Protease inhibitors: A new weapon and a new strategy against HIV

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Protease Inhibitors: A New Weapon and a New Strategy Against HIV

Kenneth D. Phillips, PhD, RN

Until recently, reverse transcriptase inhibitors have been the mainstay for treating HIV infection. Now, three protease inhibitors have been approved. Early evidence suggests that triple therapy delays the progression of HIV infection. An understanding of these new drugs and treatment strategies is imperative for clinicians. This article (1) reviews HIV’s structure and replication process, (2) discusses currently approved reverse transcriptase and protease inhibitors, (3) describes the antiretroviral drugs’ modes of action, (4) discusses important nursing implications for monitoring clients on these drugs, and (5) presents current scientific evidence regarding the effectiveness of combination therapy strategies.

Key words: Antiretroviral therapy, HIV/AIDS, protease inhibitors, reverse transcriptase inhibitors

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A decade and a half after acquired immunodeficiency syndrome (AIDS) was first identified, this life-threatening illness continues to elude a cure. Until recently, reverse transcriptase inhibitors have been the mainstay for treating HIV infection (Fischl et al., 1987; Weber, 1993; Yarchoan et al., 1986; Yarchoan et al., 1989). In 1995, a new classification of drugs, protease inhibitors, was added to the armamentarium for treating HIV infection. Although the data are limited, early evidence suggests that a combination of reverse transcriptase inhibitors and protease inhibitors delays the progression of HIV disease and prolongs the lives of HIV- infected people (Collier et al., 1996). Only one brief report regarding the use of protease inhibitors in combination therapy to treat HIV infection was found in the nursing literature (New Wave, 1996). The purpose of this paper is to review HIV’s replication process, discuss the different classifications of antiretroviral agents, describe antiretroviral drugs’ mode of action, and describe nursing implications for monitoring clients on these antiretroviral drugs.

Replication of the Human Immunodeficiency Virus

In order to understand how antiviral drugs work in combating HIV, it is important to understand the structure and life cycle of the HIV.

Structure of the Human Immunodeficiency Virus

HIV is the retrovirus responsible for AIDS (Barré-Sinoussi et al., 1983; Gallo & Wong-Staal, 1985; Montagnier, 1985). Retroviruses contain their genetic material on two single strands of ribonucleic acid (RNA) rather than deoxyribonucleic acid (DNA). HIV consists of an envelope and a core (Figure 1). The outer envelope contains two important glycoproteins, gp120 and gp41. Glycoprotein 120 enables HIV to bind to T helper cells and other host cells that have a CD4+ receptor site on
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Figure 1. Structure of the Human Immunodeficiency Virus

Figure by Tammy Simpson, University of South Carolina, College of Nursing. Used with permission.

their cell membranes, and gp41 enables the viral envelope to fuse with the host cell membrane. The envelope is lined with a viral protein, p17.

The core is surrounded by a membrane that is made up of three proteins, p24, p6, and p7. The core contains two strands of viral RNA and enzymes—reverse transcriptase, RNAse, polymerase, integrase, and protease (Fauci, 1993; Gallo, 1987, 1988; Greene, 1993; Haase, 1990). Table 1 summarizes the virus’ main components.

Life-Cycle of the Human Immunodeficiency Virus

Figure 2 represents HIV’s replication process. The Roman numerals refer to the stages in HIV’s replication process. HIV replication takes place inside host cells bearing a CD4+ marker. A brief summary of the stages of HIV replication is presented to illustrate the point in the life cycle of HIV that antiretroviral drugs work.

- **Stage I.** Glycoprotein 120 binds to the CD4+ protein on host cells.
- **Stage II.** Glycoprotein 41 facilitates fusion of the viral coat with the CD4+ cell membrane.
- **Stage III.** Once inside the cell, the virus undergoes an uncoating process and releases two single strands of RNA into the cytoplasm of the CD4+ cell.

