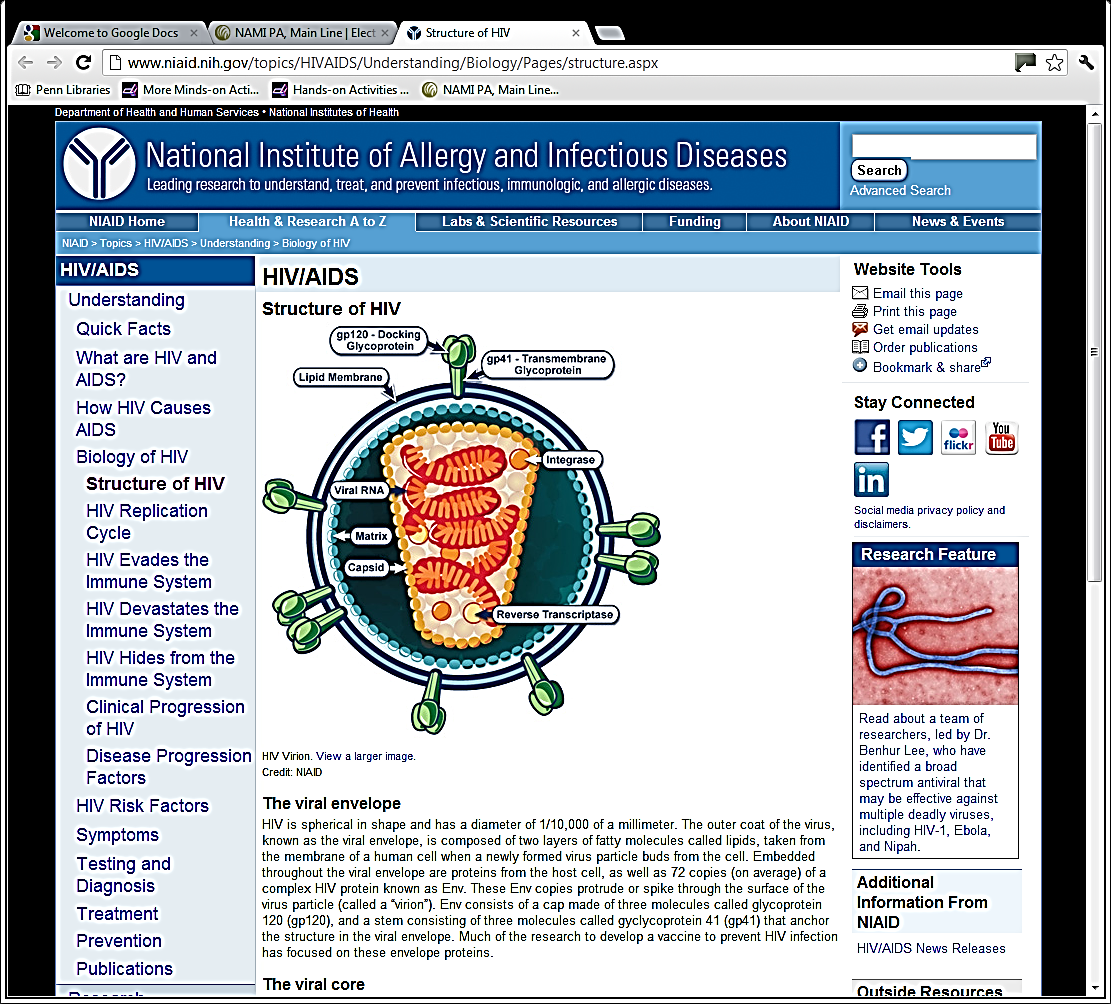
**Using Molecular and Evolutionary Biology to Understand HIV/AIDS and Treatment**[[1]](#footnote-1)

**HIV, the Human Immunodeficiency Virus**

* HIV infects and kills human immune cells. An untreated HIV infection eventually kills so many immune cells that the immune system can't fight off other infections, so the HIV-infected person becomes very vulnerable to all sorts of infections such as tuberculosis and pneumonia.
* HIV is a relatively complex virus which contains:
* RNA (which carries the genetic information that codes for the proteins in HIV viruses)
* a few specialized viral enzymes
* surrounded by:
* protein layers (organized in the capsid and matrix)
* an outer envelope (a lipid membrane similar to the cell membrane, but with viral glycoproteins).



