Background

Acquired immunodeficiency syndrome, or AIDS, was first recognized as a disease in 1981 and is associated with a depletion of T lymphocytes. It is caused by the human immunodeficiency virus, or HIV. Since the early 1980s governments and private corporations from around the world have spent hundreds of millions of dollars on HIV research. More biologists are working on HIV than on any other type of virus.

HIV basically parasitizes certain cells that are absolutely critical to the immune system, and it kills people indirectly by making them susceptible to pneumonia, fungal infections, and unusual types of cancer.

It is presently estimated that 33.2 million people will be living with HIV at the end of 2007 - 2.5 million are children under the age of 15.

New HIV infections in 2007 were estimated to be around 2.5 million. Deaths due to AIDS in 2007 were estimated to be around 2.1 million.

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Of the 7.1 million people in developing and transitional countries who need life-saving AIDS drugs, only 28% are receiving them.

In southern Africa, the adult infection rates are higher than 30%.

South Africa alone has close to 5 million people infected, and it is estimated that 7 million people will die of AIDS-related causes by 2010 if nothing is done.

By 2020, over 25% of the work force may be lost to AIDS in some severely affected regions. It is estimated that 21% of teachers in South Africa are living with HIV.

Heterosexual transmission accounts for a growing share of new AIDS cases, rising from 3% in 1985 to 31% in 2005.

Estimated number of deaths in the US through 2005 - 550,394.

Estimated number of diagnoses of AIDS in the US through 2004 - 944,305.

Women account for ~50% of all adults living with HIV worldwide.

Basic Biology of HIV

HIV is a retrovirus which means it stores its genetic information in the form of RNA rather than DNA.

It uses the enzyme reverse transcriptase to ultimately convert its RNA into double-stranded DNA.

This DNA can be incorporated into the infected cell's DNA via the action of another enzyme called integrase.

There is a third enzyme that is absolutely required for the life cycle of the virus, namely the HIV protease. Its role is to cleave viral polyproteins into functional products that are essential for viral assembly and maturation.

Life Cycle of the Virus

HIV-1 Protease: A Paradigm for Structure-Based Drug Design

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What Factors Constitute a Good Drug?

By knowing the three-dimensional structure of the HIV protease, it is possible to design compounds to fit into its so-called active site and to stop it from working. When the protease is inactivated, viral assembly can no longer occur.

In structure-based drug design, the x-ray structure of a protein with a bound drug is used to guide the design of new drug molecules. Structure-based drug design can shave off years and millions of dollars from the traditional trial-and-error drug development processes.

The HIV protease was identified as a drug target in 1988. Strikingly, it took less than eight years to get the first such drug to market, while traditional trial-and-error drug development processes can take decades and billions of dollars.

Why Solve the X-ray Structure of the HIV Protease?

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HIV protease was first determined by x-ray crystallography in 1989, and since then it has been estimated that more than 250 structures of it complexed with various inhibitors have been solved. Because of its critical role in viral development, scientists have used its structure as a starting point for drug design. Thus far eleven different "protease inhibitors" have been approved by the Food and Drug Administration (FDA). For our project, we chose the structure of the HIV-1 protease complexed with Tipranavir (Aptivus®), a nonpeptidic protease inhibitor. Typically it takes ~15 years to develop an effective and FDA-approved drug from scratch. Strikingly, in the case of the HIV protease inhibitors, it required less than eight years to develop three such drugs. Indeed, the x-ray crystallographic study of the HIV protease represents perhaps the best paradigm for structure-based drug design. This is especially important given that the virus, which causes AIDS, rapidly mutates and many strains of the virus are becoming drug resistant. There is thus a continual need for the development of new therapeutics.

Summary

In conclusion, the HIV protease is absolutely required for the life cycle of the virus. It cleaves viral polyproteins into products that are required for viral assembly. The three-dimensional structure of the HIV protease was first determined by x-ray crystallography in 1989, and since then it has been estimated that more than 250 structures of it complexed with various inhibitors have been solved. Because of its critical role in viral development, scientists have used its structure as a starting point for drug design. Thus far eleven different "protease inhibitors" have been approved by the Food and Drug Administration (FDA). For our project, we chose the structure of the HIV-1 protease complexed with Tipranavir (Aptivus®), a nonpeptidic protease inhibitor. Typically it takes ~15 years to develop an effective and FDA-approved drug from scratch. Strikingly, in the case of the HIV protease inhibitors, it required less than eight years to develop three such drugs. Indeed, the x-ray crystallographic study of the HIV protease represents perhaps the best paradigm for structure-based drug design. This is especially important given that the virus, which causes AIDS, rapidly mutates and many strains of the virus are becoming drug resistant. There is thus a continual need for the development of new therapeutics.

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