<table>
<thead>
<tr>
<th>Protein Coded</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>gp120</td>
<td>Coat glycoprotein</td>
<td>Allows the HIV to bind to CD4+ receptor sites such as T helper cells.</td>
</tr>
<tr>
<td>gp 41</td>
<td>Coat glycoprotein</td>
<td>Allows the HIV envelope to fuse with the plasma membrane of a cell bearing a CD4+ receptor site.</td>
</tr>
<tr>
<td>p17</td>
<td>Coat protein</td>
<td>Becomes part of the outer coat of the new HIV.</td>
</tr>
<tr>
<td>p24</td>
<td>Core protein</td>
<td>Forms the core capsid, which surrounds the viral RNA and enzymes.</td>
</tr>
<tr>
<td>p6</td>
<td>Core protein</td>
<td>Becomes part of the nucleocapsid.</td>
</tr>
<tr>
<td>p7</td>
<td>Core protein</td>
<td>Becomes part of the nucleocapsid.</td>
</tr>
<tr>
<td>Reverse transcriptase</td>
<td>Core enzyme</td>
<td>Converts viral RNA to a single strand of viral DNA. The strand of viral RNA and the newly formed viral DNA remain attached.</td>
</tr>
<tr>
<td>RNAse</td>
<td>Core enzyme</td>
<td>Degrades the RNA template from the DNA, leaving a single strand of DNA.</td>
</tr>
<tr>
<td>Polymerase</td>
<td>Core enzyme</td>
<td>Makes an exact copy of the single strand of DNA and causes the two strands of viral DNA to join.</td>
</tr>
<tr>
<td>Integrase</td>
<td>Core enzyme</td>
<td>Inserts the newly formed double strand of viral DNA into the DNA of the host cell.</td>
</tr>
<tr>
<td>Protease</td>
<td>Core enzyme</td>
<td>Cleaves the proteins of noninfectious, immature virions, thus making them infectious.</td>
</tr>
</tbody>
</table>

Table 1. Components of the Human Immunodeficiency Virus

Adapted from Gallo, 1987, 1988; Greene, 1993; Haase, 1990
Figure 2. Life Cycle of the Human Immunodeficiency Virus

- **Stage IV.** A single strand of DNA is copied from the RNA by the enzyme reverse transcriptase. Reverse transcriptase contains two other enzymes: RNase and polymerase. RNase is necessary to remove the RNA from the DNA copy. Then, polymerase makes another exact copy of the viral DNA and causes the two strands of DNA to join.

- **Stage V.** The newly formed double strand of viral DNA moves into the nucleus of the host cell, where it is incorporated into the DNA of the host cell by the enzyme integrase. The host cell begins to make messenger RNA (mRNA). Then, mRNA moves from the host cell nucleus to the ribosomes, where it guides the production of viral proteins. Transfer RNA (tRNA) carries amino acids from the host cell cytoplasm to the ribosomes.

- **Stage VI.** In the ribosomes, the amino acids are assembled into large, inactive precursor proteins.

- **Stage VII.** During this stage, immature virions are released from the host cell through the process of budding. These virions, which are noninfectious, contain large precursor proteins that must be broken into smaller glycoproteins, proteins, and enzymes before they become infectious.

- **Stage VIII.** By the action of protease, these large precursor proteins are split into a variety of smaller glycoproteins, proteins, and enzymes that are essential for the virus to become a mature, infectious retrovirus.

There are several points in the life cycle of HIV where a great deal of research has been directed at finding drug therapies for HIV infection. The research has been directed at preventing the: (1) binding of gp120 to the CD4+ receptor sites, (2) fusion of the viral coat with the cell membrane of the CD4+ receptor site, (3) uncoating of the virus once inside the host cell, (4) synthesis of viral...
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DNA from viral RNA by the action of reverse transcriptase, (5) degradation of viral RNA leaving it attached to the newly formed strand of viral DNA, (6) insertion of viral DNA into the host cell DNA by the integrase, (7) protein synthesis in the rough endoplasmic reticulum of the host cell, (8) budding, and (9) maturation of the newly formed HIV by the action of protease (Johnston & Hoth, 1993; Weber, 1993). Presently, the greatest success in treating HIV infection has been the use of reverse transcriptase inhibitors and protease inhibitors. Reverse transcriptase inhibitors work in Stage III by preventing transcription of viral RNA into viral DNA. Protease inhibitors work in Stage VIII by preventing the cleavage of precursor proteins into mature viral proteins.

Classifications of Antiretroviral Drugs

Reverse Transcriptase Inhibitors

Reverse transcriptase inhibitors comprise the first major effective classification of antiretroviral drugs. Reverse transcriptase is an enzyme found in retroviruses that is necessary for their replication. The reverse transcriptase inhibitors have shown effectiveness in preventing infection of uninfected CD4+ cells (Fischl et al., 1987; Lambert et al., 1990; Merigan et al., 1989; Yarchoan et al., 1989). They do not block viral production by CD4+ cells that are chronically infected (Ashorn et al., 1990; Dreyer et al., 1989; Kempf et al., 1990; McQuade et al., 1990; Meek et al., 1990; Reedijk et al., 1995; Rich et al., 1990; Roberts et al., 1990).