(Figure from HIV/AIDS, available at <http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Biology/Pages/structure.aspx>)

1. In the diagram, use arrows to indicate the names of the enzymes in the HIV virus. For both of these enzymes, what part of the enzyme name lets you know that these are enzymes?

2. Why is HIV a good name for this virus?

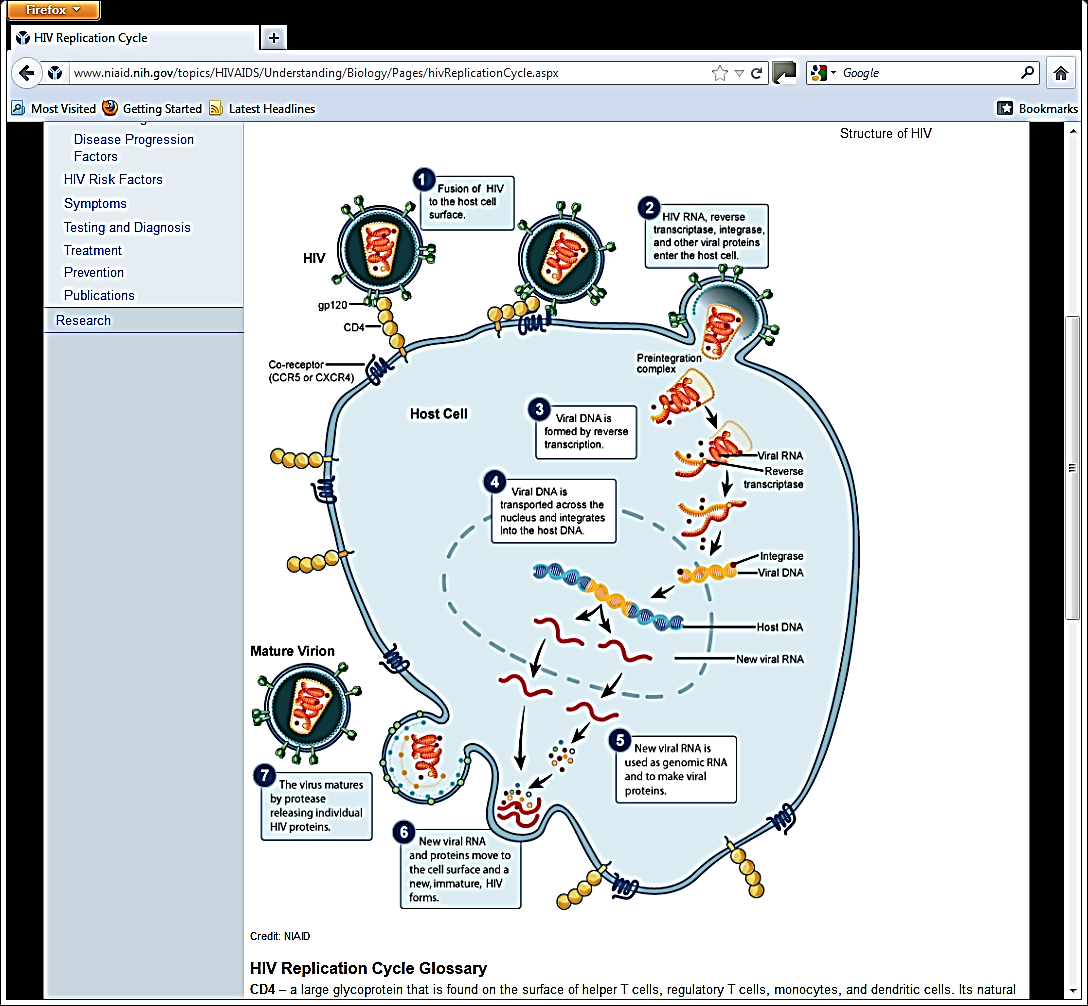
**The HIV Life Cycle**

Like all viruses, HIV can only reproduce inside a cell. HIV genetic material and enzymes enter a cell and use the cell’s molecules and organelles to produce new virus particles. To learn about the steps in this process *read*:

