Chapter Goal

Upon completion of this chapter, the reader should be able to demonstrate and apply knowledge about established and evolving science describing HIV virology, both in the cell and in the host, and
HIV Virology

to effectively counsel and educate patients and their communities regarding HIV virology.

HIV Life Cycle

Learning Objective

Discuss basic HIV virology and its relevance to current and potential drug targets.

What’s New?

Expanded discussion of viral entry and integration into the host genome is presented.

Key Points

• HIV is a member of the lentivirus subfamily of retroviruses.
• HIV enters the cell through use of the CD4 receptor and chemokine co-receptors, primarily CCR5 and CXCR4.
• The viral genome is transcribed from RNA to DNA by reverse transcriptase and integrated into the host genome by integrase.
• The HIV genome encodes 15 proteins comprising three categories: structural, regulatory, and accessory.
• After budding from the host cell, the virus matures into its infectious form through cleavage of viral precursor proteins by protease.

Viral Classification

Human immunodeficiency virus is a member of the lentivirus subfamily of retroviruses. Two distinct groups of viruses are pathogenic in humans: HIV-1 and HIV-2. Both are transmitted sexually and known to cause immunodeficiency disease. HIV-2 is less pathogenic and epidemiologically distinct from HIV-1. Subsequent discussion, therefore, focuses on HIV-1 infection and pathogenesis.
HIV-1 can be subclassified into three groups: M (major), O (outlier), and N (non-M, non-O) (Simon, 1998). The vast majority of HIV-1 infections belong to group M. Group M has at least nine known genetically distinct subtypes (or clades): A, B, C, D, F, G, H, J, and K. Occasionally, genetic material from different clades of HIV-1 may recombine within the same host to form hybrid viruses called circulating recombinant forms (Salminen, 1997).

**Viral Structure**

HIV-1 is an RNA virus, and its basic genomic structure is typical of other retroviruses. The integrated form of HIV is known as the provirus, which is flanked at both ends by a repeated sequence known as the long terminal repeats (LTRs). The genes of HIV are located in the central region of the proviral DNA and encode 15 distinct proteins divided into three classes: structural proteins (Gag, Pol, and Env), regulatory proteins (Tat and Rev), and accessory proteins (Vpu, Vpr, Vif, and Nef). In the mature HIV-1 virion, the inner capsid contains the viral RNA and key enzymes necessary for infection: reverse transcriptase, integrase, protease, and accessory proteins. (Figure 17.1). The capsid is surrounded by structural matrix protein, itself contained within the viral envelope. Composed of a phospholipid bilayer derived from the host cell, the envelope contains trimers of the viral glycoproteins gp120 and gp41. The exposed surfaces of gp120 exhibit a high level of variability, limiting the humoral immune response to circulating virus (Tilton, 2009).

**Figure 17.1**
HIV life cycle and drug targets.

**Viral Entry**

HIV gains access to its target cells via multiple interactions of viral proteins with receptors on the cell membrane (Figure 17.2). The viral glycoprotein gp120 binds with high affinity to the CD4 receptor, which normally functions as a co-receptor in the activation of helper T cells. CD4 binding induces a conformational change in gp120, exposing its binding sites for co-receptors on the host cell surface. Viral strains vary in their co-receptor usage. Those that bind the chemokine receptors CCR5 or CXCR4 are classified as R5-tropic or X4-tropic, respectively.

![Figure 17.2](image.png)

**Figure 17.2**
HIV entry into cells and drug targets.

**SOURCE:** Reproduced from Reeves and Piefer (2005) with permission from Wolters Kluwer Health.

During HIV transmission and early infection, R5-tropic strains predominate. Indeed, individuals who do not express CCR5, by virtue of genetic mutation, are highly resistant to HIV infection. Virus that remains R5-tropic is susceptible to HIV entry inhibitors, which bind CCR5 and alter its interaction with gp120. Through further evolution within the host, some HIV strains become X4-tropic, rendering them resistant to these agents. Following co-receptor binding, the viral glycoprotein gp41 inserts its hydrophobic fusion peptide into the target cell membrane, forming a pore through which the viral capsid enters (Tavasoli, 2011). This process, known as fusion, is the target of drugs that bind gp41 and prevent formation of the fusion pore.

