

A detailed illustration of an HIV virus particle, showing its characteristic spherical shape with a textured outer envelope and a complex internal structure. The virus is positioned on the right side of the blue header bar.

HIV Vaccine Research

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<http://www.nwabr.org/education/hivrequest.html>



The Science and Ethics of HIV Vaccine Research

Overview

This unit explores the scientific and ethical issues involved in clinical HIV vaccine trials using human research participants. The unit begins by examining students' current knowledge of HIV, and by reviewing HIV structure and transmission. Next, it familiarizes students with types of vaccines and with challenges related to creating an HIV vaccine. Students are encouraged to explore issues related to human research participants using basic ethical principles and historical case studies. Lastly, global issues regarding the pandemic are explored to give the students an understanding of cultural issues involved in the spread of HIV. This cultural context introduces students to ethical dilemmas inherent in the selection of human participants in global vaccine trials. The lessons culminate in having students design their own hypothetical HIV vaccine clinical trial, based upon knowledge of HIV structure, vaccine characteristics, human research participants considerations, and global contexts.

Instructional Components

Length:

5 Lessons and a culminating assessment, spanning approximately 2 weeks, depending on the number of activities and depth of review

Target Audience: Grades 7-12

Washington State Standards Targeted

- | | |
|---------|--|
| Systems | 1.1.6 Characteristics of Living Things
1.2.6 Structure and Organization of Living System
1.2.7 Molecular Basis of Heredity
1.2.8 Human Biology |
| Inquiry | 2.1.1 Questioning
2.1.2 Planning and Conducting Investigations
2.1.5 Communicating
2.2.2 Limitations of Science and Technology
2.2.4 Evaluating Methods of Investigation |
| Design | 3.1.1 Identifying Problems
3.1.2 Designing and Testing Solutions
3.1.3 Evaluating Potential Solutions
3.2.2. Relationship of Science and Technology |

National Science Standards

Correlation to National Science Standards: Grades 5-12

Unifying Concepts and Processes	Lesson 1	Lesson 2	Lesson 3	Lesson 4	Lesson 5	Assessment
Systems, order, and organization		•	•		•	•
Evidence, models, and explanation	•	•	•	•	•	•
Constancy, change, and measurement		•	•	•	•	•
Evolution and equilibrium		•	•		•	•
Form and Function		•	•			•

Correlation to the National Science Standards: Grades 9-12

	Lesson 1	Lesson 2	Lesson 3	Lesson 4	Lesson 5	Assessment
Science as Inquiry						
Abilities necessary to do scientific inquiry				•	•	•
Understandings about scientific inquiry			•	•	•	•
Physical Science						
Structure and properties of matter			•			•
Chemical Reactions			•			
Life Science						
The cell	•	•	•			•
Molecular basis of heredity	•	•	•			•
Biological Evolution		•	•		•	•
Interdependence of organisms	•	•	•		•	•
Matter, energy, and organizations in living systems		•	•			•
Behavior of organisms	•	•	•	•	•	•
Science and Technology						
Abilities of technological design			•	•		•
Understandings about science and technology	•	•	•	•	•	•
Science in Personal and Social Perspectives						
Personal health and community health	•	•	•	•	•	•
Science and technology in local, national, and global challenges	•	•	•	•	•	•
History and Nature of Science						
Science as human endeavor	•	•	•	•	•	•
Nature of scientific knowledge	•	•	•	•	•	•
Historical Perspectives	•		•	•	•	•

Essential Questions:

1. Why is there an HIV Pandemic?
2. Why is a vaccine needed to control the HIV pandemic?
3. How do vaccines usually work and why hasn't an HIV vaccine been developed?
4. How has history influenced research with human participants, and how are ethics applied in current research?
5. Which factors should be considered when developing and conducting trials?

Unit Objectives:

- The student will be able to:
1. Relate the structure, and lifecycle of HIV to challenges in vaccine development.
 2. Identify ethical issues in historic and current research trials using human research participants, and apply an understanding of those issues to the development of a student-designed research proposal.
 3. Evaluate the factors influencing the spread of HIV, both between individuals and on a global scale.
 4. Design elements of a research protocol for an HIV vaccine trial and evaluate that protocol using considerations of scientific accuracy, knowledge of human research participants testing, and ethical principles (autonomy, beneficence, and justice).

Essential Understandings:

1. Basic facts about HIV structure, transmission, research, and treatments need to be understood as background to why an HIV vaccine is currently lacking.
2. Mutations in viruses force the immune system to adapt and respond; vaccines must also stimulate an immune response. Since there is no history of a human being naturally clearing an HIV infection, a vaccine must produce an immune response which is better than that currently produced by the body.
3. Selection of human research participants for experimental research must be done carefully based upon the goals of the research and consideration of the risks and benefits to specific individuals and participant populations.
4. Pandemics are influenced by global health issues, cultural diversity, environmental context, education levels and socio-economic conditions.
5. Scientists conducting inquiry and research using human research participants must consider ethical principles based upon both past historical practices and current guidelines and regulations.
6. Examining the ethics of human research participants research encourages the use of critical and logical thinking to form positions and viewpoints.



The Science and Ethics of HIV Vaccine Research

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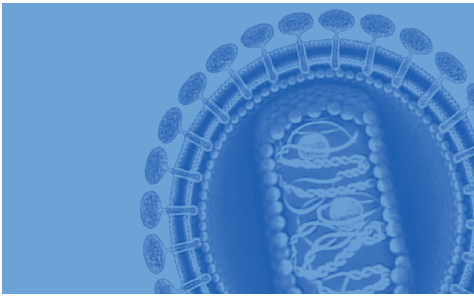
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Lesson Overview

The lessons support students in designing their own hypothetical HIV vaccine trial, based upon knowledge of HIV structure, vaccine characteristics, human research participants considerations, and global contexts.

Lesson One

Six introductory activities designed to review and assess student knowledge of HIV transmission, structure, research, and treatment are presented. The first activity (Survey — Global Awareness of HIV) can be used as a pre-unit assignment; it may also serve as a post-unit discussion.

Lesson Two

This lesson focuses on the HIV life cycle using web-based animations. Students identify possible targets for vaccine action and justify their choices based on HIV science.

Lesson Three

This lesson introduces priorities and challenges in the development of HIV vaccines. Vaccine types are compared and contrasted, and students learn about the most appropriate approaches for an HIV trial.

Lesson Four

The history of research with human participants is explored. Students hypothesize rules for such research, which may be modified after examining landmark case studies. The ethical principles and guidelines explained in the Belmont report and the UNAIDS Guidance Document are introduced. These principles form the basis upon which research is currently reviewed and approved.






Lesson Five

Students will participate in an activity to explore global cultural and socio-economic issues. They will identify issues effecting the health and welfare of different populations by continent, including HIV infection and death rates. This information will be applied when students choose a location for their vaccine trials.

Lesson Six: Evaluation

The culminating project will allow groups of students to present vaccine trial proposals to the class. Students research additional information to prepare their presentations. Presentations are evaluated and one project is chosen to be funded. As an individual assessment, students will submit a paper based on their learning during the unit; HIV structure, vaccine types and challenges, human research participants considerations, and global issues.

Symbols

-  — video
-  — discussion
-  — hands-on
-  — on-line or web based
-  — homework



Lesson 1

What Do You Know? And What Will You Do?

OVERVIEW AND SUMMARY

Core 1.1

Survey—Global

Awareness of HIV

Students survey peers and adults about HIV

Core 1.2

Pandemic: Facing AIDS

Video and Population

Bottle Activity introduce students to the global nature of HIV/AIDS.

Core 1.3

What Would You Do?

Students consider participating in a vaccine trial.

1.4 *What Do You Know? HIV*

Fact or Fallacy Game

Students categorize their HIV knowledge as Fact or Fallacy.

1.5 *Transmission Review Activity*

Students learn more about HIV transmission.

1.6 *Pandemic Circle*

Students simulate HIV infection rates over time.






Purpose

The purpose of this lesson is to review and clarify student knowledge of the science behind HIV/AIDS, including transmission. It will also challenge students to think about what they would want to know if they or someone they know were to become involved in a human HIV vaccine trial.

Method

Lesson One is divided into six mix-and-match activities, each accompanied by a symbol.

Symbols

- | | |
|---|------------------------|
|  | — video |
|  | — discussion |
|  | — hands-on |
|  | — on-line or web based |
|  | — homework |

Core Curriculum

Activities that are considered to be core to the curriculum unit are marked with the word “core”. It is recommended that teachers include these core lessons if they plan to evaluate students using the culminating project found in Lesson 6.

Essential Understandings

Basic facts about HIV structure, transmission, research, and treatments need to be understood as background to why an HIV vaccine is currently lacking.

Learning Objectives

Students will be able to:

- clarify the extent of their understanding of HIV
- examine their perspective on potential involvement in an HIV vaccine trial

Key Concepts

Review of HIV structure, transmission, research, and treatment

Prior Knowledge Needed

HIV/AIDS transmission

Basic knowledge of viral actions in infectious diseases

Basic immunology (antibodies, cell-mediated response)

Public Health: pandemic versus epidemic

Extensions

- Mock ELISA Lab – Disease Detection and Prevention
- biotech.biology.arizona.edu/labs/labs.html
- Red Disease (Phenolphthalein Activity)
- www.scienceteacherprogram.org/biology/diez2.html

Adaptations

- Web search on the statistics of HIV in student pairs if computers are available
- Pair sharing of material
- If ELL students need materials contact the Public health department and obtain translated material to use in class
- Simplify written responses as required by IEP

Assessment Suggestions

- Monitor discussions
- Review written response to both Global Awareness Survey and What Would You Do?