- "The HIV Life Cycle", available at <http://www.aidsinfo.nih.gov/ContentFiles/HIVLifeCycle_FS_en.pdf>

HIV Life Cycle: How HIV Uses an Immune Cell to Make More HIV Viruses

(Although this diagram shows the production of a single virus, an actual HIV-infected cell produces many thousands of HIV viruses.)



(Figure from HIV Replication Cycle, available at <http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Biology/Pages/hivReplicationCycle.aspx>)

3. In this diagram of the HIV life cycle:

* Use an arrow to indicate the step that requires the viral envelope glycoprotein gp120.
* Label the arrows that indicate transcription and the arrow that indicates translation.
* Label the mRNA produced by transcription.
* Write ribosomes next to the step that requires host cell ribosomes.
* Use asterisks to indicate the three types of HIV enzymes.

4. Complete the following table to explain why each of the molecules listed and the organelle is needed for an HIV virus to replicate.

|  |  |
| --- | --- |
| **Molecule or Organelle** | **Why is this needed for HIV replication?** |
| Reverse transcriptase |  |
| Nucleotides |  |
| Integrase |  |
| RNA polymerase |  |
| Ribosomes |  |
| Amino acids |  |
| Protease |  |

5. Mark with a V the molecules listed above that are part of the HIV virus.

Mark with a T the molecules and organelle that are provided by the Helper T cell.

6. Reverse transcriptase has a relatively high error rate, so almost every molecule of viral DNA produced by reverse transcriptase has at least one mutation. Many of these mutations are harmful and result in the production of HIV viruses that are unable to reproduce. Explain how a mutation in the gene that codes for the gp120 glycoprotein could result in the production of HIV viruses that would be unable to reproduce.

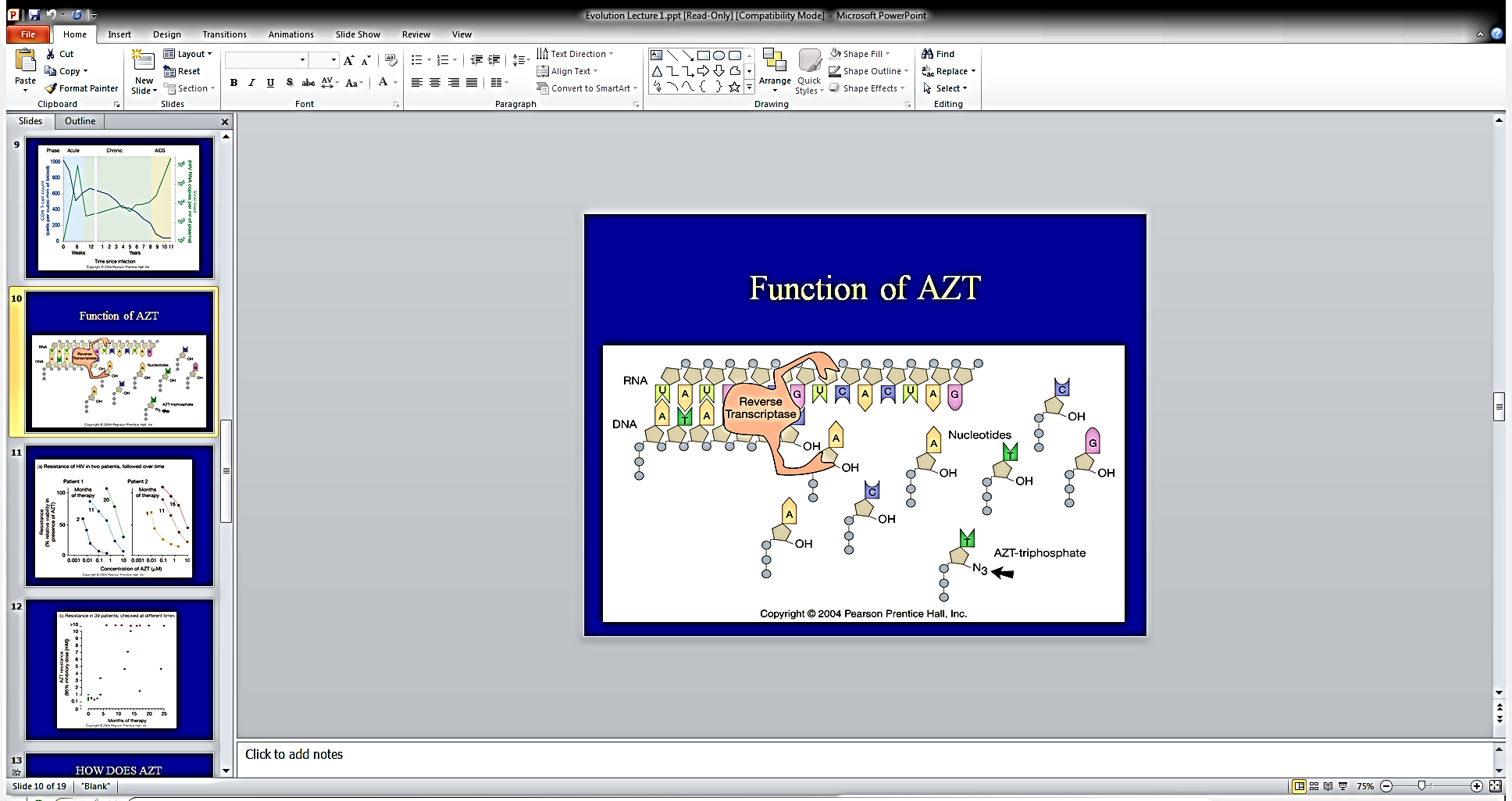
**How HIV Causes AIDS (Acquired Immunodeficiency Syndrome)**

