Is the Treatment of HIV with Protease Inhibitors Superior to that of Reverse Transcriptase Inhibitors?

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Abstract

The development of antiretroviral drugs has revolutionized the treatment of HIV. Currently, there are two categories of antiretroviral drugs available to suppress the replication of the virus: reverse transcriptase inhibitors and protease inhibitors. This paper aims to determine whether the treatment of the virus with protease inhibitors is superior to treatment using reverse transcriptase inhibitors. First, the effects of HIV are presented. This encompasses the structure and life cycle of virus. Next, the three classes of antiretroviral drugs are introduced, which are then compared according to their adverse drug reactions and interactions. Lastly, the conclusion evaluates the superiority of the protease inhibitors to the reverse transcriptase inhibitors.

Introduction

HIV/AIDS is one of the world's greatest threats for which there is no cure. The disease, which was initially stereotyped to the gay community, has now wreaked havoc on many underdeveloped and developing nations with an estimate of 3.1 million deaths in 2004 (UNAIDS, 2004). Despite an increase in the international spending to combat AIDS from 250 million dollars in 1998 to 4.8 billion dollars in 2002, the United Nations reports that the rate of infection still continues to rise (UNAIDS, 2004). In addition, the Joint United Nations Programme on HIV/AIDS, UNAIDS, has estimated the number of people living with HIV/AIDS in 2004 to be 39.4 million, which includes the 4.9 million people who acquired the disease in 2004 (UNAIDS, 2004).

In 1987 AZT was the first antiretroviral drug to be approved by the FDA and gave great hope for the eradication of the virus (Bartlett, 2001). However, the virus quickly developed resistance to the drug and

smashed any hope that an antiretroviral drug could effectively rid the body of HIV. Furthermore, the rate at which the virus mutates and its resistance to any single antiretroviral drug cause an urgency in the production of medications that could effectively suppress the virus to an undetectable level with minimal side effects. Hence, since then many daughter drugs of AZT and drugs that target other areas of the life cycle of the virus have been developed. Currently, there are two types of HIV drugs: reverse transcriptase inhibitors and protease inhibitors. This research paper aims to show the effectiveness of these two types of treatment and to investigate whether the treatment of the virus using protease inhibitors is superior to that using reverse transcriptase inhibitors. However, in order to understand how the two different inhibitors of the virus work, it is imperative to understand the structure and the life cycle of the virus. Hence, the paper first targets the structure and life cycle HIV, tracing how HIV affects the body before introducing the medications that have been developed to suppress the virus. Furthermore, the comparison of the two classes of antiretroviral medication is narrowed down to the analysis of two categories: side effects and potential drug interactions.

HIV AND ITS EFFECTS

HIV and AIDS are often times used interchangeably. However, AIDS is caused by the human immunodeficiency virus (HIV), which affects and weakens the body's immune system, allowing the body to develop life-threatening infections and cancers. The term AIDS, Acquired Immune Deficiency Syndrome, is used to define the most advanced stages of the HIV infection, that is, it applies to people who have encountered serious complications due to HIV (HIV Infection and AIDS, 2004).

Virus Structure

HIV is thought to contain two identical copies of single-stranded RNA, approximately 9500 nucleotides in length, which may be linked together to form a genomic RNA dimer (Human Immunodeficiency Virus: Structure and Pictures, n.d.). The two strands of RNA are associated with a nucleocapsid protein and are found within a bullet-shaped capsid along with other viral proteins, such as integrase and reverse transcriptase, which are essential for the maturation of the virus. The capsid is engulfed by a layer of matrix protein that is directly attached to the envelope of the virus. The HIV envelope is a phospholipid bilayer that was derived from

the host cell as the virus budded out. Throughout the HIV envelope are peg-like structures that consist of three or four gp41 glycoproteins stems capped with three or four gp120 glycoproteins (The Structure and Life of HIV, 2004). These glycoproteins are antireceptors, that is, they are involved in the attachment and fusion of the virus to the host cell.

HIV Infection: The HIV Life Cycle

HIV is a lentivirus, which is a subgroup of retroviruses known for their latency upon infection, persistent presence in the blood of the host, infection of the nervous system, and the debilitation of the host's immune system (Dubin, 2004). Retroviruses contain RNA as their genetic make up and the reverse transcriptase enzyme, which they use to convert their genome to DNA. HIV interacts with its host cells by binding to special receptors known as CD4 receptors that are found on white blood cells known as helper T lymphocytes or helper T cells or CD4+ cells, which play an integral role in coordinating the body's immune system (Gandhi et al., 1999).