Common Misconceptions

- HIV/AIDS spread is declining in the US
- It is only a disease which affects homosexuals, prostitutes, and IV drug users
- Vaccines in general are not safe
- There are a variety of misconceptions about the transmission of HIV

Publications:

Cellular and Molecular Immunology, 4th edition.

Abul K. Abbas, Andrew H. Lichman, Jordan S. Pober, W.B. Saunders ISBN I-7216-8233-2.

The Science of HIV, 2nd edition, NSTA Press, ISBN 0-87355-1605

Pandemic: Facing AIDS Education Workbook, Umbrage Editions, ISBN 1-884167-29-2

Web Sites:

The HIV Vaccine Saga – www.medimmunol.com/content/2/1/1

Pandemic: Facing AIDS – www.hbo.com/docs/programs/pandemic/

Center for Disease Control – www.cdc.gov/hiv/dhap.htm

World Health Organization – <http://www.who.int/hiv/en/>

Avert.org – <http://www.avert.org/lesson1.htm>

The Body – <http://www.thebody.com/step/immune.html>

- Good information about current treatments for HIV+ patients

The Biology Project – <http://www.biology.arizona.edu/>

Lesson 1 Activity 1

CORE

Survey—Global Awareness of HIV



Objectives

Students will be able to:

- Examine different opinions about HIV and AIDS
- Understand that opinions are not “right” or “wrong” but subjective.

Class Time

The student survey can be done as homework. Results of the survey can lead to 40-50 minutes of classroom discussion or shorter discussions throughout the unit.

Introduction

This survey is designed to help students learn what their friends, parents, and teachers know about HIV and its prevalence in the world. Students are reminded that there are no “right” or “wrong” answers when surveying opinions.

Materials

Student Handout 1.1

Procedure

Students interview three people: a friend about their own age, a parent, guardian or adult acquaintance, and a teacher or administrator. They ask each person his or her opinion to six questions about HIV and AIDS.

Homework

The survey can be distributed to students before the unit begins or on the first day.

Discussion

The answers to the survey questions can be discussed throughout the unit; teachers can highlight specific areas when the class begins learning about that topic. A discussion of the entire survey can easily last an entire period.

Assessment Suggestions

Student responses to this survey could serve as a “pre-unit/post-unit” assessment. At the end of the unit, students can back up their opinions with information they have learned throughout the unit.

Extension

Have students answer the questions themselves, in addition to surveying other people.

Symbols



— video



— discussion



— hands-on



— on-line or web based



— homework

Global Awareness of HIV Survey

This survey is designed to help our class learn what our friends, parents, and teachers know about HIV and its prevalence in the world. Be sure to let who you are interviewing know that you are interested in their opinions, not whether or not they get “right” or “wrong” answers. For each interview, record the answers to all six questions. In addition, be sure to gather the information asked for each person.

	A friend about your age Age: Grade level:	A parent, guardian, or adult acquaintance Occupation:	A teacher or administrator Subject area or position:
Why do you think there is still not a vaccine for HIV?			
Once a vaccine has been developed, where do you think it should be tested? Why?			
Do you think the US has a responsibility to the world to pay for HIV/AIDS medications or vaccines?			
Which country do you think has the greatest growing HIV/AIDS problem?			
What contributes to the increase of people with HIV/AIDS? Do you think it is different in different countries? Why?			
What do you think people should know before they participate in an HIV vaccine trial?			



Objectives

Students will be able to:

- Recognize the global nature of the HIV/AIDS pandemic.
- Better understand the personal stories of five people with HIV/AIDS from around the world.

Class Time

The video is approximately 42 minutes long; each vignette runs from 8-9 minutes.

Introduction

Pandemic: Facing AIDS is a documentary film profiling stories from around the world. Five different regions (Thailand, Brazil, Uganda, Russia and India) are highlighted, with information about what each country is facing. Questions for students are included in this lesson.

Instructions for making a visual aid (“Population Bottles”) is also included in this lesson. Using popcorn kernels and water bottles, students can see the number of people with HIV/AIDS compared to the population for each country highlighted in the video.

In addition to *Pandemic: Facing AIDS*, there are a number of other excellent media sources which can be used with this curriculum. Additional information can be found in the Extensions section of this activity.

Materials

Pandemic: Facing AIDS, Moxie Firecracker Films. Ordering information and interactive website: www.pandemicfacingaids.org for educational packet including workbook (\$50.50). Video and book available at www.umbragebooks.com; type pandemic into search box (\$40 for educator’s version). Also available on DVD at Amazon.com for \$21.99.

Student Handout 1.1

Population Bottles Materials

- 6 .5 liter clear water bottles
- 1 2 liter clear bottle
- 6 lbs of yellow popcorn
- 1 lb of red popcorn
- 500 ml graduated cylinder (or similar)
- funnel

Red popcorn kernels can be ordered from:

<http://www.amishmart.com/popcorn-colored-popcorn.html>

Symbols



— video



— discussion



— hands-on



— on-line or web based



— homework

Procedure

The five short vignettes can be shown as a whole or used independently. Some teachers prefer to show one vignette per day while using the curriculum.

To make Population Bottles:

Label the .5-L bottles Thailand, Brazil, Russia, Uganda, United States and South Africa. Label the 2-L bottle India.

Add the correct amount of yellow popcorn kernels and red kernels to the bottles, according to the chart below. Although South Africa and the United States are not highlighted in the Pandemic video, the statistics from these countries can be eye-opening for students and serve as an important comparison to the other countries.

	Total Population Amount of yellow popcorn 1 kernel = 100,000 people	Number of people living with HIV/AIDS Amount of red popcorn 1 kernel = 100,000 people
Thailand	100 ml	6 kernels
Brazil	295 ml	7 kernels
Russia	225 ml	9 kernels
Uganda	45 ml	5 kernels
United States	470 ml	10 kernels
South Africa	70 ml	53 kernels
India	1 liter 715 ml	51 kernels

Source: <https://www.cia.gov/cia/publications/factbook/index.html>

Video Discussion and Homework

Written discussion questions from the video are provided in Student Handout 1.2. An answer key is also provided.

Population Bottles Discussion Questions

Which countries appear to have about the same number of people infected with HIV/AIDS? *South Africa and India each have over 5 million people who are HIV positive.*

Which country would be most affected by the virus? Why? *South Africa; 5 million people is a much higher percentage of that country's population.*

After India and South Africa, which country appears to have the most people who have HIV/AIDS? *It is very hard to tell; Russia comes next with approximately 900,000 people who are living with HIV/AIDS. Brazil, Thailand and Uganda come next, in descending order.*

In what ways is it difficult for actual health care providers to count the number of people with HIV/AIDS in a specific country? *Not unlike our bottles, people with HIV/AIDS are often obscured. They may be fearful to tell others of their HIV status, and many people who are thought to be infected may not know it themselves yet.*

Extensions

Pandemic: Facing AIDS is one of many excellent media sources about HIV and AIDS. The following programs are also highly recommended:

A Closer Walk. A Worldwide Documentaries Production. 2002-2003. Direct Cinema Limited, P.O. Box 10003, Santa Monica, CA, 90410. This is an outstanding documentary about the impact of HIV on the world. There are very personal views of people in developing nations coping with the devastation caused by this disease. The topics brought up include increase and care of AIDS orphans, women's rights, the role of poverty and disenfranchisement on HIV risk. Physicians, activists and patients are interviewed from the U.S, India, Africa, Haiti and Ukraine. (85 min) (\$95 with public performance license) -Information about video and companion website: www.acloserwalk.org
Ordering information: www.directcinematd

Rx for Survival: A Global Health Challenge. PBS, WGBH/NOVA, 2005. This television series combines historical vignettes with contemporary documentary stories to make six one-hour programs, each focusing on a different aspect of global health. The first program, Disease Warriors, is particularly useful for this curriculum as it chronicles the groundbreaking work of early vaccine researchers. The program illustrates how the use of vaccines has made huge strides against epidemics, conquering smallpox and bringing the global eradication of polio within reach. It also documents major challenges in getting basic vaccines to those who still need them, and in creating new ones to combat modern nemeses, like AIDS. The series is augmented by a fabulous website of activities, games, debates and experiments for teachers to use in the classroom. Links to the teacher pages and purchasing information can be found at: <http://www.pbs.org/wgbh/rxforsurvival/>

The Age of AIDS. PBS Frontline, 2006. This excellent video, released on the 25th anniversary of the first diagnosed cases of AIDS, examines the political denial, social stigma, stunning scientific breakthroughs, bitter policy battles and inadequate prevention campaigns of HIV/AIDS. It also documents the continuing spread throughout much of the world, particularly in developing nations. The video is backed up by a very helpful website. <http://www.pbs.org/wgbh/pages/frontline/aids/> The four-hour series is available at no cost streaming through the same website, or can be purchased for \$39.99.

Out of Hiding, Into the World: Thembi's AIDS Diary—

A radio diary aired on April 19, 2006, All Things Considered, NPR. South African Thembi Ngubane, age 20, was given a tape recorder by radio producer Joe Richman. For a year, she recorded an intimate audio diary that brings listeners into her home, among her family, to witness her daily struggles and triumphs (22 minutes).

<http://www.npr.org/templates/story/story.php?storyId=5311801>

Information about purchasing a transcript of the story (\$3.95) can be found on the same website.

Pandemic: Facing Aids

Complete the questions below as you watch the video.

