improved Adherence	Factors Associated with Poor Adherence
<ul style="list-style-type: none"> • Patient knowledge of disease and drugs • Patient belief systems about HIV and modes of treatment • Clinician knowledge of disease and drugs • Low pill burden • Infrequent dosing schedule • No food effect on drugs • Continuous availability of drugs • Tracking treatment defaulters • Treatment support (directly observed therapy, family member, community and support group) • Develop linkage with local community-based organizations on adherence education and strategies 	<ul style="list-style-type: none"> • Drug toxicity • Heavy pill burden and frequent dosing schedule • Active illicit drug and/or alcohol use • Untreated/uncontrolled psychiatric illness • Expense of drugs, monitoring, and travel • Inconvenient appointments with clinic • Lack of adequate transportation • Lack of food, clothing, and shelter • Poor nutritional support • Young age

drug-related serious adverse event and yet cannot visit the clinic, they should be instructed to stop all ARVs until they seek the advice of a professional in the clinic.

Adherence and Treatment Support

Success with any medication depends not only on the intrinsic properties of the drugs, but also on the ability of the patient to take the medications. HIV infection is one of the most difficult chronic diseases to treat optimally. Multiple drugs must be administered, the pill burden may be high, the regimen may be complicated, toxicities are common, drug interactions may occur, food restrictions may be required, medications are expensive, the regimen carries an enormous social and psychological burden for many, and therapy is lifelong. HAART is lifesaving, yet it is anything but easy and it is very unforgiving. Less than 95% adherence to a regimen can lead to viral resistance and ultimately treatment failure (56). It has been estimated that every 10% decrease in adherence leads to a corresponding 16% increase in mortality (57).

A number of factors affect adherence (Table 17-11). These include the patient’s belief systems regarding the etiology (58), as well as their knowledge of the management and treatment of HIV infection (59). Other factors include the social, emotional, and financial status of the patient as well as the tolerability, dosing schedule, and pill burden of the drug regimen. Active use of injected drugs or alcohol, psychiatric disease, and depression are also important factors promoting non-adherence. Young people and those with a disruptive social life are also likely to be non-adherent to ART. Studies among HIV-infected patients have indicated a strong preference for once-daily dosing and compact regimens (60). Furthermore, several reports have observed a significant correlation between low pill burden and improved virologic response (61,62).

Despite the difficulties of taking lifelong treatment, improving patient adherence is possible. It is imperative to provide the patient with basic knowledge about ARVs and HIV disease and to stress the overall importance of adherence prior to initiating ART. Over the course of several visits before initiating

therapy, clinicians can take a number of steps to improve the chances of good adherence, such as discussing cultural beliefs and myths about HIV and ART; discussing the risks and benefits of ART, including dosing schedules and side effects associated with different regimens; establishing readiness and full commitment to therapy; fostering trust in the health care team; recruiting family and friends for disclosure and treatment support; and developing support groups for people living with HIV/AIDS. Activities that engage family and community members in adherence education and treatment support can both promote adherence and minimize stigma.

Upon initiating ART, clinicians can take further steps to improve the likelihood of good adherence, such as tailoring the regimen to the patient’s lifestyle; familiarizing the patient with the pills and dosing schedule; scheduling follow-up visits soon after initiation to discuss side effects and any other obstacles to taking the drugs; promptly responding to any problems by adjusting, changing, or stopping medications when needed; and treating associated conditions, such as depression, anxiety, psychotic disorders, and drug addiction. Facilitating family-based care — in which all infected members of the family are seen together at follow-up clinics for ART — is another useful strategy for enhancing adherence and successful ART.

The potential for improved adherence is also maximized when clinicians develop long-term plans for treatment and are careful to select regimens that will avoid drug interactions and side effects to the extent possible. Prescribing regimens with low pill burdens, infrequent dosing, minimal toxicities, and no food interactions are all associated with optimal adherence. Fixed dose combinations (63), pill boxes, and blister packs have all been found to be successful in increasing adherence to drugs in various resource-limited settings. Pagers and alarm clocks can also help to remind patients to take their medication. Tracking defaulters with pharmacy logs and home visits by clinic staff can be particularly useful in preventing prolonged periods of poor adherence and addressing potential problems with adherence as they arise. Other factors that may enhance adherence to ART include providing medications free of charge for those who cannot afford them. It has been suggested that a cost-sharing program could facilitate adherence to ART, although a recent report from Senegal does not support such an approach (64).

Directly observed therapy (DOT) is another way to ensure adherence, but the logistical requirements of this are often daunting, especially because HIV, unlike active tuberculosis, requires lifelong treatment. DOT is relatively easy to administer in controlled environments such as prisons, but it can also be implemented at the community level. For example, a large community-based ART program in Haiti used community health workers who visited patients daily. All patients gained weight, and fewer than 5% required medication changes due to side effects or toxicity. Among patients for whom viral load was tested, 86% had suppressed viral loads (65). Various cohort studies with DOT have observed that high therapeutic success can be achieved with PI- or NNRTI-based triple therapy regimens (66,67). The potential application of DOT-HAART in the Nigerian setting has shown promising preliminary results (68).

Adherence should be measured periodically; ideally, at every clinic visit. The most commonly used method is direct patient interview, which tends to overestimate adherence. Patient-reported poor adherence is usually accurate, however. A clinician’s estimate of the likelihood of adherence is often unreliable.

DRUG RESISTANCE

With a virion half-life of 30 minutes and a daily production of up to 10^9 virions, HIV reverse transcriptase enzyme incorporates approximately one mutation per genome per replication cycle (69). The higher the viral replication, the more frequent the mutations, with almost every single point mutation occurring daily. These mutations produce a population of diverse, yet related viral variants referred to as “quasispecies,” which are generated by the error-prone viral RNA-dependent polymerase. Whenever a mutation occurs, the fitness—or replicative capacity—of the altered virus may be enhanced, unchanged, or reduced, depending on the specific mutation and its interactions with the host immune system and the presence or absence of ARVs.

Approximately half of the virus population in plasma is cleared and replaced each day. The high turnover allows a rapid emergence of drug-resistant variants under selective pressure. To maximize its chances of survival, HIV, like other pathogenic organisms, evolves toward strains with the greatest ability to replicate in a given environment. Therefore, evolution toward wild-type virus, which typically has high replicative capacity, is favored in the absence of ARV pressure. On the other hand, when a patient is taking ARVs, viral evolution favors strains that are best able to replicate in that environment—that is, strains that are resistant to the particular drug or drugs. If the selected drug-resistant strain is of appropriate fitness, it may eventually become the dominant strain, although resistant variants are usually replaced by residual wild-type virus if the drug selective pressure is removed. Resting latently infected cells can, however, continue to harbor drug-resistant provirus.

The most effective way to interrupt the cycle of viral replication and mutation is to attain complete, durable viral suppression. Incomplete viral suppression encourages viral mutation and resistance. The factors contributing to incomplete suppression of virus replication include poor adherence, pharmacologic factors, host factors, inadequate ARV potency, and transmitted drug resistance. Mechanisms that result in HIV drug resistance include decreased drug binding, increased enzyme efficiency, nucleotide excision, increased target concentration, altered (co)receptor affinity, and altered drug transport. The factors linked to detection of resistance mutations are:

- A high baseline viral load or low baseline CD4+ count;
- Substantial but imperfect adherence (highest-risk patients);
- Injection drug use; and
- Use of drugs with low resistance development thresholds.

Drug resistance is a major problem for HIV-infected patients on ART. Among treatment-naïve subjects initiating HAART, 25% developed drug-resistance mutations during a 30-month follow-up (70), while multi-class resistance was noted in about 10% (71). Resistance testing has been observed to improve treatment outcome in patients receiving ART (72). Mutations on the reverse transcriptase and protease genes can be mapped to specific codon changes that are often correlated with viral resistance to a specific drug, subclass of drugs, or class of drugs. While measuring resistance has become more

common in the developed world, resistance testing is expensive and not available in many resource-poor countries like Nigeria. However, a fundamental understanding of viral resistance is required to treat patients, particularly those who have not responded to or failed a prior treatment regimen. Therefore, resistance testing should be embraced in tertiary health institutions as part of the process of monitoring individuals on ART in Nigeria.

Adherence is the most important factor in determining whether resistance emerges during treatment (73). The relationship between adherence and the accumulation of drug resistance is complex and variable. Drug resistance occurs at a range of adherence between 60% and 80% (74). Drug-resistance mutations that are associated with reduced viral fitness and virulence may lead to a fairly durable treatment benefit but also delay the need to modify therapy, thus allowing high-level resistance to emerge. Other mutations are associated with reducing (cross-resistance) or enhancing (hypersensitivity) the activity of some ARVs in the same or other classes.