**Reverse Transcription and Integration**

After fusion, the viral RNA is released into the host cell cytoplasm, shedding associated proteins in a process known as uncoating. The viral enzyme reverse transcriptase (RT) then produces double-stranded DNA from the viral RNA template. RT is a heterodimer composed of a functional subunit (p66) and a structural subunit (p51). The host enzyme
APOBEC3G, a natural antiviral defense mechanism present in CD4\(^+\) T cells and macrophages, causes hypermutation in the elongating viral DNA. The viral protein Vif, however, binds APOBEC3G and leads to its degradation (Table 17.1) (Tavasolli, 2011). Current therapies inhibit RT by competitive inhibition (nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)) or by an allosteric mechanism (non-nucleoside reverse transcriptase inhibitors (NNRTIs)). Pharmacologic agents aimed at blocking the interaction of Vif with APOBEC3G, or preventing dimerization of the RT subunits, may prove effective therapies in the future.

### Table 17.1 Viral Accessory and Regulatory Protein Functions

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
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<tbody>
<tr>
<td>Tat</td>
<td>Transcriptional transactivator</td>
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<tr>
<td>Rev</td>
<td>Allows unspliced viral genomes to leave the nucleus</td>
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<tr>
<td>Nef</td>
<td>Downregulates CD4 receptor and MHC class I, alters T cell activation, aids viral infectivity</td>
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<tr>
<td>Vif</td>
<td>Counters the host restriction factor APOBEC3G</td>
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<tr>
<td>Vpr</td>
<td>Facilitates the nuclear localization of the viral genome</td>
</tr>
<tr>
<td>Vpr</td>
<td>Downregulates CD4 receptor, increases viral release</td>
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The newly synthesized viral DNA then integrates into the host genomic DNA. First, the viral DNA associates with viral proteins, including HIV integrase and the nuclear localization factor Vpr, to form the preintegration complex. Once in the nucleus, a critical interaction between integrase and the host protein LEDGF/p75 directs this complex to the host DNA, with a preference for actively transcribed genes (Tavasolli, 2011). Integrase then mediates strand transfer, in which covalent bonds link the viral and host DNA. Co-opting host cell proteins, HIV relies on the cell’s normal DNA repair mechanism to complete integration. Currently available integrase inhibitors prevent strand transfer; agents targeting the interaction between integrase and LEDGF/p75 are under active investigation.

**Virus Production**

Once integrated into the host DNA, the viral genome can remain latent or undergo active expression. In active infection, viral DNA is first transcribed into mRNA. Many of the same transcription factors involved in CD4\(^+\) T cell activation also bind to the HIV LTR, promoting expression of the viral genome (Pereira, 2000). The resulting mRNA is spliced,
processed, and ultimately translated into viral proteins by the host cell machinery. In a positive feedback loop, the viral protein Tat promotes further viral transcription (Kao, 1987). The viral protein Gag mediates assembly of progeny virions; immature forms then exit the cell in a process known as viral budding. Finally, HIV protease catalyzes the cleavage of the gag-pol precursor polyprotein (p55), yielding the structural proteins that form the mature virion. Protease inhibitors prevent viral maturation and have become critical agents in antiretroviral therapy.

**Recommended Reading**


**HIV Natural History**

**Learning Objective**

Discuss the course of HIV infection and its dynamics in the host over time.

**What’s New?**

Expanded discussion of acute infection, latent infection, and viral diversity is presented.

**Key Points**

- In mucosal transmission, HIV crosses the epithelial barrier and establishes an expanding infection at the site of entry.
During acute infection, HIV disseminates to lymphatic tissue throughout the body.
The rate of fall in plasma viremia with highly active antiretroviral therapy (HAART) reflects the kinetics of different types of infected host cells.
HIV exhibits remarkable levels of diversity, both globally and within a single host.
HIV establishes latent infection in a subset of host cells, allowing it to persist despite HAART.

Establishment of Infection

In sexual transmission, HIV must first breach the epithelial barrier of the genital or rectal mucosa. This may occur via physical breaks in the epithelium related to trauma or sexually transmitted infections, particularly herpes simplex virus. HIV may cross intact mucosa via specialized dendritic cells in the genital tract or transcytosis in the gastrointestinal (GI) tract (Morrow, 2008). Upon breaching the mucosa, the virus encounters multiple potential target cells. Initial infection is likely to occur in dendritic cells, components of the innate immune system, which then deliver HIV to CD4+ T cells. In addition, the virus may directly infect local CD4+ T cells. In studies of the closely related simian immunodeficiency virus (SIV), resting CD4+ T cells are the predominant target cells at the site of entry in the vaginal mucosa (Zhang, 2004). This initial step represents a genetic bottleneck in which a large viral inoculum gives rise to a small founder population of infected cells. In heterosexual transmission, infection results from a single viral genotype in 80% of cases, with preference for the CCR5 co-receptor (Haase, 2011).