Nucleoside analogues, such as AZT, are substituted for natural substrates used to manufacture viral DNA. The growing chains of viral DNA are prematurely terminated, thus preventing viral replication. Since HIV mutates so rapidly (Martin, Redshaw, & Thomas, 1995), resistance of HIV to reverse transcriptase inhibitors and other antiretroviral drugs frequently occurs early in the course of therapy and hinders their effectiveness (Boucher et al., 1992; Fitzgibbon et al., 1992; Larder, Darby, & Richman, 1989; Reichman et al., 1993). This problem can be reduced by using drug combinations. For example, lamivudine, which is not effective when used alone, slows development of resistance to zidovudine (Eron et al., 1995). Clients taking zidovudine plus lamivudine showed significant improvements in CD4+ counts and viral load (Eron et al.). Table 2 summarizes the nucleoside analogue reverse transcriptase inhibitors.

Protease Inhibitors

Proteases are enzymes that split the peptide bonds of larger proteins into smaller proteins (Roose & Van Noorden, 1995). HIV protease helps HIV mature (Kohl et al., 1988; Peng, Ho, Chang, & Chang, 1989; Tang, Lin, Hartsuck, & Lin, 1992). HIV protease is part of the precursor protein gp160 (Buegelski et al., 1994). HIV protease autocleaves itself from the precursor protein gp160 (Buegelski, Kirsh, & Hart, 1994). Following autocleavage, gp160 is cleaved into the two glycoproteins of the viral coat (Decroly et al., 1994). Then, HIV protease promotes maturation of HIV by splitting retroviral precursor polyproteins into structurally essential glycoproteins and proteins (Krausslich & Wimmer, 1988; Robins & Plattner, 1993; Tisdale et al., 1995). Thus, HIV protease allows immature, noninfectious virions to become mature, infectious virions.

Glycoprotein 160 is a polyprotein precursor that is encoded by the gag-pol region of the HIV genome. HIV protease splits gp160 into gp120 and gp41 (Decroly et al., 1994). By chopping gp160 into its component parts, HIV protease promotes binding (gp120) of the virus to the CD4+ receptor site and fusion (gp41) of the viral coat with the CD4+ cell membrane. There are eight possible cleavage sites on gp160. Nine mature proteins are formed by the action of protease: (1) p17, (2) p24, (3) an unknown protein, (4) p7, (5) p6, (6) protease, (7) reverse transcriptase, (8) RNAse, and (9) integrase (Buegelski et al., 1994; Debouck et al., 1987; Gelderblom et al., 1990). The proteins of HIV are summarized in Table 1.

Protease inhibitors prevent maturation of newly formed virions by preventing the cleavage of HIV's polyproteins (Ashorn et al., 1990; Kohl et al., 1988; Loeb, Hutchinson, Edgell, Farmerie, & Swanstrom, 1989; Tang et al., 1992). Thus, protease inhibitors prevent immature, noninfectious viruses from becoming mature, infectious...
Table 2. Reverse Transcriptase Inhibitors

<table>
<thead>
<tr>
<th>Reverse Transcriptase Inhibitor</th>
<th>Adult Dose</th>
<th>Adverse Effects</th>
<th>Nursing Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (azidothymidine; AZT; ZDV)</td>
<td>200 mg orally q8h</td>
<td>Anemia, Granulocytopenia, Myopathy, Myositis</td>
<td>Monitor the client’s complete blood count. Instruct client to report muscle pain and fatigue.</td>
</tr>
<tr>
<td>Didanosine (dideoxyinosine; ddI)</td>
<td>Body weight &gt; 132 lbs: 200 mg orally q12h; Body weight &lt; 132 lbs: 125 mg orally q12h</td>
<td>Pancreatitis, Peripheral neuropathy, Hepatotoxicity</td>
<td>Since ddI is degraded in acid, tablets must be crushed, chewed, or dispersed in water to release the buffer or given with a buffered powder. Inform client to report abdominal pain, nausea, and vomiting.</td>
</tr>
<tr>
<td>Zalcitabine (dideoxycytidine; ddC)</td>
<td>0.75 mg orally q8h</td>
<td>Pancreatitis, Peripheral neuropathy, Mouth ulcers, Esophageal ulcers, Cardiomyopathy, Anaphylaxis</td>
<td>Inform client to report abdominal pain, nausea, and vomiting. Instruct client to monitor for signs of peripheral neuropathy.</td>
</tr>
<tr>
<td>Stavudine (D4T)</td>
<td>Body weight &gt; 132 lbs: 40 mg orally q12h; Body weight &lt; 132 lbs: 30 mg orally q12h</td>
<td>Peripheral neuropathy, Neutropenia, Hepatotoxicity, Anemia</td>
<td>Instruct client to monitor for signs of peripheral neuropathy. Observe for indication of neutropenia.</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>150 mg orally q12h</td>
<td>Pancreatitis, Peripheral neuropathy, Headache, Myalgia</td>
<td>May be administered with or without food. Inform client to report abdominal pain, nausea, and vomiting. Instruct client to monitor for signs of peripheral neuropathy.</td>
</tr>
</tbody>
</table>