Transmitted Drug Resistance

As ARV use becomes widespread in a given area, one might expect an increase in the proportion of patients who become infected with drug-resistant HIV strains. However, the emerging trend in places with a long history of ART is that transmitted resistance is low if HAART is comprehensive and widely available. Epidemiologic data from the CATCH study found the overall prevalence of HIV strains resistant to at least one ARV was 9.6% (75). The prevalence of drug-resistant HIV among patients infected for a year or less was 10.9%, compared to 7.5% among patients infected for more than one year. Data from the United States have demonstrated similar results (76). Among patients with primary HIV infection, 11.5% had resistance to at least one ARV compared to 7.5% among patients with chronic HIV infection. In both studies, the most common resistance was to NRTIs. Historical models have been used to predict that over the next decade, the rate of transmission of drug-resistant virus in Africa would remain below 5% and that most resistant strains would result from acquired, not transmitted, resistance (77).

Antiretroviral Therapy and Acquired Drug Resistance in Nigeria

The choice of HAART regimen may help to avoid resistance. Regimens that promote adherence by using pills with low toxicity, doses of one or two times a day, and fixed dose combinations will delay the onset of resistance. Other factors promoting a durable regimen include drugs that are potent, have favorable pharmacokinetic properties, and have a high barrier to resistance. The choice of the first regimen may determine future treatment options by determining the resistance pathways. There is, therefore, a need for studies to determine optimal regimens for the Nigerian ARV program. Nevirapine-containing regimens for PMTCT in the country also need to be evaluated in view of the reports of high-level resistance from the use of single-dose nevirapine (78) and the poor response—due to resistance—of these patients to subsequent nevirapine-containing HAART combinations (79).

Testing for Resistance

Drug resistance can be determined by two main techniques: genotypic and phenotypic testing. Genotypic testing detects specific mutations in the reverse transcriptase and/or protease genes. Phenotypic testing determines the relative amount of drug needed to suppress viral replication compared to a reference wild-type virus. These tests are most reliable when the viral load is greater than 1,000 copies/ml.

Genotypic tests are more readily available, have a quicker turnaround time, are less technically demanding to perform, and are relatively less costly. Another important advantage of genotyping is the ability to detect mutations that are in the process of back mutation (from resistant virus to wild-type, or “revertant” mutants), and whose amino acid sequences are between those of resistant virus and wild type virus. These partially revertant mutants may not influence phenotype, but their identification on genotypic testing offers valuable information. Genotyping has limited usefulness if the clinical significance of detected mutation has not been previously characterized, and if the mutations are multiple and complex, genotyping requires expert interpretation.

Phenotypic tests measure drug susceptibility directly. However, the assay is technically more demanding, limited in availability, and relatively expensive, and determining clinically relevant cut-offs or breakpoints is often difficult and variable. Advantages of phenotypic resistance assays include ease of interpretation and provision of meaningful information when multiple mutations are present in the same sample. Thus, phenotypic testing may be preferred to genotyping in heavily treatment-experienced patients, who harbor multiple, complex resistance mutations.

The usefulness of resistance testing is in the identification of drugs that are likely to work and, independently, not to work. These determinations may be imperfect, however, because clinically relevant mutations may not be detected by standard resistance tests if they constitute a very small proportion of the total viral pool. The more “active” drugs contained in a regimen, the greater the likelihood that the therapy will succeed.

The following situations warrant resistance testing consideration:

- Before initiating therapy in a patient exposed to possibly resistant virus, such as when a patient has been exposed to single-dose nevirapine or has had a sexual partner who was exposed;
- In patients who fail to adequately respond to first-line or second-line therapy; and
- In patients who experience viral “rebound” or a return of HIV RNA toward baseline.

Several caveats need to be considered about resistance testing: tests are most useful when the patient is on an ARV regimen; the absence of resistance to a drug that a patient has previously taken does not eliminate the possibility that the virus is resistant to that drug; if resistance to a drug is ever documented, it is assumed that the patient is likely to archive resistance virus indefinitely, regardless of subsequent test results; and expert advice is often required to interpret resistance test results.

TOXICITY

The use of ART for treating HIV-infected people in developing countries has increased significantly in the past few years and has already witnessed the gains of reduced mortality and morbidity seen in the developed world in the mid-1990s (80). Even though the adverse events of these drugs have been well documented (Table 17-12), experience in developing countries, particularly Nigeria, has been limited because of inadequate data gathering and the short duration of experience in the country.

Key Drug-Drug Interactions

The use of ARVs is complex. Drug-drug interactions can occur, posing a major challenge for treating HIV positive individuals. Interaction among drugs used in combination therapy, with other drugs, and even with food may affect the absorption, distribution, metabolism, and excretion of the various drugs used in the regimen. In general, clinically significant drug interactions occur when a change of not less than 25% of the drug concentration occurs.

The most studied interactions have been between drugs using the CYP450 enzyme system for drug metabolism in the liver. Because NNRTIs and PIs are metabolized through this system, many clinically relevant drug interactions occur with the use of these drugs. The interaction may take place via one of three pathways: as a substrate; as an inhibitor; or as an inducer. Rifampicin, rifapentine, and rifabutin all have significant interactions with NNRTIs and PIs by virtue of their ability to act as inducers of the CYP450 enzyme in the liver. Blood levels of NNRTIs and PIs are significantly reduced when combined with rifamycins.

However, the effect is least with rifabutin, hence the recommendation that rifabutin be used with NNRTIs and PIs in patients coinfecting with HIV and tuberculosis. Rifabutin is metabolized by

Table 17-12. Adverse Events to Antiretroviral Therapy	
Drug	Toxicity
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors	
<i>Class Related</i>	Lactic acidosis Hepatic steatosis Lipodystrophy (peripheral fat wasting)
<i>Drug Specific</i>	
Stavudine	Peripheral neuropathy, hepatitis
Zidovudine	Bone marrow suppression, myopathy, nausea, and vomiting
Didanosine	Pancreatitis, dry mouth, peripheral neuropathy
Lamivudine	Mild or no side effects
Abacavir	Hypersensitivity reaction, nausea
Tenofovir	Bone demineralization, renal failure
Non-Nucleoside Reverse Transcriptase Inhibitors	
Nevirapine	Rash, hepatitis, Stevens Johnson syndrome
Efavirenz	Rash, dysphoria, mood changes, vivid dreams, hypercholesterolemia, fetal abnormalities
Protease Inhibitors	
<i>Class Related</i>	Lipodystrophy (fat wasting/accumulation), hyperlipidemia, diabetes mellitus
<i>Drug Specific</i>	
Nelfinavir	Diarrhea, rash
Saquinavir	Few side effects
Indinavir	Hyperbilirubinemia, nephrolithiasis, nail changes, paronychia, dry skin, abdominal cramps
Ritonavir	Perioral dysaesthesia, flushing, hepatitis, diarrhea, nausea, vomiting, abdominal cramps
Amprenavir	Rash, nausea, diarrhea
Lopinavir	Diarrhea
Atazanavir	Hyperbilirubinaemia

CYP3A; therefore, its serum concentration is increased by PIs and delavirdine, which are inhibitors of the enzyme. As a result, rifabutin's dose has to be reduced if it is used with PIs or delavirdine. On the other hand, since efavirenz induces CYP3A and reduces serum concentrations of rifabutin, the dose of rifabutin has to be increased when they are used together. Rifampicin and rifapentine are not substrates for CYP3A, and their levels are not significantly affected by inhibitors or inducers of the enzyme. No significant interactions occur between rifamycins and NRTIs. Rifapentine is not recommended in HIV-infected patients with tuberculosis, because it is associated with rifamycin-mono-resistant relapse.

Double-boosted PIs are now increasingly used to treat heavily experienced patients in whom it is critical to suppress viral load. Lopinavir/ritonavir should not be combined with amprenavir or fosamprenavir, because reports have indicated that this combination leads to profound reduction in plasma concentrations of the drugs (81). Similarly, the concentrations of lopinavir and indinavir are reduced when boosted lopinavir is used in the combination (82). It is not necessary to increase the dose of ritonavir when saquinavir is co-administered with lopinavir/ritonavir (83). Co-administration of a newer PI, tipranavir, lowers the concentrations of boosted saquinavir, lopinavir, and amprenavir (84).