The eclipse phase refers to the period of approximately 10 days following mucosal exposure to HIV during which the virus remains undetectable in the plasma. Once a founder viral population is established at the portal of entry, it must expand locally before establishing a self-propagating infection in distant draining lymph nodes. In a chain reaction of cell-to-cell signaling, exposure to HIV induces vaginal epithelium to recruit plasmacytoid dendritic cells and ultimately more CD4+ T cells (Haase, 2011). From this locus of infection, dendritic cells may facilitate transport of HIV to draining lymph nodes. These early events may be altered to prevent infection, and they figure prominently in research on microbicides, pre-exposure prophylaxis, and preventative vaccines.

Acute Infection

Once infection is established in draining lymph nodes, activated CD4+ T lymphocytes become the predominant source of viral replication. Immune activation increases the pool of susceptible activated CD4+ T cells,
creating a positive feedback loop. An exponential increase in plasma viremia ensues, and patients may develop symptoms of the acute retroviral syndrome. HIV disseminates and infects other lymphatic tissues throughout the body. The CD4+ cell count in peripheral blood declines markedly. Meanwhile, a profound depletion of CD4+ T cells occurs in the gut-associated lymphatic tissue, where a large population of CCR5-expressing CD4+ T cells is present. Weakening of the GI mucosal immune response allows an increase in microbial translocation (Haase, 2011). This may provide a further stimulus to systemic immune activation, another positive feedback loop for the virus.

This unfolding of events in acute infection has long-term consequences for the patient. Fibrosis occurs in the lymphoid architecture, leading to incomplete immune reconstitution with HAART (Brenchley, 2004). Damage to the GI epithelium allows continued microbial translocation, likely contributing to chronic immune activation and progression to AIDS. Finally, a reservoir of latently infected cells is established, which later prevents viral eradication with HAART. In the rare cases in which HIV is diagnosed during primary infection, immediate antiretroviral therapy may have potential to limit, although not to reverse, these changes.

**Viral Kinetics and Latency**

Plasma HIV RNA levels reflect a dynamic interplay between the infection of susceptible cells and the destruction of infected cells. With initiation of antiretroviral therapy, susceptible host cells are protected from infection. Consequently, the rate of decline in the viral load following initiation of HAART reveals the kinetics of death of HIV-infected cells (Figure 17.3) (Palmer, 2011).

![Figure 17.3](image)

**Figure 17.3**

Rates of clearance of different cell populations and viral turnover.


Viral decay occurs in four distinct phases. The viral load declines dramatically in the first phase, reflecting clearance of activated CD4+ T
cells \( (t_{1/2} = 1 \text{ or } 2 \text{ days}) \), with roughly 90% of the decrease in plasma HIV occurring in these first weeks of therapy (Markowitz, 2003). The second phase, characterized by more gradual decline, correlates with the intermediate half-lives of partially activated CD4\(^+\) T cells, macrophages, and possibly dendritic cells. Plasma HIV continues to decline in the third phase, although at levels detectable only by ultrasensitive assays, and finally stabilizes at very low levels \(<1-5 \text{ copies/ml}\) in the fourth phase. Research has focused on the resting memory CD4\(^+\) T cell as the source of viral replication during these latter stages. Despite fully suppressive HAART, the proportion of resting CD4\(^+\) T cells that are latently infected shows minimal decline over time, yielding an estimated half-life of 44 months (Siliciano, 2003). By this estimate, HIV eradication would require approximately 60 years of uninterrupted HAART.