1. What steps did Margaret and other members of the Uganda Orphans Rural Development Programme take to address AIDS in their community?
2. What will happen to James and Jessica? How will their extended family and community deal with them, and other orphans like them?
3. What is harm reduction?
4. How is HIV transmitted between injection drug users?

5. What makes Brazil's approach to AIDS different from the strategies of other countries?

6. Why aren't these antiviral drugs available all over the world?

7. What was Lek's father's reaction to the stigma of HIV/AIDS? Do you think he loved his child?

8. How did Bhanu's doctors decrease the chances of her passing HIV on to her child?

9. What steps can Nagaraj and Bhanu take to ensure that their baby remains healthy?

Pandemic: Facing Aids

Answer *one* of the following questions below
on your OWN PAPER:

1. Do you know anyone in James and Jessica's situation or a similar one? Imagine what it would be like to be James or Jessica. How do you think it might feel to lose a parent to AIDS? In what ways would belonging to the AIDS orphans choir help? Why is Margaret Boogere's involvement with orphans and other vulnerable children so important?
2. How do you think Sergei and Lena have changed since learning they are HIV positive? In your own life, have you ever turned a negative experience into a positive one? Write about a moment of personal transformation in your own life or in the life of someone you know.
3. Do you think Nagaraj and Bhanu did the right thing by having a baby? Was it worth the risk? Why or why not?
4. How do you think the support of Alex's family, physician, and government health ministry have helped him? How do you think you might feel if you were HIV positive, like Alex, but did not have his access to AIDS medications and physicians?
5. Do you know anyone in Lek's family's situation or a similar one? If so, write about that experience. If not, imagine what it would be like if someone in your family were infected with HIV. How would you deal with the stigma of HIV/AIDS? Would you care for that family member at home? Would you be public about his or her HIV/AIDS status? Why or why not?

Pandemic: Facing Aids

1. What steps did Margaret and other members of the Uganda Orphans Rural Development Programme take to address AIDS in their community?

The group uses a network of volunteers to assist orphans and vulnerable children materially, spiritually and emotionally. They teach “life skills classes” and sponsor drama and singing groups. They also talk about the disease and embrace people who have contracted HIV. The orphans choir helps to build self worth in children affected by AIDS. The UORDP hopes to overcome the stigma of HIV AIDS by promoting the view of HIV/AIDS as a cause of death and as an infectious disease, not as a social punishment. Reducing stigma makes it easier to encourage prevention, treatment, and respect for the human rights of children and adults affected by HIV.

2. What will happen to James and Jessica? How will their extended family and community deal with them, and other orphans like them?

James will continue taking care of his sister Jessica when their mother dies, with very little support. The staggering number of children orphaned by AIDS puts a massive strain on already limited resources in many developing nations. When children lose both their parents, they often have to rely on the goodwill of relatives or member of the community to make ends meet, and many children are forced to assume adult responsibilities at a young age. Children affected by AIDS are more likely to miss school and have a harder time meeting basic needs such as food, shelter, and medical care. They are at greater risk for sexual abuse, labor exploitation, and other human rights abuses, and can even lose their property or inheritance rights.

3. What is harm reduction?

The goal of harm reduction programs is to decrease damage caused by a potentially dangerous activity, such as injection drug use or unprotected sex. Harm reduction attempts to convince people to reduce their risk of exposure to HIV. Programs have achieved documented success in reducing HIV infection rates.

4. How is HIV transmitted between injection drug users?

Sharing a needle with an HIV-positive person puts you at the highest risk of contracting the virus. It is a devastatingly effective way to transmit HIV. If two or more people use the same needle to inject drugs into their veins, one person’s blood can enter the bloodstream of another. The AIDS virus cannot survive outside of the body for a long period of time, but a vacuum in most needles protects the virus and preserves its ability to infect others.

5. What makes Brazil's approach to AIDS different from the strategies of other countries?

Brazil is the first developing country to make generic AIDS drugs (Highly Active Antiretroviral Therapy, or HAART) available to all HIV+ citizens who need them. Many wealthier nations have the same policy. Other developing countries, such as Thailand and Nigeria, are beginning to offer similar programs, but most cannot afford them. Much credit for Brazil's policy is due to AIDS activists and the government officials who responded to their calls for funding, research and prevention. Their persistent efforts resulting in government policy that has kept Brazil's AIDS rate low and prolonged the lives of tens of thousands of people living with HIV.

6. Why aren't these antiviral drugs available all over the world?

Antiretroviral drugs are available in many countries, but are so expensive that most people who live with the virus cannot afford to buy them. A complete course of medicines costs \$12,000 to \$15,000 a year in the United States. Countries like Brazil have made an effort to distribute generic versions of the drugs to their citizens who live with HIV. In most developed countries, governments make the drugs available to HIV+ people who need them.

7. What was Lek's father's reaction to the stigma of HIV/AIDS? Do you think he loved his child?

Lek's father and mother feared the possible negative reaction of others in their community to her condition. Being HIV+ carries with it a stigma in many cultures, including Thailand, and they were worried that other villagers would ostracize them just because they were family. Lek's parents finally had a change of heart and decided that they were prepared to risk the opinions of other villagers in order to allow their daughter to die with dignity in their home. Their risk paid off, as many villagers overcame their fear of AIDS and came to visit Lek and bring her gifts during her final weeks.

8. How did Bhanu's doctors decrease the chances of her passing HIV on to her child?

Bhanu's doctors took several steps. They administered a dose of nevirapine to her during the birthing process and to her child shortly after. They also performed a c-section on her, which reduces the risk of HIV passing from the mother to child. Experts say the virus is most often passed on during the actual birthing process when the child is exposed to blood and other fluid from the mother, but a c-section eliminates much of the potential for fluid transfer. Most children born to HIV+ women are HIV negative when they are in the womb.

9. What steps can Nagaraj and Bhanu take to ensure that their baby remains healthy?

Even if HIV+ mothers do not infect their babies during birth, there is about a fourteen-percent chance that a baby will contract HIV from infected breast milk. This risk can be eliminated if Bhanu does not breast feed Maria. Instead, she should use baby formula or kill the virus by boiling her breast milk for at least twenty minutes. They should continue to have Maria tested regularly.



Objectives

Students will be able to:

- Assess what they know about HIV vaccines.
- Consider the personal implications of participating in an HIV vaccine trial.
- Think about some ethical issues regarding the involvement of minors in clinical trials.

Class Time

Can be done as homework or in class.

Introduction

Students are given a scenario about a friend with HIV. They are asked to complete questions regarding their participation in an HIV vaccine trial.

Materials

Student Handout 1.3

Discussion

Discussion about responses can set the stage for learning about vaccines and trials, which are explored in the next lessons.

Homework

Student Handout 1.3

Symbols



— video



— discussion



— hands-on



— on-line or web based



— homework

What Would You Do?

Your best friend has just been tested and is HIV positive. Your friend, in tears, tells you they will be starting a vaccine trial to prevent infection and they need healthy volunteers. In contrast to a **therapeutic vaccine**, which is **given to persons already infected with HIV**, a **preventative vaccine** is given to a **non-infected person to prevent their contracting HIV**. The majority of HIV research (85-90%) today is directed towards a preventative vaccine. Your oldest and best friend asks you to be one of the volunteers for this clinical trial to develop a preventative vaccine against HIV.

1. What is your initial reaction and what makes you feel this way?
2. What would you want to know as a participant?
3. What fears do you have about being part of this study?
4. What would researchers want to know when conducting the trial?
5. As a minor, you are unable to give consent to participate in a medical trial. Do you think your parent(s) or guardian would give consent for you? What might be their concerns?
6. If your parent(s) or guardian give consent, would you expect your conversations with researchers and test results to remain confidential? Would your parent(s) or guardian support this?

Lesson 1 Activity 4

What Do You Know? HIV Fact or Fallacy Game



Objectives

Students will be able to:

- Work through their misconceptions about HIV/AIDS
- Learn more about HIV structure, transmission and treatment.

Class Time

40-50 minutes for activity and discussion.

Introduction

Students write down things they have heard about the structure, transmission and treatment of HIV (not things that are necessarily true) and then try to categorize them as fact or fallacy.

Materials

Black board, white board or butcher paper
Chalk or pens
Post-it notes
Student Handout 1.4

Procedure

1. Have students in pairs list 3 pieces of information they have heard (not necessarily something they know is true) about HIV/AIDS on 3 Post-it notes. One piece of information for each of the following categories:
 - HIV Structure
 - Transmission
 - Research/Treatment
2. On the board or on butcher paper construct a 3 x 3 table. Put the categories listed above down the left-hand column and put the following 3 titles across the top: Fact, Fallacy, Unsure.
3. Have the students place their post-its in the box where they think they belong.
4. Review the lists with the students correcting incorrect information and clearing up misunderstandings.
5. Have students fill out Student Handout 1.4 as they go over the information as a class.

Homework/Extensions

Have students research any information left in the “unsure” category. Is it fact or fallacy?






Discussion

The discussion can vary, depending on what students bring to the class and the expertise of the teacher. If a number of items remain in the “unsure” category, keep the class sheet up for the duration of the unit, correcting items as you learn new information.

Sources

This game is an adaptation by Simon Forrest & Annabel Kanabus of material originally published in *AIDS: Working With Young People* by Peter Aggleton, Kim Rivers, & Ian Warwick (ISBN 0-9515351-8-8) together with some new material.

Symbols

-  — video
-  — discussion
-  — hands-on
-  — on-line or web based
-  — homework

What Do You Know? HIV Fact or Fallacy Game

Directions: In the table below, write one piece of information for each of the categories. This should be something you have HEARD, not something that is necessarily true.