A number of tenofovir-related interactions have also been observed. Tenofovir increases the concentration of didanosine (85). Therefore, the enteric-coated form of didanosine at a reduced dosage of 250 mg/day should be used in combination with tenofovir. Atazanavir and lopinavir/ritonavir each increase the levels of tenofovir (86,87); hence patients receiving HAART combinations of these drugs must be monitored because of possible adverse effects. On the other hand, tenofovir causes significant reduction in the plasma concentration of atazanavir, and ritonavir boosting is recommended whenever they are used together.

The absorption of atazanavir requires low gastric pH. Thus, it should not be used with proton pump inhibitors. However, preliminary results suggest that some H₂-blockers such as famotidine can be safely administered with ritonavir-boosted atazanavir, although dosing may need to be altered (88).

The combination of tenofovir DF, lamivudine, and abacavir or tenofovir DF, lamivudine, and didanosine resulted in dramatic failures in virologic suppression (44,45), throwing into doubt the possible use of these drugs for once-daily regimens. Studies suggest that the drug interactions arising from the use of these combinations may arise from genetic barriers, rather than plasma (pharmacodynamic) interactions between the individual drugs (89).

SWITCHING DRUGS

Numerous reports have alluded to intolerability as the most common reason for failure of the first drug combination. A significant percentage (21%) of patients in the Italian ICONA study stopped their drugs because of toxicity (90). These observations — coupled with evidence linking PIs to lipid abnormalities and the effect of adherence on treatment outcomes — motivated physicians to switch patients already well suppressed from one class of ARVs to another.

The most frequent reasons for physicians to consider ARV switching are:

- to improve adherence by reducing the pill burden, removing food requirements, and reducing the dosing frequency of various drug combinations, which can be achieved by using a compact, once-daily regimen;
- to manage actual or possible toxicity; this includes not only morphologic and metabolic disturbance, but also other important adverse events, such as anemia, hypersensitivity reactions, and peripheral neuropathy;
- to reduce the risk of clinically important drug interactions, such as between nevirapine and rifampicin; and
- to take advantage of the more convenient new fixed dose formulations.

The main outcomes determining likely success of switching include: maintenance of virologic control; maintenance of CD4+ count response (and immune function); improvement, resolution, or prevention of toxicity; and improvement in patient adherence and quality of life.

People with HIV infection appear to have a strong preference for once-daily dosing and compact therapy (91). Clinical studies indicate that potential once-daily ARV regimens are as effective as past standard-of-care regimens (92). Once-daily therapy is not always superior to twice-daily regimens, however. One concern with once-daily dosing is the potential consequence of a missed dose, a phenomenon that has been described as “pharmacokinetic forgiveness.” Pharmacokinetic forgiveness of a drug is the likelihood of maintaining therapeutic concentrations of the drug despite occasional missed doses. This concept is critical when comparing once-daily regimens with twice-daily regimens. Although once-daily regimens are associated with a higher overall adherence percentage than twice-daily dosing, an important difference is that those on once-daily regimens appear more likely to miss two consecutive doses (93). Since missing consecutive doses of ARVs may be a more significant factor for resistance development than missing single doses, it cannot be assumed that the higher adherence percentage of once-daily regimens makes them better than twice-daily regimens in all situations. The relevance of these preliminary observations to the clinical outcomes of patients is being investigated.

Thymidine analogues have an increased relative risk of adverse events within the NRTI class; hence, switching to a better-tolerated agent — abacavir or tenofovir DF — may help avoid or ameliorate thymidine-analogue-associated toxicities. In this regard, stavudine carries a higher relative risk than other NRTIs for mitochondrial toxicities, including morphologic changes from lipodystrophy and lactic acidosis. In contrast, lamivudine, emtricitabine, abacavir, and tenofovir DF do not appear to be associated with limb fat loss and are less likely to induce lactic acidosis.

Switching from stavudine to tenofovir DF, but not to abacavir, is associated with lipid improvements. A newly approved once daily PI, atazanavir, which has little or no effect on lipids (94), has added another switch option. These two strategies represent new treatment approaches to lipid management.

NRTIs are associated with few clinically important drug interactions, and most can be managed by dose modification rather than drug substitution. The exception is the switch from didanosine to an alternative

Table 17-13. Defining Success and Failure of Antiretroviral Therapy

Defining Successful HAART Response	Defining Treatment Failure
HIV RNA decreases by $> 1.0 \log^{10}$ copies/ml after one month	HIV RNA does not decrease $< 1.0 \log^{10}$ copies/ml by one month
HIV RNA decreases to < 400 copies/ml by week 24	HIV RNA is > 400 copies/ml at week 24
If HIV RNA unavailable, CD4+ increase by > 50 cells/mm ³ from pretreatment levels by 24 weeks	HIV RNA increases to within $0.5 \log^{10}$ copies/ml of pretreatment levels at any time
	CD4+ decreases to below pretreatment levels

Abbreviation: highly active antiretroviral therapy

NRTI in patients planning to start hepatitis C therapy with ribavirin. The fixed-dose coformulations of abacavir/lamivudine and tenofovir DF/emtricitabine are attractive not only for treatment initiation and switching for virologically suppressed patients but also for patients coinfecting with HIV and HBV. Lamivudine, tenofovir, and emtricitabine all have dual activity on HIV and HBV, and these effects may be synergistic (95). Since all NRTIs except abacavir are mainly renally excreted, the dose of these drugs should be reduced in patients with renal insufficiency. Therefore, fixed-dose coformulations are usually inappropriate in such patients.

Treatment Failure and Indications for Change of Therapy

Defining Antiretroviral Success and Failure

Successful ART implies that a patient has taken his or her drugs and responded to treatment. A successful response is associated with a rapid decline in plasma HIV RNA and a corresponding increase in CD4+ count (Table 17-13). After one month of starting a successful HAART regimen, the plasma HIV RNA should have declined at least 10-fold, or one \log^{10} copies/ml, while the CD4+ count should have risen above the starting point. Within 12 weeks of starting therapy, approximately 80% of patients will have HIV RNA less than 400 copies/ml and the CD4+ count should have increased by approximately 50 cells/mm³ (96). The maximal effect of treatment should be observed in most patients by 24 weeks. More than 95% should have plasma HIV RNA below 400 or 50 copies/ml, depending on the assay used, and the CD4+ count increased by 50–100 cells/mm³ (97). There is greater variability in the change in CD4+ count, especially early in treatment. Of note, approximately 10% of patients have a disconnection of response in HIV RNA and CD4+ counts in that HIV RNA declines, but the CD4+ count increase is blunted. Factors associated with such reduced CD4+ cell response include: older age, a lower baseline CD4+ count, and a very low nadir CD4+ count (98). Also, tuberculosis and, less strongly, malaria have been associated with decreased CD4+ cell counts. These patients may require continued prophylaxis with cotrimoxazole for opportunistic infections if the CD4+ cell count is below 200. If the plasma HIV RNA does not decrease steadily over the first three months or it rebounds to within $0.5 \log^{10}$ copies/ml of pre-therapy values, then the HAART regimen is failing. By 24 weeks if the HIV RNA has not decreased to levels below detection (fewer than 400 copies/ml), the patient should be considered as having failed the therapy.

In addition to the laboratory changes in HIV markers, within the first few months of therapy, patients should feel better clinically if they were symptomatic prior to therapy. Typically patients describe an improved sense of well-being, weight gain, and less fatigue. They may note a decrease in oral or vaginal candidiasis, fewer herpes simplex outbreaks, improvement in skin and/or hair texture, regression of condylomata, and regression of Kaposi's sarcoma. Serum cholesterol levels may increase and triglycerides levels may decrease, corresponding to a return to pre-HIV infection status.

Patients who do not respond, or patients who have responded and are now experiencing a rebound in their plasma HIV RNA, are considered virologic or clinical treatment failures. Treatment failure has multiple causes. The most common cause is an ineffective treatment regimen either because the regimen prescribed in the first place was suboptimal or because the patient did not take the pills as instructed. Continued use of ARVs administered suboptimally will quickly lead to viral resistance and failure. Typical scenarios include: stopping just one medication because of drug intolerance or cost concerns; losing one or more medications; forgetting to take doses; sharing medications with family or friends; and selling parts of the regimen. The reason is not as important as the result: treatment failure and viral resistance.

