AIDS 101: From Abstinence to Zidovudine

Frank Romanelli

College of Pharmacy, University of Kentucky, 800 Rose Street, C117, Lexington KY 40536

PROLOGUE
Development of the Acquired Immune Deficiency Syndrome (AIDS) in Human Immunodeficiency Virus (HIV) infected individuals is now considered to be a problem of pandemic proportions. Greater then 30 million people are infected worldwide with average life expectancies in many third world countries being dramatically lowered by high infection rates. In the United States, development of AIDS and death from AIDS have both fallen dramatically, but HIV infection rates remain virtually unchanged(1). Management of HIV disease is complex and requires specialized knowledge. Pharmacists may play critical roles in the management of HIV-infected individuals as these patients will be on multiple medications for both HIV and the many opportunistic infections it causes. These medications require vigilant adherence in order to maximize and preserve antiviral efficacy.

This presentation introduces basic epidemiology/etiology and reviews fundamental physiology and pathophysiology associated with HIV/AIDS. The learner is expected to use this information to understand the mechanism of actions of various antiretrovirals used to inhibit HIV. The learner is also expected to synthesize and apply this information in the management and provision of pharmaceutical care to HIV-infected persons.

CLINICAL DESCRIPTION
In the early 1980s, previously healthy homosexual men began presenting with Pneumocystis carinii pneumonia (PCP) and other opportunistic infections(2). It soon became evident that these men were suffering from immunocompromise brought on by the human immunodeficiency virus (HIV). The virus targets CD4+ cells, resulting in damage to the immune system and leaving infected individuals susceptible to a spectrum of opportunistic infections(3).

The clinical course of HIV infection differs substantially from individual to individual. Despite this variation it has been possible to document the course of a typical infection. Sexual transmission via the genital mucosa is the most common mode of acquisition of HIV. Other modes of transmission may include: perinatal, needlestick, or exchange of blood/bodily fluids. Following infection, an acute phase ensues involving widespread replication and dissemination of the virus(4). The acute phase may be asymptomatic or manifested by constitutional symptoms including fever, weight-loss, fatigue, adenopathy, and night sweats. These symptoms may develop within days to weeks of initial exposure. While these symptoms can last from days to weeks, the mean duration is usually 14 days(3). During this phase HIV antibodies may not yet be formed and therefore antibody testing may fail to establish the diagnosis. A patient is considered “HIV-seropositive” when two consecutive HIV ELISA antibody tests are positive and confirmation has been attained via a western blot assay(5).

An asymptomatic phase usually follows the acute phase and is characterized by a reduction in both viral load and symptomology(4). The reduction in viral load is most likely due to a virus-specific immune response. Following this initial drop in viral load a steady state set-point is usually reached. Persons with higher viral load set-points are more likely to progress to AIDS. Eventually, viral replication exceeds immune response and patients progress to end-stage disease. End-stage is characterized by persistently elevated viral loads accompanied by declining CD4+ cell counts. A diagnosis of AIDS is established by a CD4+ cell count of less than or equal to 200 cells/mm3 or the presence of specific opportunistic infections(4).

The decline in CD4+ cell counts and other damage to the immune system in HIV infected individuals makes them susceptible to a number of opportunistic infections. Many of these infections are closely correlated with the number of CD4+ cells and degree of immune suppression. Commonly encountered opportunistic infections include: Pneumocystis carinii pneumonia (PCP), toxoplasmosis, Mycobacterium avium complex, candidiasis, cryptococcosis, and cytomegalovirus(4).

The availability of antiretroviral drugs has significantly extended life expectancies of individuals infected with HIV, but drug resistance threatens the efficacy of these agents(1,4,5). Characterization and delineation of resistance patterns is a critical and ongoing process. The clinical implications and ramifications of resistance on drug selection remains an area of intense research and limited information. Research examining novel antiretroviral agents with increased stability to resistance is underway. Ultimately, it is likely that an effective vaccine will be needed if our goal of HIV eradication is to be attained.

EPIDEMIOLOGY
HIV infection has reached pandemic proportions, with life spans in some under-developed nations significantly shortened due to widespread infection. As of the end of 1998, an estimated 30.6 million people worldwide are living with HIV(6). Twenty-nine and one-half million of those individuals are adults and 1.1 million are children younger than the age of 15 years(6). Approximately 41 percent of HIV-infected adults are females and trends indicate that this proportion is growing(6). Worldwide, heterosexual transmission accounts for approximately 75 percent of all infections(5). Among children and infants, perinatal transmission accounts for greater than 90 per

Am. J. Pharm. Educ., 65, 185-189(2001); received 9/14/00, accepted 3/2/01.