PIECE OF INFORMATION	FACT, FALLACY, UNSURE	WHY?
HIV Structure		
HIV Transmission		
Research / Treatment		

Transfer your piece of information to a post-it and place it in the appropriate area as demonstrated by your teacher.

Lesson 1 Activity 5

Transmission Review Activity



AVERT.ORG

Objectives

Students will be able to:

- Increase their levels of awareness of how HIV is transmitted.
- consider a variety of transmission routes.

Class Time

Up to 60 minutes depending on the number of statements used and the size of the group.

Introduction

In this activity the teacher reads statements regarding transmission of HIV and students are asked to move to areas of the room identified with signs for agreement or disagreement. The teacher then facilitates discussion following each statement, including the accuracy of the statement. Students can rearrange themselves following discussion.

Materials

- A reasonably spacious room, to allow for free movement.
- A copy of Transmission Runaround 'True/False Sheet' for yourself and the answer sheet.
- Two large sheets of paper clearly marked 'STRONGLY AGREE' and 'STRONGLY DISAGREE'
- Pins

Procedure

1. Put up the 'STRONGLY AGREE' and 'STRONGLY DISAGREE' sheets on the wall at opposite ends of the room.
2. Explain to the group as a whole that you will read out a series of statements, one at a time. Each person is to think about whether they agree or disagree with it, and move to the appropriate side of the room. It is all right to stay in the middle if they are uncertain.
3. Read the first statement. Once everyone has moved to their chosen place, ask members to choose one person near them and discuss why they are standing where they are.
4. Now ask people to choose one person standing as far away from them as possible, and to discuss the statement with them, explaining why each has chosen to be where they are.
5. Repeat the procedure with as many statements as time allows.
6. Re-assemble as a group and, going round the group, ask each individual to identify one piece of information they are confused or unclear about. Ask members of the group to clarify the issues involved and intervene yourself where necessary.

Symbols



— video



— discussion



— hands-on



— on-line or web based



— homework

Discussion

At the end of the exercise, it will be clear what areas of uncertainty remain. Individuals will have had a chance to think about ways of transmitting HIV, and to discuss these with other group members. It will also be clear that transmission routes for HIV are very specific e.g. It is not 'sex' that transmits the virus, but unprotected sex involving penetration. People can sometimes become quarrelsome during this exercise so you may need to intervene to settle disputes.

Sources

Last updated April 23, 2004 © Avert 2004, [www. AVERT.org](http://www.AVERT.org)
Modified from www.Avert.org, reproduced with permission.

True/False Question Sheet

1. You can become infected with HIV by sleeping around.
2. Injecting drugs will give you HIV.
3. You can get HIV from toilet seats.
4. If you are fit and healthy you won't become infected with HIV.
5. Married people don't become infected with HIV.
6. If you stick with one partner you won't become infected with HIV.
7. Women are safe from HIV as long as they use a contraceptive.
8. You can become infected with HIV from sharing toothbrushes.
9. If you have sex with people who look healthy, you won't become infected with HIV.
10. If you only have sex with people you know, you won't become infected with HIV.
11. Anal sex between two men is more risky than anal sex between a man and a woman.
12. You can become infected with HIV from kissing.
13. A man can become infected with HIV if he has oral sex with a woman.
14. A woman can become infected with HIV if she has oral sex with a man.
15. Condoms can stop you becoming infected with HIV.

True/False Answer Sheet

1. Sleeping around (having multiple sexual partners) increases one's risk of exposure to HIV and STDs.
2. Only if the needle/syringe and/or drug 'works' (used to prepare the drugs) are shared.
3. There are no known cases of HIV infection via toilet seats.
4. It does not matter how healthy or unhealthy you are, if you engage in risky activities you stand a chance of being infected.
5. This depends on the partners involved, what they did before they met, whether either has unprotected sex outside of the marriage or injects drugs using contaminated equipment. Marriage by itself offers no guarantees of safety.
6. As for No 5.
7. Only condoms offer women protection against HIV, and even condoms cannot offer complete safety. Other forms of contraception do not offer protection from HIV.
8. There is no evidence of transmission via this route, but it is sensible not to share toothbrushes for general health reasons.
9. Most people with HIV will look perfectly healthy. Looks are therefore a useless way of assessing risk.
10. Knowing someone well offers no reliable guide to whether or not they have HIV infection.
11. Anal sex is equally risky regardless of whether it takes place between two men or a man and a woman.
12. There is no evidence of transmission in this way, although kissing when there are sores or cuts in the mouth may pose some risk.
13. HIV is present in cervical and vaginal secretions as well as in (menstrual) blood, so there is the possibility of transmission this way.
14. HIV is present in pre-ejaculate fluid as well as in semen so there is a possibility of transmission in this way.
15. Condoms used properly will help to prevent transmission of HIV from an infected partner to an uninfected partner. Condoms are not 100% safe though. Use a lubricant which is water based, as oil based lubricants can weaken the condom. When buying condoms check the 'sell by' date. Condoms exist for both men and women.

Lesson 1 Activity 6

Pandemic Circle



Objectives

Students will be able to:

- see that the rate of infection has increased over time.
- HIV/AIDS continues to be a global challenge.

Class Time

The activity takes about 10 minutes, plus discussion time.

Introduction

This activity simulates the number of worldwide cumulative HIV infections during the last 25 years, from 1980 until 2004. Each student standing around the circle represents 3 million people. When an additional 3 million people become infected with HIV, a student steps into the Pandemic Circle. In simulating infection rates, students experience the changing rate of infection.

Materials






Yarn, string or chalk to make a 10-foot diameter circle

Pandemic Circle cards

Procedure

1. Cut out the Pandemic Circle counting cards (included).
2. Tape or draw a 10-foot diameter circle to the floor. Explain to students that this represents the planet and we will be looking at HIV infection rates over the last 25 years.
3. Hand out a Pandemic Circle card to 26 students. Tell the students that each person standing around the circle represents 3 million people (approximately the population of the Puget Sound Region).
4. Ask the class if anybody has the year 1980 on his or her card? (no). Ask why not? In 1980, there were less than 3 million people on the planet infected with HIV/AIDS.
5. Tell the class that we will be counting from 1980 to 1994. When students hear the date on their cards, they should step into the circle, thereby adding another 3 million people with HIV to the pandemic.
6. Ask the students to predict the year when the first person will step into the circle.
7. As a group, begin counting slowly from 1980 to 2004.

Symbols

-  — video
-  — discussion
-  — hands-on
-  — on-line or web based
-  — homework

Lesson adapted from Population Circle, Population Connection *People and the Planet*.
www.populationconnection.org

Cumulative HIV Infections Worldwide, 1980-2004	
Year	Number of People Infected (million)
1980	0.1
1981	0.3
1982	0.7
1983	1.2
1984	1.7
1985	2.4
1986	3.4
1987	4.5
1988	5.9
1989	7.8
1990	10.0
1991	12.8
1992	16.1
1993	20.1
1994	24.5
1995	29.8
1996	35.3
1997	40.9
1998	46.6
1999	52.6
2000	57.9
2001	62.9
2002	67.9
2003	72.9
2004	77.8

Sources

2000-2004 data from UNAIDS, *Aids Epidemic Update* (Geneva, various years); 1980-1999 data from electronic communication with Neff Walker, UNAIDS, 20 March 2000. Worldwatch Publications: *Vital Signs 2005*.

Discussion Questions

- When did most people begin stepping into the circle? What does this mean?
- Is the infection rate increasing, decreasing, or holding steady? What would this look like on a graph?
- Were there any fluctuations in the infection rates?
- Tell students that this activity simulates the cumulative number of people who have been infected with HIV worldwide; it does not take into account the number of people who have since died. When all the participants are standing in the circle, almost 80 million people are represented. There are currently thought to be about 40 million people alive today who have HIV/AIDS. Almost half the students standing in the circle would no longer be living.
- Tell students that we may not have a viable AIDS vaccine for another 10 years. What does the Pandemic Circle look like 10 years from now? What can we do about it today?

Homework

- Have students graph the data from the chart at the left.
- After graphing the data, have students extrapolate 50 years into the future, showing lines for “best case”, and “worst case” scenarios. Have them list three or more factors which would contribute to best and worst case scenarios.
- Choose some of the discussion questions for students to answer in paragraph form.

Pandemic Circle 1986	Pandemic Circle 1988
Pandemic Circle 1990	Pandemic Circle 1991
Pandemic Circle 1992	Pandemic Circle 1993
Pandemic Circle 1993	Pandemic Circle 1994
Pandemic Circle 1995	Pandemic Circle 1995
Pandemic Circle 1996	Pandemic Circle 1996
Pandemic Circle 1997	Pandemic Circle 1997
Pandemic Circle 1998	Pandemic Circle 1998
Pandemic Circle 1999	Pandemic Circle 1999
Pandemic Circle 2000	Pandemic Circle 2001
Pandemic Circle 2001	Pandemic Circle 2002
Pandemic Circle 2002	Pandemic Circle 2003
Pandemic Circle 2004	Pandemic Circle 2004



Lesson

2

HIV Structure/Life Cycle and Implications for Vaccine Development

OVERVIEW

Purpose

Prior to beginning content, the students will be introduced to their final assessment projects, including the vaccine trial proposal and reflection paper. This lesson will review with students the general structure and life cycle of the HIV virus. It will introduce them to the idea of identifying places within the life cycle to be interrupted by a vaccine.

Essential Understandings

Mutations in viruses force the immune system to adapt and respond; vaccines must also stimulate an immune response. Since there is no history of a human being naturally clearing an HIV infection, a vaccine must produce an immune response which is better than that currently produced by the body.

