How Do Antiretroviral Drugs Work?
Overview for Teachers

Purpose
The purpose of this activity is engage students in studying the HIV viral infection pathway in a human cell. Students will learn about the HIV life cycle and in small groups discuss and propose methods to prevent the spread of the infection.

Objectives
1. Students will understand how the HIV viral pathway may be interrupted to prevent the spread of the virus in an individual
2. Students will analyze the HIV viral pathway and identify stages where drugs can be used for treatment
3. Students will understand the difficulty of developing a vaccine for HIV/AIDS

Suggested Time
60 minutes

Grade Level
This activity is geared towards a high school science grade level; it is ideal for a biology or physiology class.

Prior Knowledge
Students should have an understanding of cell structure, protein synthesis, the role of enzymes in living organisms, and molecular evolution.

Topics for Follow-up Lessons
Possible follow-up topics to teach include enzyme structure, the role of various enzyme inhibitors, drugs as antagonistic inhibitors, more studies of evolution, and vaccine and drug development.

Procedure Part 1: HIV Immunity

2. While students watch the video, they will complete viewing questions on the accompanying activity sheet.
Part 2: Mystery of the Black Death

1. Students will read the article Mystery of the Black Death: Clues and Evidence on the PBS Nova Website and respond to the accompanying questions on the activity sheet.

2. Follow these questions with a class discussion reviewing the answers. Use the article questions to lead into the discussion about the group activity in Part 3.

3. The last question about the article should be used to highlight how scientists used the scientific process (hypothesis, experimental process, etc.) to test and study the effectiveness of the drugs and the infection pathways they inhibit.

Part 3: Studying the Life Cycle of HIV

1. Students will examine the HIV infection pathway based on their understanding of protein synthesis and molecular evolution. Using “The HIV Life Cycle” worksheet, they will determine at least three different target points in the pathway where medication could be developed to stop the progression of the disease in the human body and defend its effectiveness.

2. Follow this portion of the activity with a class discussion about the suggested medicinal targets they determined in the infection pathway. It may be useful to refer to an annotate life cycle worksheet with information about drug therapy.
http://aidsinfo.nih.gov/education-materials/fact-sheets/19/73/the-hiv-life-cycle

Part 4: How do Antiretroviral Drugs Work?


2. After viewing the video, students will return to their groups and discuss how their conclusions about effective targets for antiretroviral drugs differ from those that currently exist. They will then complete the questions about the video.

3. Once students have completed the questions, discuss their answers as a class. Be sure to emphasize the importance of scientific method in the process of drug testing and determination of effective drug targets to inhibit spread of disease. It is also important to highlight the concept of microbial evolution and how it is affecting the discovery of a vaccine for HIV.

Follow-up Questions for Classroom Discussion:
These questions suggest ways to expand on the topics discussed in the activity with your students. They focus on making connections between HIV/AIDS and other related topics.

1. Vaccines play an important role in limiting the spread of disease among populations and even in completely eradicating some diseases, like smallpox. How do vaccines control the spread of diseases in populations?

2. Through this activity, students have discovered that a change in the CCR-5 receptor on the cell’s surface can lead to the inability of HIV to infect a human cell. What are some of the variations caused in an HIV-infected cell’s life cycle from that of a typical cell based on this change in form?

3. How do therapeutic drugs work differently from vaccines?

4. Some communities in the world have easier access to therapeutic drugs and vaccines than others. How does access to appropriate preventative treatments for diseases affect the spread of diseases regionally and globally?

5. Vaccines work by stimulating the immune system to fight off disease. How does a vaccine create an artificial immunity to a specific disease in an individual?

6. Taxonomically, bacteria are very old and simple living organisms compared to human beings and most other living organisms. Does complexity of structure in living organisms necessarily mean they are better adapted for survival?