ones (Debouck et al., 1987; Gottlinger, Sodroski, & Haseltine, 1989; Kohl et al., 1988; Tang et al., 1992). Many antiretrovirally active protease inhibitors have been developed (Buegelski et al., 1994; Tisdale et al., 1995). The three protease inhibitors (saquinavir, ritonavir, and indinavir) that have been approved by the Food and Drug Administration (FDA) are summarized in Table 3.

Saquinavir. Saquinavir has been associated with significant increases in CD4+ cell counts and few side effects (Kitchen, Stewart, Bragman, & Weber, 1995). It
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Table 3. Protease Inhibitors

<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
<th>Adult Dose</th>
<th>Adverse Effects</th>
<th>Nursing Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td>600 mg orally q8h</td>
<td>Diarrhea, Abdominal discomfort, Nausea, Photosensitivity</td>
<td>Instruct client to take with a meal to increase absorption. Grapefruit juice may increase bioavailability. Instruct client to avoid prolonged exposure to direct sunlight until sensitivity to sunlight is known.</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>600 mg orally q12h</td>
<td>Diarrhea, Nausea</td>
<td>Instruct client to take with food. Observe for elevations in serum triglycerides, AST, ALT, GGT, CPK, and uric acid. Avoid coadministration of nonsedating antihistamines, sedative hypnotics, or antiarrhythmics (may be life-threatening).</td>
</tr>
<tr>
<td>Indinavir</td>
<td>800 mg orally q8h</td>
<td>Kidney stones, Hyperbilirubinemia</td>
<td>Instruct client not to take with meals; however, if gastric distress occurs, take with a light snack. If didanosine is also prescribed, instruct client to take the two drugs one hour apart. Instruct client to increase oral fluid intake.</td>
</tr>
</tbody>
</table>


is usually used in combination with either AZT or a nuceloside analog (Davey, Goldschmidt, & Sande, 1996). Saquinavir is more effective in combination with AZT when the client has not taken AZT previously. Since AZT has been widely prescribed in the HIV-infected cohort, some clinicians believe it may be most beneficial to combine saquinavir with either zalcitabine (ddC) or didanosine (ddl) (Davey et al., 1996).

Ritonavir. Ritonavir has been associated with significantly increased CD4+ counts (Danner et al., 1995;
Kelleher, Carr, Zaunders, & Cooper, 1996; Markowitz et al., 1995), increased CD8+ counts (Kelleher et al.), increased responsiveness to new antigens as measured by phytohemagglutinin antigen [PHA] mitogen blastogenesis (Kelleher et al.), increased responsiveness to previously encountered antigens (Kelleher et al.), and decreased viral load (Danner et al.; Kelleher et al.; Markowitz et al.). Following treatment with ritonavir, significant decreases in CD4+ cells bearing a CD38 receptor site following treatment with ritonavir have been observed (Kelleher et al.); this may be a very important finding, since an increase in these cells is associated with disease progression (Giorgi et al., 1994; Levacher et al., 1992).

**Indinavir.** In clinical trials, dramatic reductions in viral load and improvements in CD4+ cell counts have been reported in clients receiving indinavir. In fact, used in combination with AZT and 3TC, viral loads have been reduced to undetectable levels (Davey et al., 1996).