In light of this problem, increasing attention has turned to the mechanisms that maintain latent infection. Therapies that promote expression of the proviral genome, or activate resting CD4\(^+\) T cells, have the potential to speed decay of the latent reservoir, leading to eradication of HIV from patients receiving HAART. In latent infection, proviral DNA is integrated into the host genome but remains in a transcriptionally silent, but inducible, state. Several host transcription factors (NF-κB, NFAT, and P-TEFβ) and the viral protein tat promote expression of proviral DNA, but they are present at low levels in resting CD4\(^+\) T cells. In addition, histone deacetylation and DNA methylation at the HIV LTR alter the local chromatin environment, denying access to the machinery of transcription (Palmer, 2011). Drugs that prevent histone deacetylation (HDAC inhibitors) are under active investigation as a therapy to eradicate latent infection. At the level of the immune system, various cytokines promote the activation of resting CD4\(^+\) T cells. Ongoing studies are measuring the ability of interleukin-7 to deplete the latent reservoir in patients receiving HAART.

**Viral Diversity**

During untreated infection, HIV replicates at a very high rate, with roughly 10 billion new virions produced each day in a given patient. Reverse transcriptase, in contrast to DNA polymerases, lacks proofreading activity (Taylor, 2008). As a result, frequent mutations occur in the daughter viral genome, potentially altering the structure and function of viral proteins. The rapid rate of production, combined with frequent mutations, leads to the production of diverse quasispecies. Strikingly, the genetic diversity observed in a single individual after 6 years of HIV infection is roughly equivalent to that observed worldwide in influenza A virus within a given year (Korber, 2001).

This presents a unique challenge for the effort to produce an HIV vaccine. Historically, vaccines have prevented infection by stimulating antibody or cell-mediated immunity in susceptible patients. Both HIV and SIV have been shown to escape from these host immune responses by virtue of their extreme diversity. An effective HIV vaccine may need to elicit broad
immune responses that protect against multiple quasispecies and possibly other HIV subtypes. The impact of viral diversity is well known to clinicians engaged in the treatment of HIV. The administration of multiple agents, so-called drug “cocktails,” is required to suppress viral replication to levels at which drug-resistant strains are unlikely to emerge. Likewise, viral diversity underpins the importance of strict adherence to HIV therapy. More broadly, the continued evolution of HIV has necessitated the increasing use of resistance testing and the development of antiretrovirals with novel therapeutic mechanisms.

**Recommended Reading**


**Overview of Antiretroviral Therapy**

<table>
<thead>
<tr>
<th>Learning Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Discuss the goals of antiretroviral treatment.</td>
</tr>
<tr>
<td>2. Discuss the rationale for when to initiate antiretroviral therapy.</td>
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<tr>
<td>3. Discuss the current antiretroviral treatment guideline recommendations on which conditions indicate starting an antiretroviral regimen in a HIV-infected and treatment-naive patient.</td>
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<td>4. Discuss the principles for antiretroviral regimen selection in HIV-infected, treatment-naive patients.</td>
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<td>5. Discuss the principles of switching, or simplifying, antiretroviral therapy.</td>
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What’s New?

HAART is associated with the potential to decrease both viral-related and non-viral-related comorbidities, as well as reduce levels of population-based HIV transmission. Guidelines for treatment now recommend starting HAART in all who are ready for treatment, regardless of CD4+ cell count, to prevent comorbidities and transmission. Newer antiretroviral agents and regimens can improve tolerability and durable viral suppression in HIV-infected treatment-naïve patients.

Key Points

• Untreated and uncontrolled HIV replication is associated with HIV-related inflammation, accelerated aging, and a higher rate of comorbid illnesses that may be reduced with earlier initiation of HAART.
• Recent studies indicate improved clinical outcomes with treatment initiation at CD4+ cell counts greater than 500/mm³. Based on these studies, treatment is now recommended for all HIV-infected patients regardless of CD4+ cell count.
• Treatment of HIV with HAART can reduce/prevent HIV-1 transmission.
• Choice of regimen is now focused on what is the best suited for the patient and his or her comorbidities to ensure adherence and long-term durability. The factors considered include medication tolerability and toxicities, resistance, and patient comorbidities.

Introduction

Great strides have been made in antiretroviral therapy since the introduction of zidovudine in 1987. The goals of therapy have evolved from delaying disease progression to maximal viral suppression and to improvements in therapeutic options including single-tablet regimens. Following the introduction of HAART, AIDS-defining conditions and HIV-associated morbidity and mortality dramatically decreased. Treatment with HAART has been demonstrated to not only suppress viral replication and improve immunologic function but also decrease virus-related comorbidities (e.g., HIV-associated nephropathy (HIVAN) and AIDS-defining and non-AIDS-defining malignancies) and reduce HIV...
transmission. With these advances, many HIV-infected patients can now expect to live a near-normal lifetime.