Furthermore, the virus may target other cells involved in the body's immune system, such as monocytes and macrophages (The Structure and Life of HIV, 2004). In addition to binding to CD4 receptors on the host cell using its gp120 glycoproteins, interactions with co-receptors such as CCR5 or CXCR4 are needed for the virus to enter the host cell (Gandhi et al., 1999). The CCR5 co-receptor has been shown to be critically involved in the binding of the virus to the host cell, since individuals' hemizygous for mutations in the CCR5 region are resistant to infection by HIV (Pieribone, 2002/2003). Upon binding to the receptors and co-receptors, the viral envelope fuses with the cell membrane of the host cell allowing viral penetration to occur, that is, the entry of the viral genome and viral proteins (the nucleocapsid of the virus) into the cytoplasm of the cell (Pieribone, 2002/2003). The nucleocapsid is then partially dissolved to release the viral RNA and viral proteins. The viral genome is then transcribed to form double-stranded DNA using the reverse transcriptase enzyme, which was released into the host's cytoplasm during penetration. The reverse transcriptase enzyme uses nucleotides, the building blocks of DNA, found in the cell's cytoplasm to make the double-stranded DNA (Pieribone, 2002/2003). During this process of transcription various mutations occur in the viral genome (HIV, n.d.). This process of transcription of the viral genome from RNA to DNA is only possible because of the presence of the reverse transcriptase enzyme. Upon transcription, the double-stranded DNA travels to the nucleus of the cell

where it integrates itself into the cell's genome using the integrase enzyme, which was also deposited into the cell during penetration. The genetic make-up of the cell is now known as a provirus, that is, it is retroviral DNA that has been integrated into the human genome (Provirus, n.d.).

The virus now latently infects the host, that is, it remains dormant in the host cell's genome until the cell becomes activated. The latency period of the life cycle of HIV, which varies, allows the virus to replicate and multiply when the genome of the host cell is replicated and multiplied. Once the cell becomes activated, the virus uses the machinery of the cell to produce proteins, which are compiled to make new virons, virus particles. This process is implemented when the viral DNA is transcribed back to two strands of RNA, which are transported out of the nucleus. One strand is called a messenger RNA and the other strand represents the viral genome that is packed into new viral particles. Viral messenger RNAs, like all other messenger RNAs, are composed of regions known as codons that "code" for various proteins. In the case of HIV, the messenger RNA codes for proteins critical to the maturation of the virus: protease, integrase and reverse transcriptase (The Structure and Life Cycle of HIV, 2004). Proteases are enzymes that cleave long strands of proteins, known as polyproteins, to produce functional proteins. Hence, the viral protease cleaves the viral proteins to produce functional products, which assemble at the cell membrane of the host cell (Gelman, 2004). The final stage of the life cycle of the virus results in the budding of the viron out of the host cell. This occurs when functional products attach to the cell membrane to allow the formation of the nucleocaspid. The nucleocaspid then merges with the cell membrane and buds off the cells. Ultimately, the infected host helper T cells die and the body's immune system weakens (Ghandhi et al., 1999).

ANTIRETROVIRAL MEDICATIONS

In 1987, AZT (zidovudine) was the first antiretroviral drug to be approved by the FDA (Bartlett, 2001). The success of the treatment of HIV-positive patients with AZT brought forth hope of the complete eradication of the virus, since it was thought that the half-life of infected CD4 cells was 10-14 days, and therefore treatment using antiretroviral drugs could eliminate the virus in 2-3 years. However, it has been found that the half-life of the infected cells ranges from 6-44 months. This, along with the resistance of the drug, eliminated any hope for the eradication of the virus from the body (HIV and AIDS, 2004). Hence, there is currently no available treatment that will completely eradicate

the HIV virus from the body. However, the treatments available aim to drive the viral load, which is the number of virus present in the bloodstream, below any detectable limit, while increasing the CD4 cell count (USDHHS, 2004).

There are currently 20 approved antiretroviral drugs that belong to three different classes of drugs; that is, they target three different areas of the life cycle of the virus (USDHHS, 2004), as shown in Table 1 (below). These three classes include reverse transcriptase inhibitors (RTIs), protease inhibitors (PIs) and fusion inhibitors (FIs). The reverse transcriptase inhibitors are further subdivided into two groups: nucleoside/nucleotide reverse transcriptase inhibitors and nonnucleoside reverse transcriptase inhibitors. This research paper focuses on the reverse transcriptase inhibitors and the protease inhibitors.