Suboptimal adherence is not the only reason for treatment failure. Patients who fail to respond to the original regimen may actually have been infected with a resistant virus. This is particularly true in patients more recently infected in a community where ARVs are being used. For example, viral resistance to nevirapine may occur in areas where this drug is used to decrease mother-to-child transmission rates. Up to 23% of women who have taken single-dose nevirapine to decrease transmission rates may develop resistant virus, which can be transferred to their sexual partners and/or infants (99). In this setting, ideally, resistance testing should be done; if unavailable, treatment should be changed to a PI-based therapy as soon as possible.

Other reasons for treatment failure include suboptimal potency, such as triple nucleoside regimens like zidovudine/lamivudine/abacavir, stavudine/didanosine/lamivudine, tenofovir/lamivudine/abacavir, and tenofovir/lamivudine/didanosine. Studies have also observed that the combination of didanosine plus tenofovir plus an NNRTI results in high virologic failure rates in ARV-naïve, HIV-positive patients (100). Failure rates were similar to those reported for triple-NRTI therapy with several resistance mutations identified; a didanosine plus tenofovir plus NNRTI combination therapy is therefore not recommended. Other less potent regimens include nelfinavir or saquinavir (unboosted)-based treatment. The most common situation involving suboptimal potency is prior use of regimens that do not qualify as HAART, such as single or dual nucleoside regimens, single PI regimens, or PIs given with just one nucleoside analogue. Non-HAART regimens should never be used except when administered in certain PMTCT strategies.

Poor pharmacokinetics with suboptimal drug concentrations can also cause treatment failure. Poor absorption, drug-drug interactions at the gut level, inappropriate food administration, and metabolic induction by CYP450 induced by concomitant medications are all potential causes of treatment failure. Examples include: rifampicin, nevirapine, and efavirenz decrease most PI concentrations; tenofovir decreases atazanavir concentrations; didanosine and indinavir taken with food results in low concentrations; lopinavir/ritonavir, atazanavir, and tenofovir must be taken with food or concentrations are

reduced; lopinavir/ritonavir and amprenavir decrease each other's concentrations when taken together. In addition, the use of numerous traditional medicines in addition to HAART regimes may cause many yet unidentified drug interactions, which could affect the potency of the regimens.

Viral Blips

It is important to separate patients who are experiencing viral blips from those who have virologic failure. “Viral blip” refers to a transient increase in viral load to more than 50 copies/ml in a person with chronic viral suppression. It is usually random, fewer than 500 copies/ml—or fewer than 1,000 depending on the assay used—and readily returns to fewer than 50 (or fewer than 400) copies/ml without any change in treatment. The frequency of these blips is approximately 30% to 50% in patients on different chronically suppressive regimens, whether PI-based or NNRTI-based (101).

Possible explanations for the blips include: a transient release of drug-sensitive virus from latent reservoirs; an increase in target cells during infection or post vaccination; a transient increase in viral replication in relation to changes in ARV levels; and peculiar host factors. Viral blips were initially thought to represent release of resistant virus, but this notion has been disputed by the current consensus that they usually do not predict development of resistance or virologic failure. However, it has been suggested that viral blips are more common in people with very low CD4+ T cell counts at baseline (102). Moreover, patients with frequent blips have been found to have somewhat impaired CD4+ T cell recovery compared to those without blips (103). Like many aspects of the pathogenesis of HIV, our understanding of this phenomenon is evolving.

The best way to respond to these blips is still unclear because most patients who experience this phenomenon return to undetectable viral loads. The role of blips in predicting treatment failure also is not clear. The current recommendation for any rebound in viral load is to confirm the rise with a second test performed, two weeks or a month later, and in the interval to attempt to identify potential causes of the blip. Clinicians also recommend delaying viral load testing for at least two weeks to one month after vaccination or an infection.

Second-Line and Salvage Therapy

Changing therapy in patients already receiving treatment is done for one of two main reasons: toxicity or virologic failure. If patients become intolerant to a specific drug or regimen, substitutions can usually be found within the same class or from a different class. The more complicated situation involves switching from a virologic-failing regimen to a new and effective regimen, or “salvage therapy.” The choice of which salvage therapy to use is even more difficult if drug resistance data are not readily available.

When treatment fails, a comprehensive evaluation of why a patient failed—including a thorough treatment history—must be performed. For instance, if a patient was non-adherent because the regimen was too complex, it is unlikely that that person would respond to an even more complex “salvage” regimen. This type of patient may require significant in-depth counseling prior to starting a new therapeutic approach.

The first treatment failure is the one that is easiest to salvage. Typically, patients are starting a non-nucleoside-based treatment. In Nigeria, that regimen would include nevirapine or efavirenz in most

Table 17-14. First- and Second-Line Regimens in Adults and Adolescents in Nigeria

First-Line Regimen	Second-Line Regimen	
	RTI Component	PI Component
Zidovudine <i>or</i> stavudine + lamivudine <i>or</i> emtricitabine + nevirapine <i>or</i> efavirenz	Didanosine + zidovudine <i>or</i> tenofovir DF + zidovudine + lamivudine	
Tenofovir DF + lamivudine <i>or</i> emtricitabine + nevirapine <i>or</i> efavirenz	Didanosine + zidovudine <i>or or</i> didanosine + zidovudine + lamivudine	atazanavir/ritonavir <i>or</i>
Abacavir + lamivudine <i>or</i> emtricitabine + nevirapine <i>or</i> efavirenz	Didanosine + zidovudine + lamivudine <i>or</i> tenofovir DF + zidovudine + lamivudine	lopinavir/ritonavir <i>or</i>
Zidovudine <i>or</i> stavudine + lamivudine <i>or</i> emtricitabine + tenofovir disoproxil fumarate <i>or</i> abacavir	Efavirenz <i>or</i> nevirapine + didanosine <i>or</i> efavirenz <i>or</i> nevirapine + lamivudine	saquinavir/ritonavir

Notes: Nevirapine and atazanavir do not require cold chain. Tenofovir DF cannot be used with unboosted atazanavir. Lamivudine can be maintained in second-line regimens to reduce the viral fitness.

patients. When nevirapine fails, typically efavirenz will not work either, and vice versa. The alternative then is to initiate a PI-based treatment. Preferred at this junction is a ritonavir-boosted regimen, either lopinavir/ritonavir, indinavir/ritonavir, atazanavir/ritonavir, or saquinavir/ritonavir (Table 17-14).

The nucleosides may also need to be replaced. Lamivudine was likely to be included in the first regimen, and therefore the likely mutation associated with resistance is M184V. Thymidine analogue mutations, or TAMs, may also be present, particularly if the patient remained on the failing regimen for a prolonged period. A likely substitution in this situation with M184V and TAMs is the combination of abacavir plus didanosine or tenofovir plus zidovudine with or without lamivudine as an NRTI backbone. Although lamivudine loses its direct virologic potency in the presence of M184V mutation, it may be retained in the regimen as a third NRTI, because it allows for the persistence of M184V mutants that replicate poorly because of reduced viral fitness.

The second treatment failure is even more difficult to manage, especially without resistance testing. Typically, more than three drugs have to be taken. If possible, a new class of drug should be given, such as a fusion inhibitor like enfuvirtide. This drug, which is prohibitively expensive and in limited supply, is unlikely to be used in Nigeria in the near future. A newer PI, tipranavir-ritonavir, is active against many viral strains that are resistant to earlier PIs, but it is also unavailable in Nigeria at this time. In the same way, the promise of investigational drugs that are in advanced stages of development—such as CCR5 receptor antagonists TMC 114 and TMC 125—is unlikely to extend to Nigeria in the immediate future. Other strategies depend on how desperate the situation has become. “Giga-HAART”—or the administration of six or more drugs, regardless of susceptibility—has been used with modest success (104). In heavily treatment-experienced patients with multiple resistance mutations who are unable to achieve complete suppression of viremia, treatment goals become restricted to maintenance of immunologic function and prevention of clinical deterioration. In this population, ongoing HAART with even modest virologic suppression has been shown to reduce the fitness or replicative capacity of the virus

and improve clinical outcomes (105). Structured treatment interruption is generally not recommended in patients with advanced HIV/AIDS because it is associated with rapid CD4+ decline. Most studies have shown similar adverse outcomes (106), although one CD4+ guided study demonstrated a good response to HAART in HIV-infected patients with high CD4+ cell counts (107). Vigilant prophylaxis against opportunistic infections, prompt management of treatable infections and malignancies, and palliative care may be the only remaining options in these situations for many such people.