Paramount to the success of HAART is the patient’s willingness and commitment to adhere to lifelong therapy. In the past, acute and long-term adverse effects associated with HAART limited adherence to therapy, leading to treatment failure. However, with the advent of newer agents and better understanding of antiretroviral treatment management, current therapy combinations are now associated with less toxicity, reduced pill burden, and improved potency, allowing many patients to achieve greater than 95% adherence. However, additional concerns that may have a significant impact on antiretroviral treatment success include access to and the cost of long-term HAART (particularly in resource-limited areas); social and economic factors; drug–drug interactions; and comorbid medical conditions such as hepatitis B and C, liver disease, tuberculosis, cardiovascular disease, diabetes, osteoporosis or osteopenia, hyperlipidemia, renal disease, psychological disorders, and chemical dependency. Recognizing and addressing the individual barriers to adherence for each patient prior to initiation of antiretroviral therapy has had a dramatic effect on long-term treatment outcomes.

**When to Start Antiretroviral Therapy**

Similar to the goals of antiretroviral therapy, the decision of when to start therapy in HIV-infected patients has also evolved over time. Early studies demonstrated a clear benefit of combination antiretroviral therapy in patients with AIDS (defined as a CD4+ cell count <200 cells/mm³ and/or an AIDS-defining illness) and symptomatic HIV-infection (Cameron, 1998; Hammer, 1997). Subsequent studies demonstrated decreased mortality or reduced risk of disease progression in treated patients with CD4+ cell counts of 201–350 cells/mm³ (Egger, 2002; Opravil, 2002; Palella, 2003). In addition, although the baseline CD4+ cell count was the predominant marker that significantly predicted the probability of progression to AIDS and/or death, a plasma HIV viral load greater than 100,000 copies/ml was also associated with a higher probability of these risk events (Egger, 2002; Philips, 2004). These and other studies balanced the costs and toxicities of antiretroviral agents and eventually led to recommending initiation of antiretroviral treatment at CD4+ cell counts greater than 350 cells/mm³.

An analysis of 18 cohort studies in 2009 involving 21,247 patients reported a higher rate of progression to AIDS and death among patients who deferred therapy initiation until their CD4+ cell count dropped below 350 cells/mm³ compared to those who started HAART with a CD4+ cell count of 351–450 cells/mm³ (Sterne, 2009). This study advocated for initiation of HAART prior to the minimal threshold of 350 cells/mm³ but found no significant rate of progression to AIDS and/or death among two groups starting therapy with a CD4+ cell count threshold of 450 cells/mm³. Meanwhile, the investigators of a large North American Cohort (NA-ACCORD) analyzed data from 17,517 patients with asymptomatic HIV
infection and reported a higher risk of death among patients starting therapy with a CD4+ cell count less than 350 cells/mm³ compared to those who started therapy with a count greater than this threshold (Kitahata, 2009). In addition, these investigators reported a significant reduction in mortality among patients starting HAART with a CD4+ cell count of 351–500 cells/mm³ compared to patients with a count above this threshold. Although these investigators also found a mortality difference among patients starting HAART with a CD4+ cell count greater than 500 cells/mm³ (compared to a CD4+ cell count less than this threshold), there were not enough risk events to demonstrate a significant difference between the two groups. Both of these studies demonstrated the benefit of earlier initiation of antiretroviral treatment; however, the results were interpreted differently by different groups globally at that time.

This changed in August 2015 with the publication of the results of the Strategic Timing of Antiretroviral Treatment (START) trial. In this prospective, randomized, controlled trial, asymptomatic HIV-positive adults were randomized to receive HAART at CD4+ T cell levels greater than 500/mm³ or were started on HAART only after CD4+ T cell levels decreased below 350/mm³ (the deferred-initiation group). A total of 4685 patients in 35 countries were followed for a mean of 3 years and assessed for a composite end point of serious AIDS-related events and serious non-AIDS-related events, including death from causes other than AIDS, only after CD4+ T cell levels decreased below 350/mm³. The study was stopped at an interim analysis because a significant benefit was demonstrated in the immediate initiation group. All patients in the deferred initiation group were offered ART. Importantly, no increased rate of adverse effects was observed in the immediate initiation group (START Initiation Group, 2015).