Table 1: Drugs approved for HIV Infection

Nucleoside/ Nucleotide RT Inhibitors	**Non-nucleoside RT Inhibitors**	**Protease Inhibitors**	**Fusion Inhibitors**
abacavir	delavirdine	ritonavir	enfuvirtide
ddC (zalcitabine)	nevirapine	saquinavir	
ddI (didanosine)	efavirenz	indinavir	
d4T (stavudine)		amprenavir	
3TC (lamivudine)		nelfinavir	
ZDV or AZT (zidovudine)		lopinavir	
tenofovir		atazanavir	
		entricitabine	
		fosamprenavir calcium	

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

AZT, the first approved antiretroviral drug, is found in this class of drugs. There are 9 NRTIs available for the treatment of HIV infection (USDHHS, 2004). NRTIs are also referred to as nucleoside analogs or "nukes." NRTIs target the stage of the life cycle when the reverse transcriptase enzyme is converting the viral RNA to double-stranded DNA, which is later integrated into host cell's genome and used to create new viral particles (Bartlett, 2001). NRTIs mimic the nucleotides used by the reverse transcriptase to create the double-stranded viral DNA, that is, they contain faulty versions of the nucleotides. Therefore, when the reverse transcriptase enzyme uses the NRTIs they disrupt the production of the viral DNA and cause early termination of the DNA. Hence, the

HIV's viral DNA is unable to be integrated into the host cell's genome and ultimately reproduce. In addition, nucleoside RTIs, unlike nucleotide RTIs, must first be phosphorylated to their active form before they can be incorporated into the viral DNA (Nucleoside/Nucleotide Reverse Transcriptase Inhibitors, n.d.). However, NRTIs cannot completely stop the reproduction of the virus. Hence, the viruses that continue to reproduce develop resistance to NRTIs due to the production of mutant strains of the virus (Bartlett, 2001).

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

In 1996, NNRTIs or "non-nukes" were the second class of antiretroviral drugs to be approved for treatment (Bartlett, 2001). There are currently three approved NNRTIs available for treatment of HIV infection (USDHHS, 2004). Like NRTIs, NNRTIs target the reverse transcriptase enzyme's function of producing viral double-stranded DNA. NNRTIs attach themselves to the enzyme, preventing it from converting the viral RNA into DNA. Hence, once again the virus is unable to reproduce (Non-Nucleoside Reverse Transcriptase Inhibitors, n.d.). NNRTIs have been proven to be a very potent antiretroviral drug. However, resistance to the drugs occurs very easily if they are not taken as prescribed. In addition, the resistance to one NNRTI confers resistance to the entire class of NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors, n.d.).

Protease Inhibitors (PIs)

In 1996, PIs became the third class of antiretroviral medications to be approved by the FDA (Bartlett, 2001). There are currently 9 available PIs available for the treatment of HIV (USDHHS, 2004). Compared to the NRTIs and NNRTI, PIs inhibitors target a different stage of the life cycle of the virus. PIs inhibit the function of the protease enzyme, which is essential to the maturation of new viral particles (Gelman, 2004). By binding to the protease enzyme, PIs prevent the enzyme from cleaving the viral proteins to produce the functional products that assemble to form the new viral particles (How the Protease Inhibitors Work, 1996). In addition PIs have been proven to be more potent than the nucleoside/nucleotide reverse transcriptase inhibitors (Bartlett, 2001).

A COMPARISON OF TREATMENTS

The current guidelines for the commencement of antiretroviral treatment indicate that treatment is imperative for individuals with a CD4 cell count below 200. However, treatment is only recommended for a CD4 cell count above 200 if the viral load is above 55,000 (USDHHS, 2004).

Comparative studies have been conducted in order to investigate the most effective HIV antiretroviral drug in terms of virological efficacy and tolerability. The results have shown that monotherapy and dual therapies, that is, therapies that involve the use of one or two antiretroviral drugs, are not as effective as therapies that involve the use of combination therapies, which target different stages of the life cycle of the virus (USDHHS, 2004). In addition, when considering the superiority of one class of drug to another, considerations should be given to possible side effects, risk of interactions, possible resistance and dosage of the drug (Bartlett, 2001).

Side Effects

Every drug has its pluses and minuses, and will therefore have its side effects. The side effects can be as mild as nausea or as fatal as liver disease. The side effects or adverse drug reactions can be divided into two categories: toxic or allergic. The toxic side effects are caused by the drug itself and are dose dependent. They may result in drowsiness, kidney damage, liver damage or anemia, etc. (Bartlett, 2001). However, allergic reactions are caused by the immune system's response to a foreign substance in the body and are not dose related. They may result in a high fever or rashes or both (Bartlett, 2001). In general, antiretroviral drugs can cause stomach problems, which include nausea, vomiting, abdominal pain, or diarrhea; lactic acidosis; lipodystrophy; and other side effects that are particular to each drug (Bartlett, 2001). Furthermore, of the 50% of HIV patients whose treatments fail, it is estimated that 70-80% of that group has failed because of the harsh side effects that were associated with the drugs (Elion & Boyle, 2002).