Discontinuation of NNRTI-Based Regimens

Nevirapine and efavirenz have prolonged, steady-state half-lives — 25 to 32 hours for nevirapine and 40 to 55 hours for efavirenz. Both drugs remain in circulation at therapeutic concentrations for several days, and at subtherapeutic concentrations for several weeks after discontinuation. This phenomenon is subject to considerable racial and individual variability, appearing to be more prominent in people of African descent than European descent (108). Similar concerns about continued exposure to nevirapine, long after the drug had been discontinued, emerged in pharmacokinetic studies conducted on women who received single-dose nevirapine for PMTCT (109).

Simultaneous discontinuation of all the drugs in an NNRTI-based regimen is likely to lead to an undesired period of NNRTI monotherapy and predispose an individual to the development of NNRTI resistance. This risk is greatest among patients who have detectable plasma viremia at the time the NNRTI is discontinued. Although it is clear that the optimal strategy should involve discontinuation of the NNRTI first, followed by discontinuation of the NRTI backbone, less certain is the length of time that the “NRTI tail” should be continued before it is stopped as well (110). Recommendations have ranged from four to five days to as long as four weeks, but additional studies are ongoing. Another option is to switch the NNRTI to a PI and then to continue the PI plus the NRTIs for two weeks before stopping all drugs simultaneously.

ANTIRETROVIRAL THERAPY IN CHILDREN

The decision to initiate ART in a child depends on his or her age and the availability of virologic testing. Serologic diagnosis is unreliable in children younger than 18 months because maternally derived antibody may persist in the child. The clinical features of HIV infection may resemble those of many other prevalent conditions, such as malaria and malnutrition.

For HIV-seropositive children younger than 18 months with proven HIV status (DNA PCR), ART is recommended when the child has: WHO Pediatric Stage III disease irrespective of the CD4+ percentage; WHO Pediatric Stage II disease, with consideration of using CD4+ less than 20% to assist in decision-making; or WHO Pediatric Stage I (asymptomatic) and CD4+ less than 20%. If HIV seropositive status is not virologically proven but CD4+ cell assays are available, ART can be initiated when the child has WHO Stage II or III disease and CD4+ less than 20%. In such cases, HIV antibody testing must be repeated at 18 months of age to confirm HIV infection; only children with confirmed infection should continue with ART.

Table 17-15. First- and Second-Line Regimens in Children in Nigeria

First-Line Regimen	Second-Line Regimen	
	RTI Component	PI Component
Zidovudine <i>or</i> stavudine + nevirapine <i>or</i> efavirenz	Didanosine + zidovudine	Lopinavir/ritonavir <i>or</i> saquinavir/ritonavir <i>or</i> nevirapine
Abacavir + lamivudine + nevirapine <i>or</i> efavirenz	Didanosine + zidovudine	Lopinavir <i>or</i> saquinavir/ritonavir <i>or</i> nevirapine
Zidovudine <i>or</i> stavudine + lamivudine + abacavir	Didanosine + zidovudine <i>or</i> nevirapine	Lopinavir <i>or</i> saquinavir/ritonavir <i>or</i> nevirapine

Notes: Tenofovir DF is not currently approved for clinical use in children. Efavirenz is approved only in children older than three. Saquinavir/ritonavir is approved only in children weighing more than 25 kilograms. Nevirapine does not require cold chain.

For HIV-seropositive children aged 18 months or older, ART can be initiated when the child has: WHO Pediatric Stage III disease (clinical AIDS) irrespective of the CD4+ percentage; WHO Pediatric Stage II disease with CD4+ less than 15%; or WHO Pediatric Stage I (asymptomatic) and CD4+ less than 15. For children older than eight years, adult criteria for initiation of therapy are applicable.

The ideal goal of treatment is full suppression of virus to plasma HIV RNA to fewer than 50 or fewer than 400 copies/ml. This almost always means the use of HAART: an NNRTI (or a PI) and two NRTIs as recommended in the Nigerian ARV guidelines (Table 17-15) (20). Full suppression is not always attainable, particularly in children. Partial suppression is usually much better than no treatment at all. As in adults, pediatric treatment is lifelong. The first treatment regimen has the greatest chance of success, while subsequent regimens are usually more toxic and less tolerable. According to the Nigerian guidelines, the judgment about when to start ART depends on age, clinical staging, and CD4+ cell count, while the decision when to switch ARVs depends on clinical and laboratory staging, observation of toxicity, CD4+ cell count, and viral load (20).

A limited number of treatment options are available for children (Table 17-15). If children can be taught to take tablets or capsules, their options increase. Successful treatment also requires education of the parents or guardians. Successful treatment of older children may require disclosure to the child about his or her HIV status, drug education, and adherence counseling.

ANTIRETROVIRAL THERAPY DURING PREGNANCY

The decision to use ART in pregnancy is based on the premise that ART is beneficial to such women unless the adverse effects outweigh the benefits. The considerations for the use of ART should be based on four considerations: the need to use appropriate ARVs; the effects of ARV on pregnancy; the effect on transmission of HIV from the mother to the child; and the effect of the drug on the fetus. The major goal of ART in pregnancy is to achieve maximal suppression of plasma viral load to undetectable levels, even though there is evidence that women with plasma HIV RNA of less than 1,000 have minimal levels of transmission to their babies (111). Some evidence now supports the possibility of teratogenic effect of efavirenz in humans (112), in addition to the ample evidence in animal models (113). Therefore, efavirenz

Table 17-16. Antiretroviral Therapy in Individuals with Dual Infection with Tuberculosis

Category	Recommendation
Pulmonary tuberculosis and a CD4+ cell count of < 200 mm ³ or extrapulmonary tuberculosis	Start tuberculosis treatment. Start antiretroviral therapy as soon as patient tolerates tuberculosis therapy: Zidovudine/lamivudine/efavirenz Stavudine/lamivudine/efavirenz Tenofovir DF/lamivudine/efavirenz Tenofovir DF/lamivudine/zidovudine
Pulmonary tuberculosis and a CD4+ cell count of 200-350 mm ³	Start tuberculosis treatment. Start one of these combinations after completing two months of the induction phase of tuberculosis therapy with rifampicin: Zidovudine/lamivudine/tenofovir DF Stavudine/lamivudine/efavirenz Stavudine/lamivudine/nevirapine Tenofovir DF/lamivudine/efavirenz Tenofovir DF/lamivudine/nevirapine
Pulmonary tuberculosis and a CD4+ cell count of > 350 mm ³	Treat tuberculosis and defer antiretroviral therapy. Monitor CD4+ cell counts.

is best avoided in early pregnancy. When there are no alternatives, an efavirenz-containing regimen may be instituted after the second trimester in pregnant HIV-positive women coinfecting with tuberculosis.

HIV-positive pregnant women who meet the criteria for ART should begin therapy after the first trimester. According to the Nigerian PMTCT guidelines, zidovudine should be included as a component of ART whenever possible (114). Treatment should commence early enough to ensure good virologic control in patients enjoying HAART. The choice of drugs in pregnancy should include a review of prior exposure, drug resistance, and the clinical and immunological status of the mother. HIV-infected pregnant women already on ART should continue on therapy with a switch of treatment in the first trimester to include nevirapine but exclude efavirenz. HIV-positive pregnant women who do not meet the criteria for ART should have zidovudine prophylaxis from 28 weeks of pregnancy with chemoprophylaxis for the baby. (Other PMTCT interventions are discussed in Chapter 16, *this volume*.) The blood count of patients taking zidovudine should be monitored regularly because of the development of anemia, a common complication of pregnancy in Nigeria.

Of significant note is a warning by nevirapine's manufacturer, Boehringer Ingelheim, of an increased risk of hepatotoxicity in women with CD4+ cell counts above 250 cells/mm³. Other important issues include switching drugs to limit or prevent lipodystrophy, convenience of the regimen, adherence, and adverse events.

ANTIRETROVIRAL THERAPY IN HIV-INFECTED PATIENTS WITH TUBERCULOSIS

The incidence of tuberculosis has dramatically increased since the mid-1980s both in industrialized and developing countries. In Nigeria, reports from AIDS treatment centers in Jos and Lagos have observed high levels of tuberculosis coinfection among patients with HIV (115,116). Tuberculosis is the leading cause of

morbidity and mortality among HIV patients in Nigeria (117). Without treatment, more than half of HIV-infected patients coinfecting with tuberculosis are likely to die. With the correct treatment, such patients are cured after taking appropriate tuberculosis drugs for at least six months (Table 17-16). Proper treatment and isoniazid prophylaxis also prevents the spread of tuberculosis, because it makes people non-infectious. Concomitant treatment of tuberculosis and HIV is compounded, however, by the drug interactions between NNRTIs and PIs with rifampicin. Rifampicin is a potent stimulator of the P450 cytochrome enzyme in the liver and leads to dramatic reduction of the blood levels of NNRTIs and PIs to sub-therapeutic levels (118). Pharmacokinetic levels of efavirenz can be maintained by increasing the dose to 800 mg. The use of rifabutin in place of rifampicin has been recommended for people taking ART. Rifabutin is expensive, though, and scarce in resource-limited settings such as Nigeria. Other important issues in the treatment of tuberculosis/HIV-coinfecting patients include pill burden, toxicity, and adherence issues. ARV use in patients coinfecting with tuberculosis is shown in Table 17-16.