1Assistant Professor of Pharmacy Practice.
percent of infections(5). HIV infection rates in undeveloped countries far exceed rates in developed nations. It is estimated that in 1999 more than 90 percent of all new HIV infections occurred in developing countries(5). The high rates of infection and mortality in these countries have significantly affected average life spans. Lack of education, preventative efforts, and access to affordable antiretroviral medications all contribute significantly to the global spread of HIV.

In the United States (U.S.), AIDS was the leading cause of death in young American men in 1996(6). Encouragingly, new AIDS cases reported to the Centers for Disease Control (CDC) declined 12 percent from 1996 to 1997(6). Death from AIDS also fell by 47 percent from 1996 to 1997. According to the Centers for Disease Control (CDC), AIDS is no longer the number one cause of death in American males aged 25-44(5,6). This decline in disease progression is believed to primarily result from new, potent antiretroviral medications. An estimated 679,739 people are living with AIDS in the U.S. as of the end of June 30, 1998(6). Similar to worldwide trends, the number of AIDS cases among females in the U.S. has steadily increased to 22 percent since 1985(6). Among recent infections Caucasians account for the largest percentage of infected Americans at 45 percent. Men having sex with men (MSM) account for the greatest percentage of cases (35 percent) followed by injection drug users (23 percent). Transmission by heterosexual contact, while not accounting for the majority of cases in the U.S., has steadily increased since 1991 to 14 percent. Unfortunately, while U.S. AIDS-related death rates continue to decline, infection rates remain unchanged(5).

HIV is not transmitted by casual contact(6). Transmission of the virus requires the exchange of specific bodily fluids which contain viral particles(7). Blood and semen have the greatest viral burden and thus carry the highest risk of disease transmission. The virus itself appears to be highly labile, unable to survive in the environment for more than a few hours. Transmission most commonly occurs when bodily fluids are exchanged during sexual contact(8). Anal intercourse, due to its traumatic nature, carries the greatest risk of transmission, followed by vaginal intercourse and receptive oral sex(7). When used appropriately, barrier methods such as latex condoms and dental dams have been shown to reduce the risk of transmission from sexual contact. However, it must be emphasized that condoms and other barrier methods do not entirely eliminate risk.

Intrauterine transmission is the most common cause of infant and pediatric HIV infection(9). Treatment of mother and baby with zidovudine reduces the potential for perinatal transmission by up to 67.5 percent. To reduce the risk of intrauterine transmission, zidovudine should be administered at doses of 100mg PO five times per day at 14-34 weeks of gestation, followed by IV zidovudine 2mg/kg load and 1mg/kg/hour during delivery(9). The neonate should then be administered 2mg/kg PO q6h for the first six weeks of life. Since monotherapy of infected individuals including pregnant women is no longer considered acceptable, many clinicians now advocate treating women with triple highly active antiretroviral therapy. Studies are underway to determine the optimal and most cost-effective drug regimens for prevention of perinatal transmission(10).

The use of unclean needles by injection drug users is also a common mode of viral transmission. If sterile needles are not available, disinfection of used needles with bleach (5 percent Sodium Hypochlorite) should be encouraged. The implementation of standard precautions has lowered the incidence of needlesticks within occupational settings(7,8). Standard precautions dictate that blood and other high risk bodily fluids from all patients should be considered potentially infectious. Thus appropriate personal protection equipment (e.g., masks, gowns, gloves) should be employed when caring for all patients. The risk of contracting HIV from a needlestick is estimated to be 0.32 percent(11). The risk of seroconversion is increased when the source patient has end-stage disease with a high HIV titer. The use of post-exposure prophylaxis (PEP) appears to reduce the risk of transmission by as much as 79 percent(11). PEP should be offered in all cases of a needlestick involving an HIV+ patient(11,12). Current guidelines call for a three drug regimen to be initiated as soon after the exposure as possible. The three drug regimen most commonly advocated consists of a thirty day course of: zidovudine 300mg PO BID, lamivudine 150mg PO BID, and indinavir 800mg PO q8h or nelfinavir 750mg PO TID(12). Recipients of accidental needlesticks should receive HIV ELISA testing at baseline, then six weeks, 12 weeks, and six months post-exposure(13). The increasing frequency of resistant HIV strains has led some experts to advocate tailoring recommendations for PEP based on the sensitivities of the source patients virus, if known.

ETIOLOGY

HIV exists in two distinct forms, HIV-1 and HIV-2. HIV-2 appears to be a less virulent form of the virus which is usually associated with a slower clinical course. Unfortunately, 99.9 percent of HIV infected individuals within the United States are infected with HIV-1(14). HIV has remarkable capacity for both replication and mutation, producing an estimated 1010 new particles daily while generating one mutation per genome per cycle(15).