**Triple Therapy: A New Strategy**

Protease inhibitors have shown effectiveness when used as a monotherapy (Danner et al., 1995; Kelleher et al., 1996; Markowitz et al., 1995; Massari et al., 1996). However, synergistic effects have been demonstrated when reverse transcriptase inhibitors and the protease inhibitors are combined (Collier et al., 1996; Kageyama et al., 1992). The term synergy identifies the concept that the beneficial effects of two or more drugs are greater when the drugs are combined than would be expected if either of the drugs was used alone. Synergistic effects have been noted when certain reverse transcriptase inhibitors are combined: (1) zidovudine [AZT] and lamivudine [3TC], (2) zidovudine [AZT] and didanosine [ddl], and (3) zidovudine [AZT] and zalcitabine [ddC] (Merigan, 1995). HIV’s ability to develop resistance to drugs is a major obstacle to effective treatment (Richman, 1993). The term resistance refers to the concept that a previously effective antiretroviral drug becomes ineffective due to viral mutations. Viral mutations and subsequent resistance may be slowed by using a combination of drugs (Vella et al., 1995). For instance, resistance of HIV to zidovudine may be delayed by combining zidovudine with a protease inhibitor (Schapiro, Winters, & Merigan, 1995) or lamivudine (Davey et al., 1996). In cross-resistance, development of resistance to one drug results in the development of resistance to other drugs of the same classification or other classifications. Cross-resistance is extremely problematic in HIV infection. Resistance to one protease inhibitor may result in cross-resistance to other antiretroviral drugs, in particular other protease inhibitors (Chen et al., 1995; Condra et al., 1995). A mutation of only one genetic sequence results in cross-resistance to stavudine [d4T], didanosine [dDI], and dideoxycytidine [ddC] (Merigan, 1995). The term resistance-reversal connotes the concept that the development of resistance to one antiretroviral drug undoes the resistance that has developed to another drug. An example of this is the phenotypic resistance-reversal noted in the coadministration of zidovudine and lamivudine (Boucher et al., 1993; Merigan; Staszewski, 1995).

**Saquinavir, plus zidovudine, plus dideoxycytidine.** Phase II clinical trials indicate that combinations of saquinavir (SQV), zidovudine (ZDV), and dideoxycytidine (ddC) synergistically decrease HIV replication. In a study conducted by Collier et al. (1996), three treatment regimens were used: (1) saquinavir (SQV), plus zidovudine (ZDV), plus dideoxycytidine (ddC); (2) zidovudine (ZDV) plus dideoxycytidine (ddC); and (3) zidovudine (ZDV) plus saquinavir (SQV). Patients receiving a combination of saquinavir (SQV), plus zidovudine (ZDV), plus dideoxycytidine (ddC) demonstrated the greatest increase in CD4+ counts and the greatest decrease in viral load (Collier et al.).

**Ritonavir, plus zidovudine, plus zalcitabine.** The effects of a six-month regimen of ritonavir, plus zidovudine, plus zalcitabine were studied in a group of 21 patients (Abramowicz, 1996). Viral load decreased to undetectable levels in 5 of the 21 participants (Third Conference on Human Retroviruses and Opportunistic Infections, 1996) as reported in The Medical Letter on Drugs and Therapeutics.

**Indinavir, plus zidovudine, plus lamivudine.** HIV viral load decreased to undetectable levels over a four
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A month treatment period in 20 of 22 clients taking zidovudine (AZT), plus lamivudine (3TC), plus indinavir. The participants in this study had an average CD4+ cell count of 175/mm³ (Third Conference on Human Retroviruses and Opportunistic Infections, 1996) as reported in *The Medical Letter on Drugs and Therapeutics* (Abramowicz, 1996). In a separate study, a six-month course of indinavir, zidovudine, and lamivudine lowered HIV viral load to undetectable levels in 11 of 19 patients. The participants were previously untreated and had an average CD4+ lymphocyte count of 150 cells/mm³ (Third Conference on Human Retroviruses and Opportunistic Infections, 1996) as reported in *The Medical Letter on Drugs and Therapeutics*.

**Nursing Implications**

Nurses use a holistic approach in the prescription and administration of medications. Administering antiretroviral drugs requires special attention to all stages of the nursing process.

**Assessment**

A complete assessment should be performed prior to prescribing or administering any medication. When administering antiretroviral drugs, nurses need to be especially careful to determine the patient’s allergies to medications (name of medication and type of reaction) and assess past opportunistic infections and malignancies.