Due to the results of the START trial, the British HIV Association, the European AIDS Clinical Society (EACS), and the World Health Organization joined the US Department of Health and Human Services and the International Antiviral Society–USA in recommending starting all patients with HIV on ART. The data from the START trial prompted a cohesive global recommendation regarding initiation of ART for all patients with HIV/AIDS, eliminating the variability previously present for providers in different nations.

In addition to recent cohort and clinical trial data that support earlier initiation of HAART with respect to the baseline CD4+ T cell count, arguments for initiating earlier HAART also include the following: the risks associated with HIV-mediated chronic immune activation leading to end-organ damage; the risks of increased occurrence and progression of comorbid conditions such as cardiovascular disease, non-AIDS-related infections and malignancies, and liver disease; and continued viral transmission (Cohen, 2011; Donnell, 2010; Ferry, 2009; Granich, 2009; Marin, 2009). In a multicenter cohort study involving 9858 patients (age 16 years or older), investigators suggested that non-AIDS-defining conditions (e.g., cardiovascular disease, non-AIDS-related infections and
malignancies, and liver disease) were increased in association with advancing immunodeficiency (defined as a prolonged period below a CD4+ T cell count of 350 cells/mm³). This study noted that only an increased risk of cardiovascular disease and death were associated with an elevated plasma HIV viral load (>200 copies/ml), regardless of receiving HAART (the plasma viral load is considered a surrogate marker for HIV-related endothelial inflammation). Although there was also an association with liver disease-related deaths and an elevated plasma HIV viral load, patients receiving HAART appeared to have a protective effect. Another cohort of 1281 patients treated with a protease inhibitor-based regimen and followed over a median period of 7.3 years demonstrated that non-AIDS-defining conditions occurred at a higher frequency than HAART toxicities or AIDS-defining conditions (Ferry, 2009). In both of these studies, the investigators suggested that the best strategy for the reduction of non-AIDS-defining morbidity and mortality is earlier initiation of HAART. The earlier implementation of HAART was also demonstrated to reduce sexual transmission of HIV and clinical end points such as tuberculosis, bacterial infections, and death in a large cohort of serodiscordant couples in Africa (Cohen, 2011).

In addition to the recent data promoting earlier initiation of ART, the armamentarium of antiretroviral agents has expanded with many new drugs that have improved toxicity and side effect profiles, lower pill burdens, and easier dosing schedules. At the same time, our understanding of many aspects of HIV has also dramatically increased, including the impact of HIV on comorbid conditions and their effect on HIV progression, the role of mutation threshold of drugs and resistance, the importance of pharmacokinetics and drug–drug interactions, knowledge of side effects/toxicities and how to manage them, and the overwhelming impact of adherence.

**Current Treatment Guidelines**

Current US guidelines published by the US Department of Health and Human Services (DHHS, 2016) and the International Antiviral Society–USA (IAS-USA; Gunthard, 2014) are similar and reflect the data and factors discussed previously in their recommendations of and cited level of supporting evidence for treatment in the following patients:

1. Those with symptomatic acute HIV infection, an AIDS-defining condition, and acute opportunistic infections (e.g., *Pneumocystis jiroveci* pneumonia, tuberculosis, or progressive multifocal leukoencephalopathy)
2. Asymptomatic patients with a CD4+ T cell count less than 500 cells/mm³: DHHS guidelines recommend treating all HIV-infected individuals, with the strength of the recommendation depending on the baseline CD4+ T cell count: CD4+ T cell count <350/mm³ (AI), CD4+ T cell count of 350–500/mm³ (AII), and CD4+ T cell count >500/mm³ (BIII). IAS-USA recommendations are similar.
3. A rapidly declining CD4+ T cell count (>100 cells/mm³ per year) or a plasma HIV viral load greater than 100,000 copies/ml
4. Pregnant women
5. HIVAN
6. Hepatitis B (HBV) co-infection when treatment is indicated

In addition to the previous recommendations, the IAS-USA guideline also suggests initiation of HAART in patients older than age 60 years, those with active hepatitis C (HCV), and those with active or high-risk cardiovascular disease. The EACS and British HIV Association also recommend treatment in patients with comorbid conditions such as pregnancy and kidney disease. As noted previously, all of the guidelines now focus more on the patient’s barriers to adherence and readiness for therapy, as well as the presence of comorbid conditions.