Once HIV is transmitted and gains entry to the bloodstream, it seeks out CD4+ cells through receptor-mediated identification and entry (Figure I). CD4+ cells, named for their CD4+ receptors, play an integral role in the overall modulation of the immune system. With damage to CD4+ cells, the immune system is rendered dysfunctional. Within the host CD4+ cells, the virus will prepare to manufacture the necessary viral components for replication. HIV is classified as a retrovirus; therefore, its endogenous genetic material is RNA, unlike humans whose endogenous genetic material consists of DNA(16). Retroviruses transcribe RNA to DNA then back to RNA; RNA is then eventually translated into viral proteins. The transcription of RNA to DNA is accomplished by a retrovirus-exclusive enzyme known as reverse transcriptase(4). Once HIV has catalyzed the conversion of viral RNA to viral DNA, the DNA must be integrated into human DNA. This is accomplished via the viral enzyme integrase and is a necessary step in the replication cycle because HIV lacks the cellular machinery for the transcription of DNA(4). In effect, the virus takes advantage of the host CD4+ cell, which will inadvertently aid in HIV replication by transcribing the integrated piece of viral DNA into viral RNA.

After viral DNA is transcribed and viral RNA is translated, viral proteins are manufactured (Figure I). These proteins are polypeptides which require catalytic cleavage by HIV protease enzymes for activation. Upon activation of these proteins, HIV will assemble itself and depart from the host cell(4,16). The goal of this new virion is to infect another CD4+ cell and repeat the replication cycle. The processes involved in the release of the new HIV virions will result in CD4+ cell death.
As CD4+ cell counts decline (normal 800-1,000 cells/mm³), immune system function is adversely affected, and the patient is at risk for the development of opportunistic infections such as tuberculosis, Pneumocystis carinii pneumonia, mycoplasma, and toxoplasmosis(4,16). Death is usually not a result of HIV disease itself but rather from the secondary opportunistic infections or malignancies that develop.

TREATMENT

Overview

Consensus guidelines are available to guide therapy of HIV infected individuals(16,17). These guidelines are rapidly changing and clinicians should always consult the most recently available literature. Currently three different classes of antiretroviral medications are available for use (Table I). Each of these medications acts to inhibit at least one key step in the HIV replication cycle. Zidovudine was the first drug indicated for the management of HIV infection. Subsequently, many agents have been added to the HIV armamentarium(16). Concentrated efforts by virologists and clinicians have made HIV pharmacotherapy an area of intense development and research. Treatment decisions must be individualized - taking into account guidelines, patient preference, cost, adverse

### Table I. HIV inhibitors

<table>
<thead>
<tr>
<th>Generic reverse transcriptase inhibitors</th>
<th>Dosing</th>
<th>Trade name</th>
<th>Common adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine AZT</td>
<td>200mg PO TID</td>
<td>(Retrovir®)</td>
<td>Marrow suppression</td>
</tr>
<tr>
<td>Didanosine ddl</td>
<td>300mg PO BID</td>
<td>(Videx®)</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Didanosine ddl</td>
<td>&lt;60kg 125mg bid</td>
<td>(Videx®)</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Didanosine ddl</td>
<td>&gt;60kg 200mg bid</td>
<td>(Videx®)</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Zalcitabine ddC</td>
<td>0.75mg TID</td>
<td>(Hivid®)</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Stavudine d4T</td>
<td>40mg BID</td>
<td>(Zerit®)</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Lamivudine 3TC</td>
<td>150mg BID</td>
<td>(Epivir®)</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Abacavir ABC</td>
<td>300mg BID</td>
<td>(Ziagen®)</td>
<td>Hypersensitivity reaction</td>
</tr>
<tr>
<td>Zidovudine AZT</td>
<td>1 capsule BID</td>
<td>(Combivir®)</td>
<td>Marrow suppression</td>
</tr>
<tr>
<td>Lamivudine 3TC</td>
<td></td>
<td></td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Abacavir ABC</td>
<td></td>
<td></td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>200mg qdX2 weeks, then 200mg BID</td>
<td>(Viramune®)</td>
<td>Rash, diarrhea</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>400mg TID</td>
<td>(Rescriptor®)</td>
<td>Rash, headache</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>600mg Qhs</td>
<td>(Sustiva®)</td>
<td>Rash, CNS disengagement</td>
</tr>
<tr>
<td>Saquinavir (Hard gel)</td>
<td>600mg TID</td>
<td>(Invirase®)</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Saquinavir (Soft gel)</td>
<td>1200mg TID</td>
<td>(Fortavase®)</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>600mg BID</td>
<td>(Norvir®)</td>
<td>Drug interactions, GI distress, perioral tingling</td>
</tr>
<tr>
<td>Indinavir</td>
<td>800mg TID</td>
<td>(Crixivan®)</td>
<td>Nephrolithiasis, increased bilirubin</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>750mg TID</td>
<td>(Viracept®)</td>
<td>Diarrhea, nausea</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>1200mg BID</td>
<td>(Agenerase®)</td>
<td>Nausea, rash</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>3 capsules BID</td>
<td>(Kaletra®)</td>
<td>Nausea, rash</td>
</tr>
</tbody>
</table>