Paradoxical worsening of tuberculosis is defined as a transient worsening of disease at a pre-existing site or the development of new tuberculosis lesions while a patient is on appropriate antituberculosis therapy. It is thought to be due to improved *M. tuberculosis*-specific immune responses. Risk factors for paradoxical reaction include: a low baseline CD4+ T cell count, a high viral load, and initiation of ART within two months of initiating antituberculosis therapy. These reactions, which may be seen in 7% to 30% of patients, tend to occur within days to weeks of initiating ART, but may be delayed for several months. Moreover, they may occur in one-third of HIV-infected patients started on ART and tuberculosis therapy at the same time (119).

Possible manifestations are worsening adenopathy, enlarging central nervous system lesions, or increased pulmonary infiltrate. Patients may have an increase in the size of the cutaneous response to tuberculin tests, while those who were previously anergic may develop a cutaneous response to tuberculin. Other previously described manifestations are tenosynovitis, pleural effusion, meningitis, superior vena cava syndrome, and peritonitis. These reactions are indicative neither of drug resistance nor treatment failure, and they usually subside spontaneously after about 10 to 40 days. Moreover, non-steroidal anti-inflammatory agents may provide some relief (120). Severe cases may require temporary interruption of HAART; however, no change in tuberculosis treatment is needed except in the most severe cases.

The approach to tuberculosis diagnosis and treatment differ markedly between developed and resource-limited countries. In many resource-limited settings, positive sputum smear alone is used for tuberculosis diagnosis, and additional information is derived from chest X-ray. Mycobacterial culture and resistance testing are often unavailable, or are available but prohibitively expensive. Empiric treatment for tuberculosis is common. Routine laboratory tests to monitor the adverse effects of tuberculosis treatment may be unavailable. Instead, patients are educated about symptoms of drug toxicity to facilitate early reporting and appropriate treatment. Detailed information about treatment of tuberculosis in resource-limited settings can be obtained from WHO treatment guidelines.

Another significant difference between resource-limited and developed countries is the use of primary prophylaxis or secondary prophylaxis after full treatment for active tuberculosis. Primary prophylaxis is recommended in patients with positive Mantoux test if active tuberculosis can be definitively excluded.

Table 17-17. Effects of HIV on HBV and HBV on HIV

Effects of HIV Coinfection on HBV	Effects of HBV Coinfection on HIV
<ul style="list-style-type: none"> • Markers of replicative HBV (high HBV DNA titer and HBeAg) are more commonly present • Lower transaminases, despite higher HBV DNA* • Decreased conversion from HBsAg and HBeAg positivity to anti-HBs and anti-HBe positivity • Poorer response to interferon • Increased risk of developing lamivudine resistance • Increased risk of liver cirrhosis • Increased liver-related mortality 	<ul style="list-style-type: none"> • HBV increases HIV replication rate (controversial) • Lower CD4+ cell count due to hypersplenism in patients with cirrhosis • No proof that HBV influences the eventual outcome of HIV infection

*Lower transaminases occur because hepatic inflammation in HBV infection is not caused by direct cytopathic effect of the virus; rather, it correlates with host immunologic response. Thus, neonates and immune-compromised people tend to have lower transaminase levels.

ized to isoniazid plus sulphadoxine-pyrimethamine or placebo. Compliance with isoniazid was poorer than with sulphadoxine-pyrimethamine, but patients who received the combined prophylactic regimen had a significant decrease in tuberculosis recurrence, anemia, and wasting. There was also a trend toward improved survival (122). While these and other studies (123) suggest a potential beneficial effect of secondary prophylaxis, they do not provide answers to several critical issues, such as the impact of HAART on the apparent benefits, the optimal regimen for secondary prophylaxis, and the impact of secondary prophylaxis on the emergence of drug-resistant *M. tuberculosis*. The WHO does not yet endorse secondary prophylaxis, and additional studies are needed before secondary prophylaxis can be included in routine care standards.

ANTIRETROVIRAL THERAPY IN DUAL INFECTIONS WITH HIV AND HEPATITIS

Nigeria's high HIV-1 seroprevalence rate of 5.0% (5) and its high HBV carriage rate of 10.3% in the general population (124) have created opportunities for coinfection with HIV and HBV. This is made possible because HIV and HBV (and HCV) share the same modes of transmission. The prevalence of HBV in HIV-infected individuals ranges from 20% to 42% in Nigeria (125-127). Important virologic, epidemiological, and clinical interactions between HIV and HBV have been described. For example, people with HIV/HBV coinfection have a greater rate of chronic liver disease, higher viral loads of HBV, and accelerated progression of liver disease. (128). Table 17-17 summarizes these interactions.

Effects of Hepatitis B Virus on HIV Infection

The primary goal of treating chronic HBV is to halt progression of liver disease by suppressing viral replication. Until recently, the only antiviral agents available for treatment for HBV were lamivudine

However, several studies in resource-limited areas of tuberculosis endemicity have suggested that secondary tuberculosis prophylaxis may also be efficacious. The first study, conducted in Zaire, found decreased relapse rates when rifampin and isoniazid were given for an additional six months after completing a standard course of treatment (121). In a study in Abidjan, Côte d'Ivoire, HIV-infected patients who completed treatment for active tuberculosis were random-

and interferon- α 2a and - α 2b. The availability of tenofovir, adefovir, and entecavir has expanded HBV treatment options. Tenofovir, lamivudine, and emtricitabine are effective against both HBV and HIV. Yet HBV lamivudine resistance occurs at a rate of approximately 20% per year, while resistance to tenofovir is much less frequent. Tenofovir is effective against lamivudine-resistant and probably emtricitabine-resistant strains of the virus. Preliminary studies have suggested that regimens that contain both lamivudine and tenofovir produce better HBV suppression than those with lamivudine alone (129). Emtricitabine plus tenofovir probably has similar effects. Thus, HAART regimens that contain tenofovir; emtricitabine or lamivudine; and a third agent have the potential to render multiple benefits for coinfecting patients.

Since the introduction of suppressive combination ART, survival in HIV-infected people has been extended. Data are scarce on the clinical course of prolonged HIV/HBV coinfection and the effects of HAART in this setting. Nonetheless, a study of people coinfecting with HIV and HBV has revealed that responses to HAART were inferior relative to those of people infected only with HIV (130). Although both patient groups achieved similarly significant immunologic responses to treatment, coinfection was associated with excess risk of virologic failure and of death. Virologic response was impaired in coinfecting subjects, however, frequently as a result of interruptions in treatment driven by hepatic complications (Table 17-17). Furthermore, coinfecting patients are more likely to develop hepatitis after HAART initiation (131,132), and they face a higher risk of hepatic decompensation and hyperbilirubinemia (133). The confluence of these events significantly contributes to the greater risk of liver-related mortality that occurs in coinfecting people (134,135).

Patients with HIV/Hepatitis C Coinfection

HCV is a flavivirus with single-stranded RNA that is capable of very rapid replication, leading to the daily production of approximately 10^{12} virions. This replication rate is faster in HIV/HCV-coinfecting people than in HCV mono-infected patients (136), and HAART has been shown to drive HCV's genetic diversity (137). Six genotypes have been characterized with significant geographic variation (138). Previous reports have observed that HIV/HCV-coinfecting people experience more rapid progression of liver fibrosis and greater morbidity and mortality from liver disease than those infected with HCV alone (139). The accelerated pace of hepatic decline in HCV/HIV-coinfecting patients occurs in part because they have diminished cellular immune responses to HCV infection, characterized by weak HCV-specific CD8+ T cell and CD4+ T cell immune activity (140). Thus, they are less able to clear HCV viremia after initial infection (141). Because of this, liver cirrhosis occurs in 15% to 25% of coinfecting patients within 10 to 15 years after HCV infection compared to only 2% to 6% of people with HCV infection alone (142). Liver-related mortality is also greater in coinfecting patients (143). Factors that predict progression to advanced liver fibrosis (the most prognostic indicator of the development of cirrhosis) in people coinfecting with HIV and HCV include: CD4+ T cell counts of fewer than 200 cells/mm³; alcohol consumption; and an HCV infection duration of more than 40 years (144).