The long-term side effects of NRTIs are usually associated with the damage the drugs cause to the mitochondrion (organelles that provides the cell with energy) of the cells (Bartlett, 2001). This damage results in the build up of lactic acid, which consequently results in the destruction of red and white blood cells, muscle pain, wasting away of the limbs, fatigue and peripheral neuropathy (numbness). More serious side effects include destruction of the cells of the liver (lactic acidosis)

and pancreas. In addition, when used in combination with PIs, NRTIs cause the loss and redistribution of fat, that is, lipodystrophy (Elion & Boyle, 2002). Furthermore, life threatening reactions are associcated with all NRTIs, whether it be from the allergic reactions associated with Abacavir or the fatal pancreatitis associated with Didanosone.

The long-term side effects of PIs include elevation of blood sugar level with development (or worsening) of diabetes, elevation of body fat (triglycerides) and cholesterol and lipodystrophy (Vernochet et al., 2004). In addition, less common side effects caused by PIs include liver toxicity and bone damage. However, six out of nine PIs have not been labeled with any pertinent "black box warning" (any special warning of problems that may be associated with the use of the drug) by the FDA (USDHHS, 2004). The side effects of PIs are usually associated with its interaction with other drugs.

The long-term side effects of NNRTIs appear to be milder than those of NRTIs or PIs; including stomach problems, headaches, rashes, dizziness and drowsiness. However, fatal hepatoxicity (liver damage) is associated with the use of Nevirapine. Furthermore, two out of the three NNRTIs available for the treatment of HIV are not associated with any "black box warning" (USDHHS, 2004).

Drug Interactions

When choosing an antiretroviral drug considerations should be given to other drugs that are being used by the HIV-positive patient. Drug interactions can be broadly classified according to those that affect the pharmacokinetic or pharmacodynamic properties of other drugs (Faragon & Piliero, 2004). The pharmacokinetic drug interactions alter such properties as the concentration and half-life of the drug, while pharmacodynamic interactions alter pharmacological activities of the drug without causing changes in the concentration or other pharmacokinetic properties (Faragon & Piliero, 2004). Most drug interactions that occur with HIV medications are those that result in the change of pharmacokinetic properties of the drugs due to the changes in the rate of absorption, distribution, metabolism or elimination of the drugs (Faragon & Piliero, 2004). It has been documented that the most drug interactions are associated with NNRTIs and PIs, since they are metabolized in the same pathway as many other drugs (Margolese, 2003). NNRTIs and PIs are metabolized in the liver by the CYP3A4 isoenzyme in the cytochrome P450 (CYP450) system (USDHHS, 2004). Examples of other drugs that are used for non-HIV treatment but are metabolized in the same pathway include drugs such as lipid-lowering

agents, calcium channel blockers, immunosuppressants, anticonvulsants, erectile dysfunction drugs, antifungal drugs, oral contraceptives, and methadone (USDHHS, 2004). In addition, herbal medications such as St. John's Wort should be avoided with any antiretroviral medication, especially PIs (Andrade et al., 2001).

Unlike NNRTIs and PIs, NRTIs are not metabolized in the cytochrome P450 (CYP450) system. Hence, NRTIs are only associated with minimal drug interactions (Faragon & Piliero, 2004). Drug interactions that do occur with NRTIs are usually pharmacodynamic in nature. Examples include the co-administration of the NRTIs zidovudine and stavudine, which are both thymidine (a nucleotide involved in the making of the double-stranded DNA from the viral RNA) analogs competing for the same site on the growing double-stranded viral DNA (USDHHS, 2004). Some pharmacokinetic interactions that are associated with the use of NRTIs are mainly reported as an increase in Didanosine concentration when co-administered with Tenofovir, which also causes a decrease in the PI Atazanavir.

However, the combination of NNRTIs and PIs with other drugs that are metabolized by the CYP3A4 enzyme results in drug interactions. For example, Nevirapine and Efavirenz are inducers of the CYP3A4 enzyme, while Delavirdine is an inhibitor. Hence, the use of Nevirapine and Efavirenz results in the reduced concentration of drugs that are metabolized in the same pathway, while Delavirdine causes an increase in drug level and drug toxicity (Faragon & Piliero, 2004).