Learning Objectives:

- Students will gain a greater understanding about the structure and life cycle of HIV
- Students will apply their understanding about the life cycle of HIV to identify targets of interruption
- Students will be able to explain how mutations occur and why they can create challenges to developing effective vaccines

Key Concepts

HIV Structure and Life Cycle

Prior Knowledge Needed

Basic HIV/AIDS background information

Immune system and how vaccines work in the immune system

Materials

Overhead projector or LCD Projector (optional)

Computer Lab for students

Paper and pencils

Copies of Student Worksheets

Prep Time

Teacher may want or need to do some background reading so they are comfortable with the content area of HIV structure and life cycle.

Prepare copies and overhead transparencies if necessary

Class Time

1-2 days depending on the depth and level of discussion

Timeline:

- 1 week before activity:
 - Reserve computer lab
 - Make copies of student handouts

Extensions

- Investigate naturally occurring mutations that make people resistant to HIV infection
- Explore possible links between resistance to HIV and survival of historical diseases such as Black Plague
- Have students write and create a children's story book with diagrams to teach and illustrate the HIV virus life cycle and how it has been able to evade researchers in developing a vaccine.

Adaptations

- Make a Power Point presentation to explain HIV life cycle and relate it to the virus's ability to evade researchers' attempts to engineer an effective vaccine.
- See Day One for ELL and IEP adaptations

Assessment Suggestions

- Review WebQuest answers
- Monitor students' responses during debrief and discussion
- Analyze responses given in reflective paragraphs

Common Misconceptions

- HIV+ people are all infected with the same virus
- A vaccine has not been developed because of government conspiracy
- The only reason a vaccine has not been developed is because not enough funding is available

ADDITIONAL RESOURCES

- See Appendix for
 - Review of HIV – Background
 - HIV Life Cycle Review Materials
- See Appendix for Selected Possible Interventions of HIV Life Cycle (within HIV Sample Lesson)
- HIV Life cycle – Additional Animation
 - <http://www.learner.org/channel/courses/biology/units/hiv/index.html>
This very helpful website has animations detailing the immune system, HIV infection, HIV receptors, and the HIV DNA vaccine. It also has a number of still images, expert interviews and an online textbook.
 - www.roche-hiv.com/Newsandfeatures/animations/animations_multimedia.cfm
Short animations including HIV lifecycle, fusion and cell entry, attachment inhibition, co-receptor inhibition, and fusion inhibition
 - www.roche-hiv.com/Newsandfeatures/animations/lifecycle/lifecycle_animation.cfm?link=HIVTreatment
No discussion of mutations but good information and good step-by-step animations
 - www.cellsalive.com/hiv2.htm
This contains some good information but is somewhat dated and has information that is still being debated

Lesson 2 Activities

SUMMARY

- 2.1 *Explanation of Final Assessment Projects*
- 2.2 *Invitation to Learn*
- 2.3 *HIV Life Cycle WebQuest*
- 2.4 *Debrief and Discussion*
- 2.5 *HIV Vaccine Expository Paragraphs*
- 2.6 *Homework Reading Assignment*

2.1. Explanation of Final Assessment Projects

Option A – Individual Essay

Each student will be expected to write a paper explaining the basics of HIV vaccine development. They will be writing paragraphs of this paper following each lesson and then compiling them into a final product.

Option B – Group Research Proposal Presentation

As a group, students will assume the role of scientists and design a vaccine strategy for a Phase I trial. They will need to identify the HIV life cycle target and recommend a population for testing. Be sure students understand more information will follow.

Option C – Research Proposal Review as a member of an Institutional Review Board

Working either individually or as a group, students review a mock research proposal seeking to gain IRB approval. The IRB evaluates whether or not the research proposed should proceed.






2.2 Invitation to Learn

1. Play Roche animations for the class
 - www.roche-hiv.com//Newsandfeatures/animations/animations_multimedia.cfm
 - www.roche-hiv.com/Newsandfeatures/animations/lifecycle/lifecycle_animation.cfm?link=HIVTreatment
2. How would a vaccine or treatment interrupt the life cycle of HIV?

2.3 HIV Life Cycle WebQuest

1. Choose one of the following websites and have students complete companion worksheet in pairs. *Note: Can show NOVA animation to the class and then have students complete worksheet for second animation in pairs.*
 - www.pbs.org/wgbh/nova/aids/action.html
 - Good animation about life cycle but does not discuss mutations
 - Be sure to stress mutations during debrief discussion
 - www.sumanasinc.com/webcontent/anisamples/majorsbiology/lifecyclehiv.html
 - contains information specific to mutation of HIV on slide 4

Symbols

-  — video
-  — discussion
-  — hands-on
-  — on-line or web based
-  — homework

2. For teachers without access to computer labs or LCD Projectors:

- Give students worksheet to complete as teacher shows the animations to the class
- Print copies of the animation slides and use as transparencies; walk through and aid students in completing the worksheet

2.4 Debrief and Discussion



1. Teacher should facilitate debrief of worksheets with the students. Be sure to reference final assessment projects. Encourage discussion of the following:

- Mutations of HIV and implications for vaccine development
- Cells targeted by HIV and implications for body response
- Possible places of interruption of life cycle for treatments or vaccines

2.5 HIV Vaccine Expository Paragraphs



1. Ask students to write 1 paragraph about each of the following for homework:

- Describe the structure and life cycle of HIV
- What are possible targets for interrupting the HIV life cycle?

2.6 Homework Reading Assignment



- Have students read “HIV Vaccines Explained” by the US Department of Health and Human Services Feb. 2004. This provides background information to set the stage for Day Three.
- See the end of Lesson 3 for the hardcopy
- www2.niaid.nih.gov/Newsroom/mayday/pdf/HVAD2005_HIVvaccinebrochure.pdf

Teacher Information

HIV Life Cycle WebQuest

In order to give students a greater understanding of the life cycle of HIV, animations or diagrams are suggested. There are two websites below with suggestions (and student worksheets) to be used with each.

www.pbs.org/wgbh/nova/aids/action.html

- Give students worksheet and allow them to use computers to complete; discuss as a class when finished
- Give students worksheet and use LCD projector or other method to show students the website from one class computer; discuss and complete worksheet together

www.sumanasinc.com/webcontent/anisamples/majorsbiology.lifecyclehiv.html

- Give students worksheet and allow them to use computers to complete; discuss as a class when finished
- Give students worksheet and use LCD projector or other method to show students the website from one class computer; discuss and complete worksheet together
- Print out slides and convert to Transparencies and walk through as students complete worksheet

The HIV Life Cycle WebQuest

Use the website <http://www.pbs.org/wgbh/nova/aids/action.html> to answer the following questions about the HIV virus.

Click on Viral Entry

1. To what cell type does the HIV virus attach itself?
2. Explain how HIV is able to enter these cells.
3. How important are the receptors on the cell membrane to HIV entry? Why?
4. Why do some HIV+ individuals show no sign of the disease?

Click on Viral Gene Transfer

5. What must RNA do before it can become incorporated into the host cell's DNA?

6. How are new viral proteins built using the host cell's machinery?

Click on Viral Exit

7. How is HIV spread inside the body?

8. Why are HIV patients susceptible to other infectious agents?

Wrap-up Question

9. Based on what you have learned, hypothesize why it is so difficult for the human body to fight HIV like it does other viruses.

The HIV Life Cycle WebQuest

Use the website <http://www.pbs.org/wgbh/nova/aids/action.html> to answer the following questions about the HIV virus.

Viral Entry

1. To what cell type does the HIV virus attach itself?

The animation shows an HIV particle attaching itself to a lymphocyte. Lymphocytes, which include helper T cells and killer T cells, are small white blood cells that are critical in immune defense and are HIV's principal target. (HIV can also attach itself to macrophages, which also have CD4 receptors on the surface. Macrophages are large white cells whose job it is to "clean up" foreign material by engulfing it.)

2. Explain how HIV is able to enter these cells.

The binding process is facilitated by a molecule on the surface of the HIV particle called gp120. Gp 120 binds to two chief receptors (CD4 and CCR5) on the outside of the host cell, much like a key fitting into a lock. Once the viral particle has successfully binded to the host cell, its core can pass through the cell wall into the cell's cytoplasm.

3. How important are the receptors on the cell membrane to HIV entry? Why?

Very important. If the HIV particle can't bind with the host cell, it can't enter the cell and insert its RNA inside the host cell. (It is not mentioned in the animation, but some HIV has adapted to use a different co-receptor, CXCR4)

4. Why do some HIV+ individuals show no sign of the disease?

They may be missing the gene (or have mutations in the gene) that makes the CCR5 receptor, so that a defective protein or no protein is made. Without this receptor, the HIV particle does not fully bind and cannot easily enter the host cell.

Viral Gene Transfer

5. What must RNA do before it can become incorporated into the host cell's DNA?

It must form a double-stranded viral DNA using the single-stranded viral RNA as a template. It uses an enzyme known as reverse transcriptase to help do this.

-
6. How are new viral proteins built using the host cell's machinery?

The viral DNA integrates itself into the host's DNA. The DNA is then transcribed into RNA, which migrates out of the nucleus (which houses the host's DNA) into the cytoplasm. There, new viral proteins are built using the viral RNA as a blueprint. More specifically (and not mentioned in the animation), the RNA is translated into viral proteins using the host's ribosomes, amino acids, and cellular machinery to make these building blocks that can then self assemble into new virus particles.