**Nucleoside analogues.** Data from a complete blood count, lymphocyte subset enumeration, and a chemical profile should be available prior to administering a nucleoside analogue. Six assessments must be performed before administering a nucleoside analogue: First, ensure that the patient does not have anemia (hemoglobin < 9.5 g/dl) or granulocytopenia (< 1000/mm³). If either is present, special precautions are needed when administering zidovudine. Second, check for elevated serum creatinine, which could make the patient more prone to drug toxicity. Third, assess patients for a history of pancreatitis, symptoms of pancreatitis (i.e., abdominal pain, nausea, and vomiting), risk factors for pancreatitis (i.e., cholelithiasis and ethanol abuse), and elevations in either serum amylase or serum lipase, which may indicate pancreatitis. Pancreatitis is a potentially lethal side effect of nucleoside analogues. Fourth, assess for early signs of peripheral neuropathy (i.e., intermittent numbness, tingling, or pain in hands or feet). Fifth, perform a complete nutritional assessment (i.e., height, weight, serum albumin, serum transferrin, serum prealbumin, and a 24-hour diet recall). Sixth, if the client is female, assess her pregnancy status. Zidovudine has been shown to be effective in preventing the vertical transmission of HIV from the mother to the fetus without harming the fetus when administered after the first 14 weeks of pregnancy. However, drugs other than zidovudine have not been as thoroughly tested in pregnancy. The other nucleoside analogues should be given during pregnancy only when the benefits clearly outweigh the risks. See Table 2.

**Protease inhibitors.** No major toxicities have been observed as a result of taking either of the three approved protease inhibitors. However, coadministration of ritonavir and non-sedating antihistamines, sedative hypnotics, or antiarrhythmics may produce life-threatening situations such as oversedation, respiratory arrest, or cardiac arrest (see Table 4, Abramowicz, 1996; Olin, 1996). Coadministration of these drugs with protease inhibitors other than ritonavir has led to similar life-threatening reactions. Always identify all the drugs the client is taking before prescribing or administering ritonavir.

**Plan**

During the planning phase, measurable goals are mutually established between the client and the nurse. In addition, the nurse makes a thorough assessment of all the patient’s drugs, including over-the-counter and street drugs. In addition to the drug, route, dosage, and frequency, the nurse must know whether the client is
Table 4. Examples of Nonsedating Antihistamines, Sedative Hypnotics, and Antiarrhythmics*

<table>
<thead>
<tr>
<th>Nonsedating Antihistamines</th>
<th>Sedative Hypnotics</th>
<th>Antiarrhythmics</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astemizole</td>
<td>Alprazolam</td>
<td>Amiodarone</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Clorazepate</td>
<td>Bepridil</td>
<td>Cisapride</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>Encaainide</td>
<td>Clozapine</td>
</tr>
<tr>
<td></td>
<td>Estazolam</td>
<td>Flecaainide</td>
<td>Meperidine</td>
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<td></td>
<td>Flurazepam</td>
<td>Propafenone</td>
<td>Piroxicam</td>
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<tr>
<td></td>
<td>Midazolam</td>
<td>Quinidine</td>
<td>Propoxyphene</td>
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<td></td>
<td>Triazolam</td>
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<td>Rifabutin</td>
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<tr>
<td></td>
<td>Zolpidem</td>
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</tbody>
</table>


* Not an inclusive list

able to take the medication independently. If not, does he or she have adequate social support to help with taking the medications? Does the client have adequate resources for obtaining the drug (i.e., money, insurance, transportation)? Since it is never enough to simply say, “Take your medicine,” nurses must plan methods for teaching the client about the medicines, and must make themselves available to answer questions that arise after the client leaves the office. For instance, the client may ask, “It is my birthday. Can I have a glass of wine with my medications?” Nurses can help the client find a way to procure the prescribed medications and to incorporate these medications into his or her life. Be familiar with industry, social, or governmental compassionate drug programs for indigent patients.

Implementation

Clients should be taught the name, dosage, route, and frequency of any drug being prescribed. Apprise the client of possible side effects and any special precautions that must be taken while taking a particular drug. Provide written instructions in addition to verbal ones. Inform the client that current drugs are not a cure and will not prevent the transmission of HIV. Table 5 outlines additional client instructions.

Evaluation

Evaluation is an ongoing process and is performed at every contact with the client. Assess for past or present opportunistic infections or malignancies. A complete blood count should be drawn at frequent intervals and the results evaluated. If the client develops anemia or granulocytopenia, a drug may need to be withdrawn, the dosage changed, or another drug such as epoetin alfa recombinant or granulocyte colony stimulating factor added. Liver, pancreatic, and renal values also should be assessed at regular intervals.

Evaluation of antiretroviral therapy is based on viral markers. Three viral markers have been more significant than others in monitoring disease progression and treatment effectiveness: CD4+ cell counts, p24 antigenemia, and viral load.