**ANSWER KEY**

*HIV/AIDS is not curable with the drugs currently available. Why is this the case?*

HIV is a retrovirus. Retroviruses are a group of viruses that cause AIDS and some types of cancer. They carry their genetic information in the form of RNA and then copy it into DNA to be integrated into the cell’s nucleus. Unfortunately, there is no cure for HIV at this time. There are only ways to control HIV and attempts to keep it from progressing into AIDS. In this activity, you will learn what challenges exist to develop drugs to cure HIV.

Part of your assignment will be to discover – the same way scientists do – how to treat HIV/AIDS. You will present your findings to the class through diagrams and descriptions and compare your deductions to those of actual scientists today.

**Part 1: HIV Immunity**

1. What is the benefit of studying the extreme situations in a viral infection?

By studying the extreme situations we can learn about how these cells differ from normal cells and can find ways to alter normal cells to eventually cure the disease.

2. How does HIV infect a cell?

HIV requires two receptors on the surface of the cell in order to bind. These are the CD4 and the CCR5 receptors. Once HIV binds to these receptors, it fuses with the cell’s membrane and can enter the cell through endocytosis.

3. What are some possible ways people can be resistant to HIV?

People can lack one of the CCR5 receptors on the surface of the cell. Scientists also speculate there could be a genetic immunity.

4. Why is it useful to learn about how people can become immune to HIV?

The hope is that this knowledge can help in developing a vaccine against AIDS.

Part 2: Mystery of the Black Death


1. How is studying a virus different from studying a bacteria?

Viruses require a host cell to survive and reproduce, therefore there must be some sort of host organism for them to invade and grow. Bacteria are self-contained and reproduce on their own as long as they have sufficient media to grow and survive.

2. What evidence is there that a relationship exists between individuals with ancestors who survived the plague and those resistant to HIV?

Both seem to have mutated CCR5 receptors (delta 32) on the surfaces of their cells, which prevent the invading organisms from being able to bind and invade.

3. What is a type of drug mentioned in the article that is used to inhibit HIV from affecting a cell? How does it work?

Fusion-Inhibitor drugs inhibit HIV from entering the cell by preventing the virus from binding to the cell.
**Parts 3: Studying the Life Cycle of HIV**

Looking at “The HIV Life Cycle” document, identify at least three more stages in the lifecycle, in addition to the one identified in the article. Propose a drug that can be developed to prevent HIV at each of the three stages. Develop a hypothesis about how this drug would work and discuss how you could test your hypothesis. Think about what you would look for to indicate that the drug was effective in blocking HIV at a particular stage.

Draw and explain your group’s response below. You will share your findings with the class, so be sure to explain in a clear and well-supported manner.

Students should be able to identify drugs that stop the progression of HIV by inhibiting the effectiveness of HIV enzymes.

These stages are:

1. Stopping reverse transcriptase from being able to transcribe a DNA molecule from the virus’ RNA
2. Stopping integrase from being able to integrate the transcribed DNA into the cell’s own DNA
3. Protease-inhibitors that prevent the enzymes to be cleaved from the newly translated protein chain

**Part 4: How do Antiretroviral Drugs Work?**

Watch the *How do Antiretroviral Drugs Work* video from the Koshland Science Museum’s *Infectious Disease* exhibit. In your group compare your findings about how antiretroviral drugs can interrupt the life cycle of HIV to the information from the video, then respond to the questions below.

1. How do your findings compare to those of scientists? How close were you in identifying stages in the infection pathway targeted by current drugs?

   These answers will vary depending on how close students were to the drugs discussed above.

2. Currently, what is the standard way to treat an HIV infection with medicine? Why is this the case?
The best method to treat HIV currently is to give infected individuals a cocktail of drugs that prevents HIV from spreading in their bodies at different stages of the process. This is important because of the high mutation rate of the virus; if the virus evolves resistance to one drug it will be stopped by another.