Viral Exit

7. How is HIV spread inside the body?

The new HIV particles move out of the cell, where they head off to infect other cells and perpetuate the life cycle. This process repeats itself continuously, with many thousands of HIV particles produced simultaneously in the body.

8. Why are HIV patients susceptible to other infectious agents?

After repeated assaults by viral particles, very key host cells (CD4 T helper cells) die, having exhausted their energy and molecular building supplies while generating HIV viruses. This suppresses a patient's immune system and leaves him or her open to infection by other infectious agents, including bacteria, fungi, and other viruses.

Wrap-up Question

9. Based on what you have learned, hypothesize why it is so difficult for the human body to fight HIV like it does other viruses.

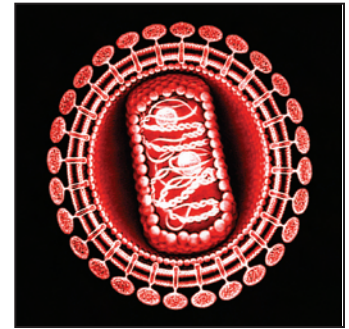
HIV attacks the very system (the immune system) that protects the body from foreign invaders.

The HIV Life Cycle

Use the following website to answer the following questions about the HIV virus.

<http://www.sumanasinc.com/webcontent/anisamples/lifecyclehiv.html>

You may use step-through or narrated to complete this worksheet. You may find that using the narrated first, and then following with the step-through will be the best way to get the most information.



1. Explain, in as much detail as possible, how the HIV virus enters a cell.
2. Name the part of HIV that interacts with the receptor on the host cell. What is the name of the host cell receptor?
3. What happens to the lipid membrane of the virus?
4. Which parts of HIV enters the cell? Which parts remain outside the cell?
5. List the organelles the animation shows inside the host cell.
6. What converts the viral RNA into DNA?

-
7. Why is there a high mutation rate in HIV?
 8. Describe the role of integrase. Why is it so important for HIV?
 9. Based on what you already know about genetics, what does it mean for the host cell, now that the viral DNA has become a part of the Host Cell Genome?
 10. Summarize the steps between integration of the viral DNA into the host DNA and assembly of new viral particles.
 11. What is unique about how HIV viral particles exit the host cell? (Hint: What do they take with them???)
 12. Based on what you have learned, hypothesize why it is so difficult for the human body to fight HIV like it does other viruses.

The HIV Life Cycle

Use the following website to answer the following questions about the HIV virus.

<http://www.sumanasinc.com/webcontent/anisamples/lifecyclehiv.html>

1. Explain, in as much detail as possible, how the HIV virus enters a cell.

HIV has surface proteins called gp120 that attach to cells that have CD4 receptors on their surfaces. CD4 is found on the immune system's helper T (T_H) lymphocytes and on scavenger cells called macrophages. The binding to CD4 proteins and other cell-surface proteins, called co-receptors (not shown in the animation) allows the virus to fuse with the cell. The lipid membrane of the virus incorporates into the cell's membrane, while the viral core enters the host cell.

2. Name the part of the HIV virus that interacts with the receptor on the host cell. What is the name of the host cell receptor?

The gp120 is the part of HIV that interacts with the CD4 receptors (and co-receptors not shown on the animation) on the host cell.

3. What happens to the lipid membrane of the virus?

It gets incorporated into the membrane of the host (helper T or macrophage) cell.

4. Which parts of HIV enters the cell? Which parts remain outside the cell?

The viral core, which has the RNA and some copies of reverse transcriptase inside it, enters the host cell. The lipid membrane becomes incorporated into the host's membrane.

5. List the organelles the animation shows inside the host cell.

The animation shows the nucleus, rough endoplasmic reticulum (ER), and Golgi apparatus. The cell membrane and cytoplasm are sometimes considered organelles.

6. What converts the viral RNA into DNA?

The enzyme reverse transcriptase copies the RNA into complementary DNA, then the enzyme ribonuclease H destroys the original RNA strand. Reverse transcriptase then synthesizes a second DNA strand using the first strand as a template.

7. Why is there a high mutation rate in HIV?

Reverse transcriptase has a high error rate and frequently leaves mutations in the copied DNA. The mutations result in variant forms of HIV which a) allow HIV to evolve quickly (as shown in the animation), or b) cause the virus to be inactive (not shown in the animation).

8. Describe the role of integrase. Why is it so important for the HIV virus?

Integrase enzymes splice the viral DNA into the host cell's chromosomal DNA. The viral DNA must be spliced into the host DNA so that the host cell can be commandeered to make HIV components for new viral assembly.

9. Based on what you already know about genetics, what does it mean for the host cell, now that the viral DNA has become a part of the Host Cell Genome?

Once the viral DNA is integrated into the host cell DNA, it becomes part of that cell's own genome. It is no longer "foreign" and cannot be distinguished from the cell's original DNA.

10. Summarize the steps between integration of the viral DNA into the host DNA and assembly of new viral particles.

The viral DNA that has been incorporated into the host DNA instructs the cell to make viral RNA strands. These RNA strands contain the information to produce full-length viral RNA molecules, capsid proteins, envelope proteins other proteins needed for viral assembly. All of the components gather at the membrane and assemble to become complete viruses. They then bud off from the host cell.

11. What is unique about how HIV viral particles exit the host cell? (Hint: What do they take with them???)

They coat themselves with pieces of the cell's own membrane.

12. Based on what you have learned, hypothesize why it is so difficult for the human body to fight HIV like it does other viruses.

HIV infects the very cells in the immune system which are programmed to fight off foreign invaders. With a destroyed immune system, the body is vulnerable to a host of diseases.

Although HIV does have some components of the host cell, it is recognized as foreign, and the immune system makes a strong immune response to it. The reason that it cannot be easily eliminated is for two major reasons: (1) the viral proteins are constantly changing and "escaping" the immune response; and (2) because the virus is integrated into the host's DNA, viruses are produced continuously through the life of the infected patient.



Lesson

3

Vaccines

OVERVIEW

Purpose

The purpose of this lesson is to introduce students to the various types of vaccines available. Students will use what they have learned in this lesson and in the previous lessons to identify which types of vaccines are most useful for developing an HIV vaccine. They will be asked to provide rationale for their choices based on safety, effectiveness and the HIV life cycle.

Essential Understandings

- Basic facts about HIV structure, transmission, research, and treatments need to be understood as background to why an HIV vaccine is currently lacking.
- Mutations in viruses force the immune system to adapt and respond, vaccines must also stimulate an immune response. Since there is no history of a human being naturally clearing an HIV infection, a vaccine must produce an immune response which is better than that currently produced by the body

Learning Objectives

- Students will be able to:
 - Summarize key features of vaccine types including advantages and disadvantages
 - Analyze different vaccine types for their suitability in use for HIV vaccine development and support their choice
 - Connect vaccine type choice to HIV structure and life cycle
 - Gain an understanding as to why the making of an HIV vaccine has been so difficult.

Key Concepts

Many different vaccine types exist, some are inappropriate for HIV vaccine trials (live-attenuated, killed/inactivated, and toxoid).

Careful selection of vaccine type ensures that participants will not contract HIV from the vaccine.

Many vaccines that stimulate antibody response utilize viral surface proteins or the genes that code for them.

Prior Knowledge Needed

Basic immunology

HIV Structure and Life Cycle

Materials

Student Handouts from: Understanding Vaccines (NIH Publication pp22-36) found at the end of this lesson,
www.niaid.nih.gov/publications/vaccine/undvacc.htm

Vaccine Type Comparison Table

Animations:

- Why is Making an HIV Vaccine so Hard?
<http://www.nwabr.org/education/hivchallenges.html>
- Types of Vaccines
<http://www.nwabr.org/education/vaccinetypes.html>

Prep Time

Time needed to copy Student Handouts

Class Time

1-2 days depending upon the depth of discussions

Timeline

- 1 week before activity:
 - Prepare overheads (if needed) and student handouts

Extensions

- Students can be assigned a particular vaccine type and research in more depth and present to class
- Class can research how each vaccine type has been used in preventing other diseases
- Stop the Virus! HIV Research Strategies Lesson Plan (see Appendix)

Adaptations

- See Day One for IEP and ELL adaptations

Assessment Suggestions

- Monitor answers on table and during discussion
- Evaluate homework paragraphs

Common Misconceptions






- Participants might become infected with HIV from the vaccine
- Positive HIV antibody test results arising after vaccination indicate HIV infection

Lesson 3 Activities

SUMMARY

- 3.1 *Invitation to Learn*
- 3.2 *Vaccine Type Jig-Saw Activity*
- 3.3 *Debrief and Discussion*
- 3.4 *HIV Animations*
- 3.5 *HIV Vaccine Expository Paragraphs*

Symbols

-  — video
-  — discussion
-  — hands-on
-  — on-line or web based
-  — homework

3.1 Invitation to Learn



1. Facilitate discussion with students about what vaccines they have received.
2. Ask students if they know of people who have had disease whose spread is now controlled by vaccinations such as measles, mumps, and rubella (MMR vaccine) and chickenpox (varicella vaccine). While these diseases have not been eradicated fully, they are well-controlled in the U.S. Programs such as those run by the Gates Foundation and the Rotary Club seek to ensure distribution of these vaccines to children in the developing world.
3. Vaccines work by stimulating the immune system to produce antibodies and immune cells that recognize the antigens—foreign proteins—in the vaccine. These antigens are normally found in harmful pathogens (viruses and bacteria) which cause disease. The idea is to prepare the immune system so that if a person is exposed to the pathogen later, the immune system can respond and prevent an illness from developing.