CD4+ cell counts. The normal CD4+ cell count ranges from 589 to 1505 cells/µl (Fischbach, 1996). T helper/inducer cells (CD4+) are invaded and destroyed by HIV. So a decline in CD4+ cells generally signifies disease progression (Flaskerud & Ungvarski, 1995) and
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Table 5. Client Instructions

Instruct client to:

1. Recognize and report the signs and symptoms of peripheral neuropathy (i.e., numbness, tingling, or pain in the hands and feet).
2. Recognize and report the signs and symptoms of acute pancreatitis (i.e., abdominal pain, nausea, or vomiting).
3. Recognize and report early signs and symptoms of anemia (i.e., shortness of breath, increased weakness, tiredness, fatigue, lightheadedness, dizziness, or palpitations).
4. Drink 2–3 liters of fluids per day.
5. Report signs of opportunistic infections in the mouth (i.e., furry tongue, mouth lesion, or thrush), in the vagina (i.e., itching, burning, redness, or discharge), or in the rectum (i.e., itching, drainage).
6. Avoid nonprescription medications unless approved by a healthcare provider.
7. Take drugs as scheduled to maintain an appropriate blood level of the drug.
8. Avoid drug “holidays” (periods when the drug is not taken), which may allow the development of resistant strains of HIV.
9. Take saquinavir, ritonavir with food.
10. Take didanosine, indinavir, or zalcitabine on an empty stomach.
11. Take stavudine, zidovudine, or lamivudine with or without food.
12. Chew, crush, or disperse didanosine in water before swallowing to release the buffer or to take it with a buffered powder.
13. Understand that the long-term side effects of these drugs remain unknown.
14. Take prophylactic drugs to prevent opportunistic infections and malignancies.
15. Use contraceptives to prevent pregnancy while taking antiretroviral drugs (remind the client that effective barrier methods are needed to prevent the transmission of HIV).

indicates that the treatment strategy should be re-examined (Davey et al., 1996).

CD4+ cells can be destroyed by four processes: (1) binding of gp120 can lead to preprogrammed cell death known as apoptosis; (2) binding of gp120 can terminate cell division known as anergy; (3) gp120 on the surface of virions budding from the surface of an infected CD4+ cell can bind to CD4+ receptors on other CD4+ cells, causing them to tear; or (4) multiple CD4+ cells clump together in a process known as syncytium formation, resulting in the death of many CD4+ cells at one time (Peterson, 1995).

Antiretroviral treatment has been reserved for a CD4+ cell count less than 500 cells/mm³. Therapy should be initiated in clients who have a progressive decline of CD4+ cells to 500 cells/mm³ or in clients with a CD4+ cell count greater than 500 cells/mm³, if their CD4+ cells are rapidly declining (Davey et al., 1996). Undoubtedly, new recommendations will be forthcoming regarding combination therapy.

The CD4+ cell count is an indirect marker of HIV replication. Therefore, the cell count may rise in response to an infection other than HIV or decline transiently in response to stimuli other than increased viral replication (Davey et al., 1996; Harrigan, 1995; Merigan, 1995). This limits the significance of the CD4+ cell count in tracking the progression of the disease or the effectiveness of therapy. In fact, it remains controversial whether CD4+ counts have utility in predicting disease progression or survival (Choi, Lagakos, Schooley, & Volberding, 1993). However, in general, a significant reduction of the CD4+ cell count suggests that the treatment strategy needs to be re-examined and that the treatment plan may need to be changed (Davey et al., 1996).

p24 antigenemia. Another test that is used as a marker of disease progression is the p24 antigen test. The p24 antigen is one of the core proteins. Early after infection antibodies to p24 appear. In the p24 antigen test, a spectrophotometer is used to measure the optical density that develops when p24 antigen in a patient’s serum complexes with recombinant p24 antibody and is subjected to the enzyme linked anti-p24 ELISA test. The greater the optical density, the greater the concentration of p24 antigen in the patient’s serum. Antibody forma-
tion is one of the major problems associated with this reliability of this test. In vivo, the HIV-infected person makes antibodies to p24 in his or her serum. These antibodies attach to the p24 in the serum. In vitro, the recombinant antibodies are unable to attach to the p24 antigen unless the serum is treated with an acid wash. This acid wash procedure releases the attachment of the p24 antigen-antibody complex, but it decreases the reliability of this test. Therefore, its usefulness as a marker of disease progression is limited (Piliero & Libman, 1996).

The p24 antigen test provides diagnostic information in infants born to HIV-infected mothers. In the early months after delivery, maternal antibodies to HIV and other maternal antibodies persist in the infant. The infant with antibodies to HIV may or may not be HIV-infected. The presence of p24 antigen in the serum of the newborn allows early diagnosis and treatment of HIV infection (Cooper & Pelton, 1996).