HCV does not appear to alter the natural course of HIV infection in any significant way. However, it was initially suggested that the recovery of CD4+ T cells in response to potent HAART was blunted in those who were HCV/HIV coinfecting (145); subsequent studies failed to show similar findings (146). On the other hand, the initiation of HAART is often accompanied by a paradoxical increase in HCV viremia in coinfecting patients, which explains some of the immune reconstitution hepatitis flare. It appears that an initial increase occurs in all patients, but it is prolonged only in those with low CD4+ cell counts (147). The biological explanation for this increase is still uncertain. Nonetheless, there is increasing evidence that immune restoration through HAART may slow the course of liver disease progression in individuals with HIV/HCV coinfection (148). It has therefore been recommended that hepatitis C should be treated aggressively in coinfecting patients. Best results occur among those with a pretreatment CD4+ cell count of greater than 350 cells/mm³. However, treatment of coinfecting patients is complicated by drug interactions and poor tolerance of therapy. Potential toxicities may outweigh the benefits when the pretreatment CD4+ cell count is less than 200 cells/mm³.

Three large randomized controlled trials of interferon-based therapy in patients who were coinfecting with HIV and HCV have now been completed: the AIDS Clinical Trials Group study (149); the APRICOT (AIDS Peginterferon Ribavirin International Co-infection Trial) study (150); and the RIBAVIC study (151). These studies compared recombinant interferon alpha-2b plus ribavirin to peginterferon alpha-2b plus ribavirin. Overall, the results of these studies showed that patients who were treated with peginterferon had a better-sustained virologic response than with standard interferon. The sustained virologic response was less in coinfecting patients than previously seen in HCV mono-infected patients. Treatment in the RIBAVIC study was discontinued in 42% of patients, and 31% had severe adverse events, suggesting that therapy was tolerated relatively poorly in this group. Toxicity may be enhanced in individuals treated with HAART, and even more in those treated concurrently with HAART and the combination of interferon and ribavirin. Ribavirin should not be coadministered with didanosine because of a drug-drug interaction that has been associated with potentially fatal hepatic decompensation, pancreatitis, and lactic acidosis (152).

HIV-2 INFECTION

HIV-2, the second HIV that causes immunodeficiency and AIDS, is found predominantly in West Africa, including Nigeria. Since the mid-1990s, HIV-2 prevalence in Nigeria seems to be diminishing, while various recombinant forms of HIV-1 are expanding rapidly in Nigeria (153). HIV-2 is five times less transmissible than HIV-1 (154), is associated with lower viral loads, and has a slower rate of disease progression (155).

Little is known about the best approach for treatment of HIV-2. Immunodeficiency develops slowly; therefore, it is unclear whether ART significantly slows progression. Some NRTIs such as zidovudine appear to be less active in HIV-2 than in HIV-1 (156). Moreover HIV-2 is not susceptible to NNRTIs and may have multiple pre-existing PI mutations leading to resistance (157). Monitoring infection by HIV-2 viral load assay is difficult due to the lack of a HIV-2-specific assay. It appears that triple-NRTI regimens—such as lamivudine, zidovudine, tenofovir (the DART regimen), or lamivudine, zidovudine, and

abacavir—may be useful, although this has not been rigorously tested. More research and clinical experience are needed to determine the most effective treatment for HIV-2 infection.

POST-EXPOSURE PROPHYLAXIS

The magnitude of risk associated with a particular exposure to HIV tends to be influenced by the nature of the exposure and the status of HIV disease in the source patient. The risk of transmission following percutaneous occupational exposure is about 0.3% (158), which is lower than the risk of transmitting HBV or HCV. This risk can be reduced if ARVs are immediately administered and continued for the recommended one month. Post-exposure prophylaxis (PEP) is unnecessary if the exposed worker is already known to be HIV seropositive. For all others, baseline HIV tests should be performed and PEP initiated as soon as possible. Rapid HIV tests can be used to determine the HIV serostatus of the source person. However, the tests may be falsely negative during the window period, which is the time between detectable HIV antigens and the development of HIV antibody.

For occupational exposures, the health care worker and index patient should be tested for HIV before administration of PEP. A three-drug regimen should be provided as soon as possible to the health care worker for four weeks. Complete blood count and chemistry should be done after two weeks with HIV testing conducted at 12 and 24 weeks. If negative at 24 weeks, the health care worker can be considered to be uninfected. Rigorous evaluations of PEP programs have not been done, although such programs are not 100% efficacious in preventing infection. In an analysis of 57 voluntarily reported cases of occupationally acquired HIV infection, 14% of the health care workers acquired HIV infection despite receiving PEP (159). Although poor adherence due to the adverse effects of ARV drugs was implicated in some prophylaxis failures, other patients failed because the infecting virus was resistant to the prophylactic ARV drugs. Therefore, choosing the initial regimen should involve careful consideration, ideally with expert consultation, of the source patient's treatment experience and the local epidemiology of ARV resistance.

The choice of a PEP regimen should be based on the type of exposure and the status of the source patient (17). Also, drug resistance that is known or suspected to be present in the source patient should be considered. A three-drug regimen should be recommended when the source person is known to be infected with HIV and has markers of high infectiousness such as symptomatic disease, a high viral load, or a low CD4+ cell count. Three-drug regimens are also preferred if exposure involves a large-bore needle, deep injury, or visible blood on the needle, or if the needle was just removed from the source person's blood vessel. The three-drug regimens are generally similar to standard HAART regimens, but drugs with a high incidence of adverse reactions should be avoided. For example, nevirapine has been associated with severe cases of hypersensitivity reaction when used for prophylaxis (160). Since some of these reactions have been fatal, the use of nevirapine in PEP regimens should be avoided. The adverse events associated with nevirapine—including life-threatening rash and hepatic failure—are more common in HIV-uninfected, immunocompetent individuals (161). If possible, an alternative drug should be substituted, such as efavirenz, remembering that efavirenz cannot be used in patients who are pregnant

or contemplating pregnancy. Alternative drugs include any PI-based three-drug regimens and even triple nucleoside regimens, such as zidovudine/lamivudine/abacavir (Trizivir®) or zidovudine/lamivudine/tenofovir.

A two-drug regimen may be considered if exposure is limited to a few drops or splash on mucous membrane or disrupted skin, provided the source patient does not have any marker of high infectiousness. The two-drug regimens typically consist of two NRTIs (such as zidovudine plus lamivudine). Even in relatively low-risk situations, some clinicians prefer three-drug regimens, although there are no proven advantages and toxicity may be increased. In situations in which the HIV serostatus of the source person is unknown, prophylaxis may be prudent after careful assessment of the specific situation.

A complete blood count and chemistry should be done after two weeks of PEP, and testing for HIV should be repeated at 12 and 24 weeks. If negative at 24 weeks, the health care worker can be considered to be uninfected. Low risk exposures such as body fluid contact with intact skin do not require prophylaxis. Although pregnancy is not a contraindication to PEP, it is necessary to closely monitor for adverse effects.

PEP following unprotected intercourse has not been studied in depth, although some health departments and treatment centers do provide such services. If clinically appropriate, the same regimen as the above should be employed. A similar approach has been taken in many areas of the world when a man suspected of being HIV positive has raped a woman.

The inability of PEP to prevent HIV transmission 100% of the time emphasizes the importance of using strategies that prevent exposure in the first place. Since accidental HIV exposure is a source of emotional turmoil, all patients should be offered psychological support and education on how to avoid future exposure. STI treatment, hepatitis prophylaxis, and emergency contraception may be important, depending on the nature of the exposure.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Immune reconstitution or restoration, the improvement of previously compromised immune function, usually follows successful HAART (162). Although generally advantageous, it is sometimes associated with an inflammatory syndrome—called immune reconstitution syndrome, immune restoration disease (IRD), immune response reaction, or immune reconstitution inflammatory syndrome (IRIS)—especially in people who were severely immune compromised at baseline. Its onset is usually temporally related to the restoration of immunologic response to specific antigens in patients on HAART. Most cases occur within the first three to six months of treatment, but cases have been described as late as two years after initiation of HAART (163). IRIS occurs more commonly in patients who have CD4+ T cell counts of fewer than 50–100 cells/mm³ at the time ARV therapy is initiated, especially if treatment leads to a greater than two- to fourfold increase in the CD4+ cell count (164). Additionally, the risk of IRIS is increased in patients who are ART naive, patients who start ART within 30 days of being diagnosed with an opportunistic infection, and those who have at least a 2 log¹⁰ drop in viral load within 90 days of initiating ART (165).