Like NNRTIs, PIs have many complex drug interactions. However, all PIs are potent inhibitors of the CYP3A4 enzyme and cause an increase in the concentration of other medications co-administered with them (USDHHS, 2004). Hence, PIs increase the adverse drug reactions that are experienced by antiretroviral medications and other medications that have side effects. Therefore, numerous medications must be avoided when taking PIs. In addition, Ritonavir is the most potent inhibitor of the CYP3A4 enzyme, and also an inhibitor of the CYP2D6 enzyme and an inducer of the CYP1A2 and CYP2C9 enzymes, which are other enzymes found in the CYP450 system, as shown in Table 3 (Faragon & Piliero, 2004). An advantage of this property of Ritonavir is its co-administration with other PIs metabolized by CYP3A4 enzyme, in order to 'boost' their concentration (Chrisman, 2003).

CONCLUSION

Comparative studies have shown that monotherapy is not an effective treatment for the HIV infection (USDHHS, 2004). As

summarized in Table 2 (below), no one drug alone, whether it be a reverse transcriptase inhibitor or a protease inhibitor could effectively treat the virus. This is due to the resistance that mutated forms of the virus confer to any medication when used independently. Research has shown that the best therapy for HIV is a combination of at least three drugs (Bartlett, 2001). This combination, referred to as the Highly Active Antiretroviral Therapy or 'HAART,' was later changed to Potent Antiretroviral Therapy upon the addition of the protease inhibitors in 1995 (USDHHS, 2004). However, the combination is still commonly recognized as HAART.

Table 2: A summary of the class comparison of PIs, NRTIs and NNRTIs

Class	Class Advantage	Class Disadvantage
PI	Save NNRTI for future use Longest prospective study data including data on survival benefit	Metabolic complications - fat maldistribution, dyslipidemia, insulin resistance CYP3A4 inhibitors & substrates - potential for drug interactions (more pronounced
NRTI	Established backbone of combination antiretroviral therapy	Rare but serious cases of lactic acidosis with hepatic steatosis reported with most NRTIs
NNRTI	Less fat maldistribution and dyslipidemia than PI-based regimens Save PI options for future use	Low genetic barrier to resistance (single mutation confers resistance) Cross-resistance among NNRTIs Skin rash Potential for CYP450 drug interactions

(Source: Adapted from USDHHS, 2004)

Clinical trials have devised regimens that have proven to be successful in the treatment of the virus. Today there are three different

combinations that are recommended to "treatment-naïve" patients (individuals who have never taken antiretroviral medications), which are based on the following combinations: triple NRTI-based, NNRTI-based (1 NNRTI + 2 NRTIs) and PI-based (1 or 2 PI + 2 NRTIs) regimens (USDHHS, 2004).

The triple NRTI regimens have shown many advantages that reduce the risks of adverse drug reactions, since they have fewer drug-drug interactions and a low pill burden due to the availability of a fixed dose combination drug, Trizivir (zidovudine + lamivudine + abacavir). However, triple NRTI regimens have been proven to be less potent than NNRTI-based and PI-based regimens, and to eventually become ineffective (USDHHS, 2004).

Like the triple NRTI regimens, NNRTI-based regimens also have the advantage of low pill burden. In addition, NNRTI-based regimens have the advantage of fewer adverse drug reactions than those that contain NRTI or PI, which would allow HIV-positive patients to adhere to their regimen (Project Inform, 2001). However, only a single mutation in the virus is needed to confer resistance to a NNRTI drug, which causes cross-resistance to the other two NNRTIs (USDHHS, 2004).

The introduction of the protease inhibitor to the HIV regimen dramatically enhances the treatment of the virus and allows increased patient survival (Martinez, 2000). Protease inhibitors allowed the prolonged suppression of the virus and consequently the increase in the CD4 cell count (USDHHS, 2004). In addition, the use of ritonavir to boost the concentration of other PIs allows a lower pill burden and lower drug toxicity. However, PIs are associated with side effects that sometimes outweigh their great advantages, since patients are unable to adhere to their regimens. Hence, even though PIs are successful in treating the virus, many factors have to be taken into consideration when PI-based regimens are selected due to their potential drug interactions, toxicity and metabolic abnormalities (USDHHS, 2004).

The treatment of HIV will continue to be a life-long process, since no drug has been developed that can completely eradicate the virus from the body. In addition, no one drug can effectively treat the virus due to the development of mutations. Furthermore, no one form of drug can be shown to be superior to the others, since many factors have to be considered when evaluating the efficacy of the drug. Hence, even though protease inhibitors have been shown to allow prolonged suppression of the virus, they are associated with too many fatal complications to be labeled as being superior to NRTIs and NNRTIs.

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