* HIV infects Helper T cells and reproduces inside these cells. Helper T cells are immune cells that stimulate other types of immune cells to fight infections. Helper T cells are killed by HIV infection; e.g., when many viruses bud out from an infected Helper T cell, this damages the cell membrane which kills the Helper T cell.
* For a while, the body is able to replace many of the Helper T cells that are killed by HIV infection. However, if the HIV infection is not treated effectively, the body eventually is unable to produce enough Helper T cells, so levels of Helper T cells decrease and the immune system cannot fight infections effectively.
  + At this point, the HIV-infected person has AIDS = Acquired Immunodeficiency Syndrome, which includes very high vulnerability to infectious diseases, increased risk of cancers caused by viral infections (e.g. cervical cancer), and symptoms such as weight loss and fatigue.

**Treatment** **of HIV Infections**

Early Success

The medication, AZT, was developed to treat HIV infection. AZT works by blocking the enzyme reverse transcriptase, so the HIV virus can't replicate. An AZT molecule is very similar to the normal T nucleotide, so AZT can fit in the active site of reverse transcriptase and be added to the growing DNA strand in place of a T nucleotide. However, unlike the normal nucleotides, AZT has no place to attach the next nucleotide in the growing DNA strand, so the reverse transcriptase enzyme becomes stuck and is inactivated.



(figure from Evolutionary Analysis, Fourth Edition by Freeman and Herron, 2007)

Problem

AZT treatment was very effective initially, but, in almost every patient, AZT lost its effectiveness within a year or two. The population of HIV viruses in each treated person evolved resistance to AZT due to:

* mutations in the HIV gene that coded for the reverse transcriptase molecule
* natural selection that favored HIV viruses that had a mutation that increased resistance to AZT (e.g. a mutation that changed the active site of reverse transcriptase so AZT no longer fit in the active site).

Evolution of resistance to AZT (or other medications against HIV) is rapid due to:

* the high rate of mutation (due to the high rate of errors by reverse transcriptase)
* rapid production of lots of new HIV viruses (so there is lots of opportunity for natural selection).