The clinical presentation depends on the antigen(s) against which the inflammatory response is directed. IRIS to cytomegalovirus, *M. tuberculosis*, *Cryptococcus neoformans*, *Pneumocystis carinii* pneumonia (PCP), and herpes zoster have well described (166). Other conditions that have been associated with IRIS include herpes zoster, HCV, progressive multifocal leukoencephalopathy, HBV, PCP, sarcoidosis, Guillain-Barre syndrome, toxoplasmosis, hemorrhagic cystitis due to BK virus, focal encephalitis probably due to parvovirus B 19, and leprosy.

Making a diagnosis of IRIS is often clinically challenging because it has to be differentiated from adverse drug reactions, natural progression of HIV/AIDS, and the worsening of underlying conditions not related to immune reconstitution. This is further complicated by the fact that its clinical presentation and course often differ from the typical findings in HIV-infected patients who have the same infection, but who are not on HAART. In tuberculosis, this may manifest as paradoxical clinical worsening while on tuberculosis treatment. The viral load is likely to be low and the CD4+ T cell count increased during IRIS, whereas the opposite is true in those with AIDS progression. However, increased CD4+ cell counts alone do not automatically indicate that a clinical syndrome is due to immune reconstitution. Conversely, the absence of a rise cannot be always used to exclude IRIS, because the syndrome can occur before the CD4+ cell count has risen significantly as long as there has been functional immune reconstitution. A decrease in the patient's viral load relative to the pre-HAART level, on the other hand, is a more consistent finding in IRIS (144). General steps in the management of IRIS are: treatment of the offending pathogen to reduce antigen load; continuation of HAART, except in extreme cases; and careful use of anti-inflammatory agents (steroids). Although patients with IRIS have higher hospitalization rates and undergo more invasive procedures during the acute illness, their long-term outlook is good (167). Compared to patients without IRIS, they have better virologic suppression and even show a tendency toward better survival (165).

CHALLENGES AND FUTURE DIRECTIONS IN TREATMENT AND CARE IN NIGERIA

In February 2001 the federal government of Nigeria launched a program aimed at providing HAART to adults and children nationwide. Private institutions such as oil companies, nongovernmental organizations, and state governments have offered additional access. By the end of 2005, about 50,000 individuals infected with HIV in Nigeria had received HAART from the Nigeria ART program with support from the U.S. President's Emergency Plan For AIDS Relief (PEPFAR) and the Global Fund for AIDS, Tuberculosis and Malaria. However, this number will still be less than 10% of the estimated 800,000 to 1,000,000 Nigerians who require access to ART. The recent presidential directive seeking to enroll 250,000 people on ART by 2006 will further increase the number of HIV-infected people on treatment.

A 2004 assessment of HIV/AIDS care in Nigeria by USAID (168) observed several key findings critical to scaling up the Nigerian ARV program. Their findings included: the current ART capacity fell far short of the number of patients requiring treatment; public facilities providing ART experienced severe

budgetary constraints, limiting their ability to provide HIV services; the patient bore 35% of the financial burden of the ART, an enormous amount affordable only to a few Nigerians; and private sector ART services were limited because only a few patients could afford them. In addition, most public facilities were aware of national policies, guidelines, and protocols on HIV/AIDS service delivery and followed some of these guidelines and protocols; however, such documents were rarely obtainable at the sites where they were most needed. The authors suggested that all these components need to be addressed before any meaningful scaling up of ART services can take place.

Other obstacles to the scaling up and sustainability of ART in Nigeria include a lack of political commitment at the state and community levels, poor laboratory monitoring, a weak health infrastructure, a lack of well-trained personnel to deliver ART, a poor information management system, and the lack of adequate coordination in the implementation of ART.

The arrival of Global Fund, PEPFAR, and World Bank funding for the scale up of ART in Nigeria has dramatically increased the number of people accessing drugs. The cost of drugs, which had been a rate limiting factor in ART scale up, can further be reduced by purchasing drugs in bulk, using generic regimens, and taking advantage of parallel importation. In addition, local manufacture of ARVs is inevitable if delivery of ART is to cope with the huge numbers waiting to access these drugs. Tiered laboratory monitoring of patients is highly recommended. This allows for the use of simple monitoring tools, including manual CD4+ cell counts, at the level of community and secondary health institutions while reserving monitoring with plasma viral load and automated CD4+ cell counts for centers of excellence, medical research institutions, and tertiary health institutions. This will further reduce budgetary costs while preserving the quality of care. It is critical to address the weak laboratory and clinical infrastructure that exists in Nigeria, as ART is a comprehensive program. Hence, it is important that the capacity of the whole health system be improved to deliver not only ARVs, but also all related services, such as voluntary counseling and testing, treatments of STIs and opportunistic infections, and psychosocial support.

The lack of resources also demands that the implementation of new and innovative approaches to the monitoring of HAART — such as the use of DOT-HAART, peer education from support groups, and community involvement with education — support adherence and HIV prevention. The huge gaps in trained personnel requires a massive capacity building of all cadres of people involved in the delivery of ART, including physicians, pharmacists, laboratory staff, and counselors. Initiating programs with simple and limited drug options is also helpful, as it saves more complex regimens for failed therapy. An essential component of strengthening the health system is motivating and retaining trained and skilled personnel.

For an ART program in Nigeria to succeed, therefore, the following must be assured:

- A sustainable supply of adequate high-quality drugs (ART and opportunistic infection prophylaxis) and testing kits free of charge;
- Adequate resources to ensure the provision of drugs on a long-term basis;
- Adequate funds for training health care providers;

- Establishment of reference laboratories for monitoring drug toxicities, viral loads, and resistance. Monitoring of patients' blood chemistries, CD4+ cell counts, and viral loads should be made free and done at least twice per year;
- Establishment of commodity management systems to prevent stock outs;
- A management information system to track programs, patients, and supplies, and to provide necessary data for evaluation; and
- The program must emphasize and carry out operational research, including the conduct of clinical trials to optimize current and future treatment options in Nigeria.

CONCLUSION

The decision to commence ART should be based on the degree of immunosuppression using symptoms and CD4+ cell counts as indicated in the Nigerian ART guidelines. Patients should not start therapy until they have received enough education to understand what HIV is, as well as how the treatment works and what the various treatment options are. They must also appreciate the importance of adherence and, as much as possible, the use of treatment-support partners should be encouraged to facilitate their adherence to ART. Patients should be motivated and ready to start ART before they begin the medication. ART must be provided as a comprehensive treatment embracing not only ARVs, but also regular counseling, psychological support, prophylaxis and treatment of opportunistic infections, and nutritional support.

Virtually all regimens with at least three drugs are effective. However, most triple NRTIs are less effective. The main differences are complications, pill burden, tolerability, toxicity, monitoring requirements, potency, drug interactions, refrigeration, pregnancy, and comorbid conditions. The choice of regimens should be based on considerations of potency, tolerability, convenience, long-term toxicity, and drug resistance. It is wiser to start from a simple but potent regimen and move on to complicated regimens later when resistance develops. It must be remembered that the first regimen remains the best opportunity for providing durable virologic response; therefore, the decision about the initial regimen for each individual patient must be carefully made.

The goal of treatment, particularly in ARV-naïve patients, remains the maintenance of an undetectable viral load, a progressive rise in the CD4+ cell count, and a decline in the frequency and severity of opportunistic infections. Therefore, any progress short of these yardsticks may be associated with decreased durability and portend the development of drug resistance.

Community involvement through education, preparedness, support activities, and mobilization can greatly enhance drug adherence and must form a key strategy for achieving durable viral suppression. To succeed, an ART program must incorporate plans for sustainability, including: advocacy for political commitment (federal, state, and local, as well as private); involvement of the state and private sector; development of ART policies; updating of guidelines on ART and opportunistic infections; capacity building (infrastructure and personnel); and operational research with robust monitoring and evaluation.

Finally, the strategy that may prove useful with the massive scaling up of ART programs in Nigeria is one that encourages a community-based approach, with ART services provided at no cost to the patients in a tiered-delivery model that does not jeopardize the quality of care. This strategy provides the delivery of ART from zonal centers of excellence through tertiary centers to state and district facilities that meet minimum requirements for ART and to community-based facilities that do not meet minimum requirements for ART but can provide care and support services, such as voluntary counseling and testing and referrals.

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