The immune system has two separate arms. One arm is responsible for the cell-mediated response. In this arm, certain kinds of immune cells called killer T cells are produced that can destroy infected cells. These killer T cells are sometimes called CD8+ T cells. Another kind of immune cell is the helper T cell, and these cells help coordinate the other parts of the immune response. Helper T cells are sometimes called CD4+ T cells and are what are measured when people refer to “CD4 cell counts” in HIV infection.

The second arm of the immune response is called the antibody or humoral response. Here, special cells called ‘B cells’ recognize the antigen and produce antibodies that can attach to it. When these antibodies attach to the antigen on the pathogen they “neutralize” it. This means that the pathogen can no longer infect cells and cause infection.

Once T or B cells have been exposed to a foreign antigen, they produce memory cells that remember that antigen. If the pathogen with that antigen enters the body at a later time, these memory cells can respond quickly and strongly to stop any infection and disease. So, for example, if someone who has been vaccinated against measles is exposed to the measles virus, his or her body will immediately recognize the virus and will destroy it. It is possible to download a poster of ongoing trials of preventative HIV vaccines and view all the current HIV trials underway globally online at: <http://www.iavireport.org/trialsdb/>

(from the International Aids Vaccine Initiative, IAVI - www.iavireport.org/vax/primers/vaxprimer11.asp)

3.2 Vaccine Type Jig-Saw Activity



1. Divide students into six groups. Provide readings from “Understanding Vaccines” NIH Publication (included at the end of this lesson). Each group will read about a different vaccine type and discuss the completion of their column on the table.
2. Reorganize class into mixed groups. Be sure that at least one person from each of the six original groups is present.
3. Students will teach their other group members about the vaccine type they have learned about and assist each other in completing their tables. Direct students to actively teach and discuss, not pass papers around to be copied.
4. The Types of Vaccines animation (see Activity 3.4, below) contains much of the information found in the NIH publication and can be used to support this Jig-Saw Activity.

3.3 Debrief and Discussion



1. Facilitate discussion about content covered in jig-saw activity. Be sure to focus on which vaccine types are suitable for development of an HIV vaccine.
2. Lead students to the conclusion that recombinant vector, subunit, and DNA vaccines are the most promising for preventive HIV vaccines.
3. It must be strongly emphasized that some approaches cannot be used for HIV (live attenuated, inactivated/killed). One of the greatest impediments to healthy volunteers’ willingness to participate in preventive HIV vaccine trials is the fear that they will become infected with HIV from the vaccine.
4. Be sure students can connect learning from previous days to today. Discuss specifically why construction of an HIV vaccine is challenging at this time given both the mutation rate of HIV and the targeting of immune system cells. See Activity 3.4, below, for an animation that specifically explores the challenges of making an HIV vaccine.

3.4 HIV Animations

These animations have been created for this lesson and can be used in a number of ways. The teacher may choose to use them as an introduction to the lesson, as concept reinforcement during the lesson, or as individual homework after the lesson.

1. Why is Making an HIV Vaccine so Hard?

This interactive animation explores the scientific challenges faced by researchers in developing an HIV vaccine. It can be found at: <http://www.nwabr.org/education/hivchallenges.html>

2. Types of Vaccines

What are the different types of vaccines? What are the advantages and disadvantages of each type? Which types are being pursued for an HIV vaccine? Found at: <http://www.nwabr.org/education/vaccinetypes.html>

3.5 HIV Vaccine Expository Paragraphs

Ask students to write 1 paragraph about each of the following:

- The different types of vaccines currently available or in research which are most promising for preventing HIV infection
- The challenges associated with creating an HIV vaccine (see homework reading for additional information)

Vaccine Types

Student Handout

NAME _____ Date _____ Period _____

	Live Attenuated	Killed (inactivated)	Subunit (Protein)	Toxoid	DNA Vaccine	Recombinant Vector
Definition and Example						
Advantages						
Disadvantages					Still in experimental stages.	Still in experimental stages (but immune response to the vector can limit use to one to two times.)
Suitable for Preventive HIV vaccine? (Y or N) Provide explanation why.						

Vaccine Types

KEY

	Live Attenuated	Killed (inactivated)	Subunit (Protein)	Toxoid	DNA Vaccine	Recombinant Vector
Definition and Example	Contain a weakened version of the living microbe. Ex: cholera, measles, mumps, rubella, yellow fever	Disease-causing microbe killed with chemicals, heat or radiation. Ex: cholera, flu, hepatitis A, plague, rabies, Japanese encephalitis, Salk polio vaccine	Only the antigens from a microbe are used to stimulate the immune system. Ex: Hepatitis B, pertussis, some pneumonia	A "detoxified" version of a toxin from a bacterium. Ex: tetanus, diphtheria	Give the genes (DNA) that code for antigens directly to cells; those cells then make antigens necessary to stimulate the immune system. Ex: tests include malaria, influenza, herpes, HIV	Uses a virus or bacterium as a carrier ("vector") to deliver DNA to cells. Those cells then make antigens (as with DNA vaccines). Ex: rabies, measles and HIV
Advantages	Good "teachers" of the immune system. They elicit strong cellular and antibody responses. Lifelong immunity with 1-2 doses.	More stable and safer than live vaccines. Doesn't require refrigeration. Easily stored and transported	Low chance of adverse reactions, since most of the microbe is missing. Targeted to very specific parts of the microbe.	Immune system learns to fight off "safe" version of toxin and can then recognize toxic version.	Evokes strong antibody and cellular responses. Relatively easy and inexpensive to produce. Can't cause the disease.	Closely mimics natural infection, which stimulates the immune system well.
Disadvantages	Vaccine could mutate to a virulent form and cause disease. Not good for people with compromised immune systems. Need refrigeration.	Immune response not as strong as for live vaccines. Booster shots required.	Difficult to identify the specific antigens needed for a vaccine.	Only works against bacteria; viruses don't make toxins.	Still in experimental stages.	None given in the reading, but immune response to the vector can limit use to one to two times.
Suitable for Preventive HIV vaccine? (Y or N) Provide explanation why.	No. Too risky to use for a lethal disease that already mutates quickly on its own.	No. There is the possibility of not fully inactivating the virus.	Yes. These have been tried but have been unsuccessful. These would target a humoral immune response (see page 15).	No. Works only with bacteria and HIV is a virus.	Yes. Elicits a "cell-mediated immune response" (see p. 13). Although this is a promising HIV vaccine type, so far the immune responses have been very weak.	Yes. Elicits "cell-mediated immune response" (see p. 13 in handout).

Understanding VACCINES

What They Are How They Work



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of Allergy and Infectious Diseases

Understanding VACCINES

What They Are How They Work



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Introduction

This booklet contains information about vaccines: what they are, how they prevent disease, how they are made and tested, and what vaccine research might achieve in the future. For more in-depth information about vaccines, consult resources at your local library or ask your health care provider.

The Internet can be a valuable source as well. Start with the National Institutes of Health (NIH) Web site at www.nih.gov for information on the broad range of research supported by NIH. For information on vaccine research, a good place to start is www.niaid.nih.gov, the Web site for the National Institute of Allergy and Infectious Diseases (NIAID). Another good source is MEDLINEplus, an information service of the National Library of Medicine www.nlm.nih.gov/medlineplus/. There is also information on vaccines on the Web site of NIAID's Dale and Betty Bumpers Vaccine Research Center, www.vrc.nih.gov. Finally, a list of Web sources about vaccine concerns, myths, and safety issues appears on page 41 of this booklet.

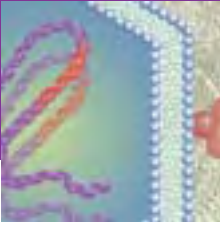
Note: Words in bold are defined in the glossary at the end of this booklet.

What Is a Vaccine?

Chances are you never had diphtheria. You probably don't know anyone who has suffered from this disease, either. In fact, you may not know what diphtheria *is*, exactly. (To find out, see “Diphtheria: Remembering an Old Disease.”) Similarly, diseases like whooping cough (**pertussis**), measles, mumps, and rubella may be unfamiliar to you. In the 19th and early 20th centuries, these illnesses struck hundreds of thousands of people in the United States each year, mostly children, and tens of thousands of people died. These diseases were frightening household words. Today, they are all but forgotten. That change happened largely because of vaccines.

Chances are you've been vaccinated against diphtheria. You even may have been exposed to the bacterium that causes it, but the vaccine prepared your body to fight off the disease so quickly that you were unaware of the infection.

Vaccines take advantage of your body's natural ability to learn how to eliminate almost any disease-causing germ, or **microbe**, that attacks it. What's more, your body “remembers” how to protect itself from the microbes it has encountered before. Collectively, the parts of your body that recall and repel diseases are called the **immune system**. (We'll take a closer look at the immune system in the section “How Vaccines Work.”) Without the immune system, the simplest illness—even the common cold—could quickly turn deadly.



Diphtheria: Remembering an Old Disease

On average, your immune system takes more than a week to learn how to fight off an unfamiliar microbe. Sometimes that isn't soon enough. Stronger microbes can spread through your body faster than the immune system can fend them off. Your body often gains the upper hand after a few weeks, but in the meantime you are sick. Certain microbes are so powerful, or **virulent**, that they can overwhelm or escape your body's natural defenses. In those situations, vaccines can make all the difference.

Traditional vaccines contain either parts of microbes or whole microbes that have been killed or weakened so that they don't cause disease. When your immune system confronts these harmless versions of the germs, it quickly clears them from your body. In other words, vaccines fix the fight but at the same time teach your body important lessons about how to defeat its opponents.