3. You have seen how people develop a natural immunity to certain infectious diseases through vaccines. Why don’t we have a vaccine for HIV? *Think about why HIV is effective at spreading so quickly throughout the body.*

This is due to the high mutation rate of HIV. Because HIV mutates so frequently, every HIV virus in an infected individual is potentially different. Vaccines are only effective against certain strains of a virus, and so developing one for HIV where an individual may have tens of thousands of different strains in his/her body proves extremely difficult. Currently, antiretroviral therapy is the best and only way, aside from attempts to control the spread through prevention, to treat HIV/AIDS.

This activity addresses the following Next Generation Science Standards and Common Core State Standards for high school.

**Next Generation Science Standards Standards**
- [ ] **HS-LS1 From Molecules to Organisms: Structures and Processes**: HS-LS1-1, HS-LS1-2, HSLS1-3
- [ ] **HS-LS4 Biological Evolution: Unity and Diversity**: HS-LS4-4

**Science and Engineering Practices**
- Developing and using models
- Planning and carrying out investigations
- Constructing explanations (for science) and designing solutions (for engineering)

**Crosscutting Concepts**
- Cause and effect: Mechanism and explanation.
- Systems and system models.
- Structure and function.
- Stability and change.
Common Core State Standards ELA/Literacy

- **Literacy in Science and Technical Subjects (Grades 11 and 12):** RST.11-12.1,
- **Writing (History/Social Studies, Science, and Technical Subjects):** WHST.9-12.2, WHST.9-12.7, WHST.9-12.8, WHST.9-12.9
- **Speaking and Listening (Grades 11 and 12):** SL.11-12.5

Mathematics

- **Standards for Mathematical Practice:** MP.2, MP.4
- **Functions – Interpreting Functions:** HSF-IF.C.7
- **Functions – Building Functions:** HSF-BF.A.1
The HIV Life Cycle

1. **Binding and Fusion:** HIV begins its life cycle when it binds to a **CD4 receptor** and one of two **co-receptors** on the surface of a CD4+ **T-lymphocyte**. The virus then fuses with the host cell. After fusion, the virus releases RNA, its genetic material, into the host cell.

2. **Reverse Transcription:** An HIV enzyme called reverse transcriptase converts the single-stranded HIV RNA to double-stranded HIV DNA.

3. **Integration:** The newly formed HIV DNA enters the host cell's nucleus, where an HIV enzyme called integrase "hides" the HIV DNA within the host cell's own DNA. The integrated HIV DNA is called provirus. The provirus may remain inactive for several years, producing few or no new copies of HIV.

4. **Transcription:** When the host cell receives a signal to become active, the provirus uses a host enzyme called RNA polymerase to create copies of the HIV genomic material, as well as shorter strands of RNA called messenger RNA (mRNA). The mRNA is used as a blueprint to make long chains of HIV proteins.

5. **Assembly:** An HIV enzyme called protease cuts the long chains of HIV proteins into smaller individual proteins. As the smaller HIV proteins come together with copies of HIV's RNA genetic material, a new virus particle is assembled.

6. **Budding:** The newly assembled virus pushes out ("buds") from the host cell. During budding, the new virus steals part of the cell's outer envelope. This envelope, which acts as a covering, is studded with protein/sugar combinations called HIV glycoproteins. These HIV glycoproteins are necessary for the virus to bind CD4 and co-receptors. The new copies of HIV can now move on to infect other cells.

**Terms Used in This Fact Sheet:**

- **CD4 receptor:** A protein present on the outside of infection-fighting white blood cells. CD4 receptors allow HIV to bind to and enter cells.
- **Co-receptor:** In addition to binding a CD4 receptor, HIV must also bind either a CCR5 or CXCR4 co-receptor protein to get into a cell.
- **T-lymphocyte:** A type of white blood cell that detects and fights foreign invaders of the body.

**For more information:**
Contact your doctor or an AIDSinfo Health Information Specialist at 1-800-448-0440 or [http://aidsinfo.nih.gov](http://aidsinfo.nih.gov).

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