**Selection of an Initial Antiretroviral Regimen**

Currently, there are more than 27 different antiretroviral agents that consist of six different mechanisms of action aimed at providing maximal viral suppression when used in combination (DHHS, 2016; Gunthard, 2014). The available classes of agents include NRTIs, NNRTIs, protease inhibitors, fusion inhibitors, CCR5 receptor antagonists, and integrase strand transfer inhibitors (INSTIs). When considering what treatment combination to start, providers should tailor the regimen based on the following factors:

1. Patient readiness and barriers to adherence
2. Cost, convenience (e.g., pill burden), dosing frequency, potential drug toxicities, and potential drug–drug interactions
3. Pregnancy state or potential among women of childbearing age
4. Comorbid conditions (e.g., cardiovascular disease, liver disease, kidney disease, co-infection with HBV and HCV, psychiatric disorder, and chemical dependency)
5. Viral resistance testing results (if available)

Historically, treatment regimens evolved from the use of one or two NRTIs to a combination of two NRTIs and a third antiretroviral agent. Combination therapy with three or four NRTIs has demonstrated antiviral activity but either lacks comparable data with other regimens or has been shown to be inferior to other combination regimens (DART, 2006; Gulick, 2004). Because most clinical trial data have been based on the use of two NRTIs, the treatment strategy for the past two decades has consisted of using two NRTIs with a third agent from a different class. Although this has been used with success, recent research has led to different approaches, such as class-sparing regimens. In particular, there has been an interest in nucleoside-sparing regimens to avoid metabolic toxicities and viral resistance while maintaining maximal viral suppression (Riddler, 2008).
Recommendations for antiretroviral regimens are similar among the DHHS (2016) and IAS-USA (Gunthard, 2014) guidelines as well as the British (Ahmed, 2015) and European (EACS, 2015) guidelines. The differences in the recommended agents are based on differing interpretations of clinical data. All of these combination regimens have been demonstrated to be efficacious. However, all individual antiretroviral agents and regimens have different pharmacokinetic profiles, drug–drug interactions, side effects, and toxicities. The optimal choice of agents for a regimen is dependent on the specific needs, situation, and comorbidities of the individual being treated. The critical issues to consider are adherence barriers and lifestyle (e.g., once- vs. twice-daily regimens, need for coadministration with food, and coformulated agents), comorbidities (e.g., hepatitis B, pregnancy, and kidney disease), and tolerability (side effects that the patient can tolerate). The successful regimen will be that which is well-tolerated and well-suited for the individual’s lifestyle.

The guidelines have been drafted with the average patient and provider in mind. However, alternative regimens and strategies may also be effective for specific individuals. One of the important issues in the current treatment of HIV is the management of comorbidities and medication toxicities. Combinations listed as alternative or acceptable in the guidelines may be particularly well-suited for specific situations and should not be discouraged for the individual patient with those characteristics. Other treatment regimens may not currently have adequate data to allow them to be recommended as preferred or alternative regimens. Because our knowledge of antiretroviral agents is constantly changing, when new data are available, some agents or combinations may well be recommended or removed from the list of acceptable alternatives. The addition of new classes to our armamentarium also means that we do not yet know about many possible treatment combinations including agents such as the CCR5 antagonists and integrase inhibitors or the best combinations of these and other classes. A recent phase IIb randomized controlled trial with antiretroviral-naive adults showed that the investigational INSTI, cabotegravir, plus NRTIs had potent antiviral activity during 24 weeks of initial treatment compared to treatment with efavirenz. When these patients switched to cabotegravir plus rilpivirine (NNRTI), antiviral activity was found to be the same as that of dual NRTIs and efavirenz at the end of a 96-week follow-up period. This study adds to the data that suggest that certain two-drug regimens, without NRTIs, might be acceptable for ART-naive patients (Margolis, 2015).

In the future, it is quite possible that the recommended combinations will change based on new data revealing efficacious combinations with the least toxicities (including metabolic, cardiovascular, and renal) and best long-term durability in formulations that facilitate adherence.
When to Switch or Simplify Antiretroviral Therapy

Side effects or toxicities due to antiretroviral medications are often encountered in clinical practice. Because patients may have to take antiretroviral medications for a lifetime, side effects and toxicities must be addressed to avoid metabolic complications, decreased adherence, and virologic failure due to nonadherence. With the advent of newer agents with improved toxicity profiles, easier dosing schedules, and fewer pills, providers are often confronted with the question of whether to change individual agents or whole regimens. Although the optimum time for changing therapy remains undetermined, most studies have investigated changes in therapy for patients who have been controlled on a HAART regimen for at least 6 months. Reasons considered for changing therapy in patients controlled on their current regimen include the following (DHHS, 2016):