More Recent Successes

Researchers developed multiple different types of medications to combat HIV infection. To learn about these medications, *read* "HIV Drugs and the HIV Life Cycle", available at <http://www.thewellproject.org/en_US/Treatment_and_Trials/Anti_HIV_Meds/Lifecycle_and_ARVs.jsp>

The other crucial advance was the strategy of treating each patient with a combination of several medications that are effective against at least two different viral molecular targets. These drug combinations are known as a drug cocktail or HAART = Highly Active Antiretroviral Therapy. (Medications to fight HIV are called antiretroviral medications because HIV is a retrovirus, i.e. An RNA virus that uses reverse transcriptase to produce viral DNA that is incorporated into the host cell's DNA.)

HAART has dramatically improved long-term success in treating HIV because HAART reduces the evolution of resistance to medications for two reasons:

* + The combination of several antiretroviral medications very much reduces the number of HIV viruses produced, resulting in fewer mutations and less chance for a resistance mutation to occur.
  + Even if a resistance mutation for one of the medications does occur, this mutated HIV virus is usually prevented from reproducing by the other medications in the drug cocktail.

Still Some Problems

Problems with HAART include:

* + Many people experience side effects (including common, uncomfortable side effects, as well as more serious harmful effects on health).
  + Even with effective treatment, HIV persists in some cells in the body, so treatment with HAART must be continued indefinitely. (Treatment prevents HIV replication but does not eliminate HIV DNA from the body's cells and, if the HIV DNA in a cell is inactive, the body's immune cells cannot detect and eliminate it.)
  + Patients often need to change one or more of the medications due to side effects and/or the development of resistance to a medication. (Resistance can develop despite the use of HAART.) Eventually, a patient can run out of effective medications to use.

7. Explain how AZT can delay the development of AIDS in an HIV-infected person.

8. Suppose that an HIV-infected person has one Helper T cell that contains mutated viral DNA that codes for reverse transcriptase molecules that are resistant to AZT. This Helper T cell produces many thousands of AZT-resistant viruses. Meanwhile, the other HIV-infected Helper T cells produce many millions of AZT-sensitive viruses. Thus, the HIV population in this person has thousands of AZT-resistant HIV viruses and millions of AZT-sensitive HIV viruses. Complete the following table to predict what will happen to this population of HIV viruses, depending on the type of treatment.

|  |  |
| --- | --- |
| Treatment | Would you expect AZT-resistant viruses to become common in the population?  Explain why or why not. |
| No treatment |  |
| AZT only |  |
| AZT + an integrase  inhibitor and a  protease inhibitor |  |

Explain why giving several antiretroviral medications simultaneously (HAART) has been so much more successful in preserving the health of HIV-infected individuals, compared to giving several antiretroviral medications sequentially (i.e. first one medication and then another and then another).

9. An ideal medication to treat a viral infection should block the action of a molecule that is needed by the virus, but is not needed by human cells (thus minimizing the risk of harming human cells and producing harmful side effects). Explain how the medications that are used to treat HIV illustrate the principle that an ideal medication should block the action of molecules needed by the HIV virus but not needed by human cells.

10. Explain why scientists needed to understand both the molecular biology of HIV and the process of natural selection in order to develop effective treatments for HIV.

11. A population of HIV viruses exposed to any single antiretroviral medication typically evolves resistance to this medication within a year or two. In contrast, populations of humans exposed to HIV for many years have not yet evolved significant resistance to HIV infection. Why has evolution been so much more rapid in HIV populations than in human populations?

12. A person is newly diagnosed with HIV infection and has never been treated with any antiretroviral medication. However, laboratory tests show that this person is infected with a strain of HIV that is resistant to AZT. How could this happen?

1. By Dr. Ingrid Waldron, University of Pennsylvania, © 2012. Teachers are encouraged to copy this Student Handout for classroom use. A Word file (which can be used to prepare a modified version if desired) and Teacher Notes, and comments are available at <http://serendipstudio.org/exchange/bioactivities> . [↑](#footnote-ref-1)