**Viral load.** Viral load is a significant step in treating HIV infection. HVA RNA levels have greater power to predict disease progression than CD4+ cell count alone (O’Brien et al., 1996). Since viral load is a direct marker of viral replication, it does not rise and fall in relationship to the white blood cell count. However, HIV viral load can transiently increase in the presence of illnesses such as pneumonia or influenza (Sax & Flory, 1996). Viral load measures the presence of viral RNA in the plasma, but not in other tissues (Davey et al., 1996).

Four methods are currently used to measure viral load: (1) quantitative competitive polymerase chain reaction [PCR], (2) nucleic acid sequence-based amplification [NASBA], (3) branched-chain DNA [b-DNA], and (4) the ampicor microwell plate assay (Harrigan, 1995).

In the early, asymptomatic stage of HIV infection, viral load may be about 5,000 virions/ml (Merigan, 1995). It rises as the disease progresses and declines in response to effective antiretroviral therapy (Davey et al., 1996). In advanced stages of HIV infection, viral load may be as much as 1 million virions/ml (Merigan). A rise in viral load indicates increased viral replication. A reduction in viral load greater than 0.5 log₁₀ following initiation of treatment indicates that the antiretroviral therapy is effective (Davey et al., 1996). If a client’s viral load fails to drop or does not drop by 0.5 log₁₀ following treatment, the approach should be re-evaluated, and the care plan may need to be modified (Davey et al., 1996). Viral load determinations are recommended at baseline, prior to beginning antiretroviral therapy, and approximately one month after beginning or changing antiretroviral therapy (Sax & Flory, 1996). Table 6 summarizes the interpretation of HIV viral load testing.

**Special Considerations**

Clients should be advised to avoid “drug holidays” (periods of time when drugs are not taken). Drug holidays permit activation of viral replication and increase the risk of mutation and the development of resistant strains. Resistance to one protease inhibitor may be conferred on other protease inhibitors and thus limit future treatment options.

Avoid coadministration of nonsedating antihistamines, sedative hypnotics, or antiarrhythmics. When these drugs are administered with the protease inhibitors, life threatening or lethal complications may arise (Olin, 1996). Examples of each of the nonsedating antihistamines, sedative hypnotics, and antiarrhythmics are provided in Table 4.

Avoid coadministration of antiretroviral drugs with similar adverse effects (Merigan, 1995). For instance, avoid simultaneous use of didanosine [ddI] and dideoxycytidine [ddC], because acute pancreatitis and peripheral neuropathy are adverse reactions of both drugs (Davey et al., 1996; Merigan).

Nurses approach every aspect of patient care holistically, including the prescription and administration of medications. Quite often, nurses work more closely with the client than other clinicians. The nurse’s responsibility goes far beyond prescription and administration of a medication. Nurses help people find resources to procure medications, teach them the effects and side effects of their medications, teach them how to take their medication to obtain maximum benefit, and help them find ways to incorporate drug therapies into their lives. When an informed decision is made by the client to discontinue antiretroviral therapy, the nurse supports the client.
Protease Inhibitors: A New Weapon and a New Strategy Against HIV

Table 6. Interpretation of HIV RNA Viral Load

<table>
<thead>
<tr>
<th>Viral Load</th>
<th>Clinical Significance of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10,000 copies per mm³</td>
<td>Low risk of disease progression</td>
</tr>
<tr>
<td>10,000 to 100,000 copies per mm³</td>
<td>Moderate risk of disease progression</td>
</tr>
<tr>
<td>&gt; 100,000 copies per mm³</td>
<td>High risk of disease progression</td>
</tr>
</tbody>
</table>

Adapted from Sax, P., & Flory, J. (1996). Information for patients: Viral load testing. AIDS Clinical Care, 8, p. 31

Discussion

Protease inhibitors and triple therapy provide a new level of hope in the search for an effective treatment for HIV infection (Wlodawer & Erickson, 1993). However, the advent of HIV protease inhibitors presents new research questions. Which combination of drugs is best for a particular group of clients? At what point should a client be started on a particular combination of drugs?

Although slower than that of zidovudine, development of resistance to HIV protease inhibitors has been noted (Markowitz et al., 1995; Martin et al., 1995; Tisdale et al., 1995). This resistance reminds us that the search for definitive prevention and treatment must continue. The progress made with triple therapy is very encouraging. Strategies for treating HIV infection are rapidly increasing. Nurses, especially advanced practice nurses providing care for HIV-infected individuals, must keep current with new medications that are being released. Existing drugs, new drugs, combinations of those drugs, and direct measurement of RNA viral load will allow individualization of treatment strategies.

References