1. Reduce pill burden or dosing frequency
2. Reduce short- or long-term toxicity and enhance tolerability
3. Change food or fluid requirements
4. Minimize drug–drug interactions
5. Optimize ART regimen for pregnancy or in case of pregnancy

Switching to a simplified, less toxic regimen in patients with an extensive treatment history remains complex. Simply changing one agent may or may not be possible, and a complete review of the patient’s treatment history, resistance testing, treatment tolerance, and drug–drug interactions should be conducted prior to designing a new regimen.

In general, two approaches to changing therapy in the virally suppressed patient have been utilized: changing one agent to another agent within the same class (within-class simplification) or changing one agent to an alternate class (out-of-class simplification) (DHHS, 2016). Changing one agent to another agent within the same class can potentially be associated with less toxicity, improved dosing schedule, and lower pill burden with newer and coformulated agents. For example, it is reasonable to change from drugs with higher toxicity rates and more frequent dosing, such as zidovudine or stavudine, to agents with improved toxicity profiles and less frequent dosing, such as tenofovir or abacavir (DHHS, 2016). Although previously viewed as less toxic, the NRTIs tenofovir, abacavir, and lamivudine are not without adverse long-term events. In a 2013 population-based study of approximately 100 patients, these NRTIs (stavudine and didanosine were not studied) were shown to inhibit telomerase activity, leading to accelerated shortening of telomere length in mononuclear cells (tenofovir was found to be the most potent inhibitor). This study suggests that NRTIs are a potential factor in contributing to HIV-associated accelerated aging, and switching patients off NRTI-based regimens may become a higher priority in the future (Leeansyah, 2013).
Other changes, such as switching from one NNRTI to another, may help to reduce toxicities and adverse side effects. In a randomized trial involving 38 men switching from efavirenz to etravirine due to central nervous system toxicity, researchers reported a significant reduction in adverse events in patients whose regimen was changed to etravirine, with all participants maintaining a suppressed viral load at 24 weeks (Waters, 2011). In addition, in a recent analysis of four randomized clinical trials, researchers found that patients on efavirenz were twice as likely to experience suicidal thoughts or attempt to or actually commit suicide as those not receiving efavirenz (Mollan, 2014).

The majority of studies investigating class switches have evaluated the replacement of a protease inhibitor agent to an alternative class, such as an NRTI, NNRTI, or integrase inhibitor. This can be done to reduce the toxicities experienced by the patient or to change to a simple, once-daily coformulated agent. Although this is generally successful in patients without resistance, it can lead to virologic failure in patients with previous underlying resistance, as was demonstrated in the SWITCHMRK study, in which patients who were randomized to change from boosted lopinavir to raltegravir had improved serum lipid concentrations. The study was terminated at 24 weeks due to a higher failure rate than that of those who remained on lopinavir/ritonavir (Eron, 2010).

Summary

Currently, the critical issues in antiretroviral treatment are focused on the individual patient. Adherence and the patient’s barriers to adherence remain paramount. These must be addressed prior to treatment initiation in order to achieve treatment success. Once the patient is “ready” for therapy, the key issues in the future will be the patient’s medical comorbidities and medication toxicities. The WHO, EACS, and British HIV Association guidelines now recommend treatment of all HIV-infected individuals, regardless of the CD4+ count. The choice of agents/regimen is now dictated by the patient’s comorbidities and lifestyle. Switching to newer agents must be done prudently, with careful consideration of the patient’s resistance history and comorbidities. Just as there has been enormous progress in the past, it seems probable that we will continue to witness significant change in the future as we seek to find the optimal treatments for our patients.

Questions and Answers

This chapter in *Fundamentals of HIV Medicine* has accompanying questions that can be answered for continuing medical education (CME) credit. To access these questions, visit www.cmeuniversity.com and enter course ID 11635 in the “Find Post-test/Evaluation by Course” field. Access to CME credit expires April 2018.
Recommended Reading


Volberding PA, Deeks SG. Antiretroviral therapy and management of HIV infection. Lancet. 2010; 376(9734):49–62.

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HIV Virology


Acknowledgments

The authors thank William Wright, MD, a contributing author of previous editions of this chapter.