*Bind to and inhibit the enzyme responsible for the conversion of viral RNA to viral DNA.

*Binds to and inhibit reverse transcriptase enzyme; structurally distinct from NRTIs.

*Bind to and inhibit protease enzyme. Protease enzyme normally cleaves and activates HIV pro-proteins.
In designing antiretroviral drug regimens, clinicians should always consider drug-drug interactions. Interactions involving increased metabolism of antiretrovirals may result in sub-therapeutic drug concentrations and failure due to the premature development of resistance. Management of drug interactions is a particular challenge since patients may be prescribed multiple medications for both HIV as well as opportunistic infections. Appropriate references should always be consulted to identify and evaluate drug interactions in this population(22).

Subsequent to the initiation of antiretrovirals, viral loads should be closely monitored. In cases of treatment failure, where a previously undetectable viral load has increased or viral load is unresponsive to therapy, patients should be started on three new antiretroviral medications(23). Ideally, the patient should be treatment naïve to the three new medications selected. Addition of a fourth drug to a failing regimen is inadequate and often yields the same results as monotherapy. In cases of drug toxicity or adverse effects, it is appropriate to substitute one drug from the same class without altering the other components of the regimen(23).

The success of combination antiretroviral therapy is highly dependent upon patient adherence(24,25). Vigilant adherence is the best protection against the development of resistance. Adherence is particularly critical among those patients using protease inhibitors. The rapid development of resistance to these drugs and the high incidence of intra-class cross-resistance makes them particularly susceptible to treatment failure in non-adherent patients(25). Adherence is a challenge for many HIV+ patients because of various factors including: high pill burdens, cost, adverse effects, and lifestyle modifications. When counseling patients, clinicians should ensure that the topic of adherence is stressed. Time should be devoted to assessing a clear understanding of HIV disease and specific treatment goals.

Many patients who are placed on three drug antiretroviral regimens achieve and maintain undetectable viral load values for prolonged periods of time. These patients will however continue to harbor the virus within lymph nodes and CNS tissue(26). Transmission of the virus is still possible and patients should be advised to use latex condoms and other methods of barrier protection. The ability to suppress viral replication over a long period of time has raised the issue of antiretroviral medication discontinuation. While, sustained undetectable viral loads have been achieved in large numbers of patients, when antiretrovirals are withdrawn, previously dormant virions begin to once again actively replicate(26). Until further trials are completed, it would be premature to discontinue antiretroviral medications in response to sustained undetectable viral load values.

The search for new and effective antiretrovirals continues. Emphasis has been placed on the development of medications with simplified dosing regimens and reduced pill burdens. Existing medications are also being combined in various ways to simplify dosing regimens. These combinations often take advantage of drug interactions. For instance, because of ritonavir’s inhibitory effects on the metabolism of saquinavir, the two drugs have been combined in a BID dosing regimen(21,25). Currently this regimen is considered salvage therapy and is generally considered only when conventional therapeutic interventions have been exhausted.

A novel approach to the inhibition of viral replication involves the use of the chemotherapeutic agent hydroxyurea(27). Hydroxyurea is a ribonucleotide reductase inhibitor which may have some efficacy in reducing viral replication by potentiating the mechanism of action of the NRTIs, particularly didanosine. While considered salvage therapy, if hydroxyurea is employed it should be combined with didanosine. Neutropenia has been a major dose-limiting adverse effect of hydroxyurea.
CONCLUSION
HIV continues to be one of the most significant infectious diseases of this century. Antiretroviral drug therapy appears to slow progression of the disease to some extent but does not appear to have any curative potential. Until an effective vaccine is developed antiretrovirals must be used judiciously and efficacious to maximize quality of life amongst HIV-infected individuals. Vaccine research while ongoing has been hindered by limited animal models, low response rates, and lack of a recovery model.(28,29). As the number of patients living with HIV and AIDS continues to increase, pharmacists must be prepared to provide effective disease state management and counseling for this special population. Perhaps more so than with any other disease state, medication adherence and knowledge are central to improved outcomes.

References