In 1900, diphtheria killed more people in the United States than cancer did. Caused by the toxic bacterium *Corynebacterium diphtheriae*, this upper airway infection often results in a grayish, thick membrane that grows in the throat and obstructs breathing. Other symptoms include fever, hoarseness, and coughing. Most diphtheria deaths resulted not from blocked airways but from the paralyzing **toxin** the bacterium secretes, which can cause the heart or other organs to fail. During the 1990s, an average of only three diphtheria cases among U.S. residents were reported each year.

Vaccine Benefits

You and Your Community

Once your immune system is trained to resist a disease, you are said to be **immune** to it. Before vaccines, the only way to become immune to a disease was to actually get it and, with luck, survive it. This is called **naturally acquired immunity**. With naturally acquired immunity, you suffer the symptoms of the disease and also risk the complications, which can be quite serious or even deadly. In addition, during certain stages of the illness, you may be **contagious** and pass the disease to family members, friends, or others who come into contact with you.

Vaccines, which provide **artificially acquired immunity**, are an easier and less risky way to become immune. Vaccines are one of the few medicines that prevent a disease from occurring in the first place, rather than attempting a cure after the fact. It is much cheaper to prevent a disease than to treat it. According to one analysis, every dollar spent on vaccinating children against **rubella**, or German measles, in the United States saves nearly \$8 in costs associated with treating the disease.

Vaccines protect not only you but everyone around you. If your vaccine-primed immune system nips an illness in the bud, you will be contagious for a much shorter period of time, or perhaps not at all. Similarly, when other people are vaccinated, they are less likely to give the disease to you. So vaccines



*Community immunity:
If a critical number of
people in a community
are vaccinated against
a particular illness, the
entire group becomes
less likely to get the
disease, even those
who are not vaccinated.*

protect not only individuals, but entire communities. That is why vaccines are key to the public health goal of preventing diseases. If a critical number of people within a community are vaccinated against a particular illness, the entire group becomes less likely to get the disease. This protection is called **herd immunity**, or community immunity.

On the other hand, if enough people in a community forgo vaccinations, diseases can reappear. In 1974, the Japanese government stopped vaccinating against pertussis because of public concern about the vaccine's safety and because no one had died from the disease the previous year. Five years later, a pertussis epidemic in Japan sickened 13,000 people and killed 41. In 1989, low vaccination rates allowed a measles outbreak in the United States. The epidemic resulted in more than 55,000 cases of measles and 136 measles-associated deaths.

Harmful Microbes

Vaccines protect against infectious diseases caused by microbes—organisms too small to see without a microscope. Many microbes, such as **bacteria**, are made up of only one cell. **Viruses**, mere snippets of **genetic material** packed inside a membrane or a protein shell, are even smaller.

Humans evolved an immune system because the world is teeming with these organisms. Many of them don't bother us; the bacteria that normally live in your digestive tract are, in fact, beneficial. But other microbes break into and take up residence in your body, using your warmth, nutrients, and tissues to survive and reproduce—and doing you great harm in the process.

Here are a few examples of some of the most serious disease-causing microbes for which vaccines exist.

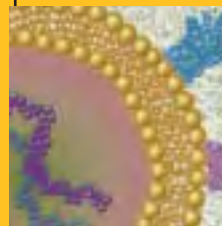
- Variola virus, which causes smallpox, was once the scourge of the world. This virus passes from person to person through the air. A smallpox infection results in fever, severe aches and pains, scarring sores that cover the body, blindness in many cases, and, often, death. There is no effective treatment. In the 18th century, variola virus killed every seventh child born in Russia and every tenth child born in Sweden and France. Although vaccination and outbreak control eliminated smallpox in the United States by 1949, the disease still struck an estimated 50 million people worldwide each year during the 1950s. In 1967, that figure fell to 10 to 15

million because of vaccination. That same year, the World Health Organization (WHO) launched a massive vaccination campaign to rid the world of smallpox—and succeeded. The last natural case of smallpox occurred in Somalia in 1977.

- The highly infectious poliovirus, the cause of polio, once crippled 13,000 to 20,000 people every year in the United States. In 1 out of 200 cases, this virus attacks the spinal cord, paralyzing limbs or leaving victims unable to breathe on their own. In 1954, the year before the first polio vaccine was introduced, doctors reported more than 18,000 cases of paralyzing polio in the United States. Just 3 years later, vaccination brought that figure down to about 2,500. Today, the disease has been eliminated from the Western Hemisphere, and public health officials hope to soon eradicate it from the globe. In 2001, only 537 cases of polio were reported worldwide, according to WHO.
- The toxic bacterium *Bordetella pertussis* likes to set up home in the human respiratory tract, where it causes whooping cough, also known as pertussis. The wracking coughs characteristic of this

Vaccine-Preventable Infectious Diseases

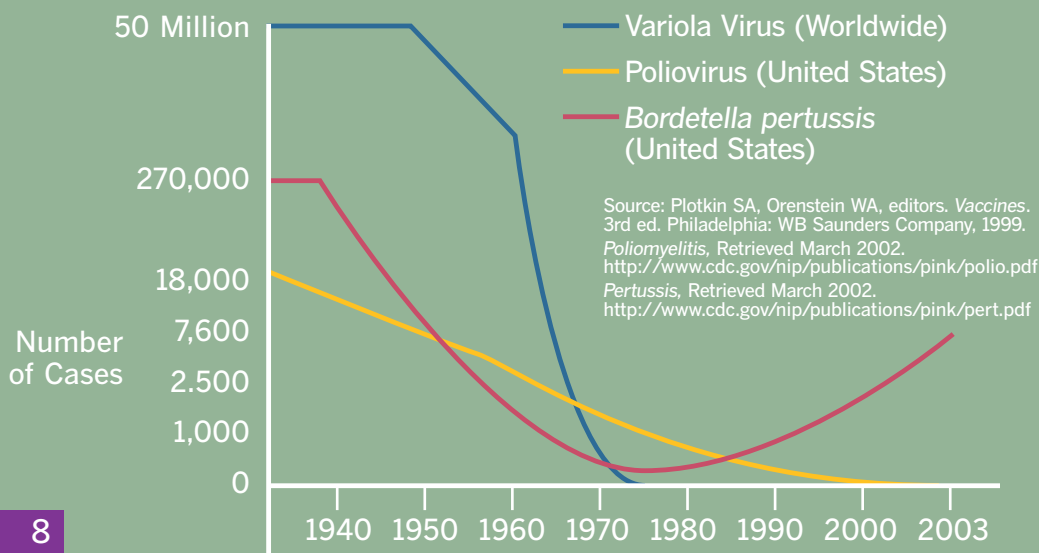
Anthrax
Bacterial meningitis
Chickenpox
Cholera
Diphtheria
Haemophilus influenzae type b
Hepatitis A
Hepatitis B
Influenza
Measles
Mumps
Pertussis
Pneumococcal pneumonia
Polio
Rabies
Rubella
Tetanus
Yellow fever



disease are sometimes so intense the victims, usually infants, vomit or turn blue from lack of air. Before scientists created a vaccine against the bacterium, 115,000 to 270,000 people suffered from whooping cough each year in the United States; 5,000 to 10,000 of those died from it. After the vaccine was introduced in the United States in the 1940s, the number of pertussis cases declined dramatically, hitting a low of about 1,000 in 1976. More recently, pertussis has been on the upswing in the United States, reaching 4,600 cases in 1994 and 7,600 in 2001. The reasons for the increase are complex. The disease strikes in cycles, and the immunity provided by the vaccine wanes over time, leaving some people susceptible in their teen years and as adults.

Other familiar diseases that vaccines protect against include chickenpox, hepatitis A and B, and *Haemophilus influenzae type b* (Hib). Hib causes meningitis, an inflammation of the fluid-filled membranes that surround the brain and spinal cord. Meningitis can be fatal, or it can cause severe disabilities such as deafness or mental retardation. This disease has nearly disappeared among babies and children in the United States since the Hib vaccine became widely used in 1989.

Vaccines at Work



What do cows have to do with vaccines?

The word “vaccine” comes from the Latin word *vaccinus*, which means “pertaining to cows.” What do cows have to do with vaccines? The first vaccine was based on the relatively mild cowpox virus, which infected cows as well as people. This vaccine protected people against the related, but much more dangerous, smallpox virus.



Dr. Edward Jenner

More than 200 years ago, Edward Jenner, a country physician practicing in England, noticed that milkmaids rarely suffered from smallpox. The milkmaids often did get cowpox, a related but far less serious disease, and those who did never became ill with smallpox. In an experiment that laid the foundation for modern

vaccines, Jenner took a few drops of fluid from a skin sore of a woman who had cowpox and injected the fluid into the arm of a healthy young boy who had never had cowpox or smallpox. Six weeks later, Jenner injected the boy with fluid from a smallpox sore, but the boy remained free of smallpox.

Dr. Jenner had discovered one of the fundamental principles of immunization. He had used a relatively harmless foreign substance to evoke an immune response that protected someone from an infectious disease. His discovery would ease the suffering of people around the world and eventually lead to the elimination of smallpox, a disease that killed a million people, mostly children, each year in Europe. By the beginning of the 20th century, vaccines were in use for diseases that had nothing to do with cows—rabies, diphtheria, typhoid fever, and plague—but the name stuck.

How Vaccines Work

The Immune System

To understand how vaccines teach your body to fight infection, let's first look at how the immune system fends off and learns from a naturally occurring infection. Then we'll examine how vaccines mimic this process.

Imagine you are a dock worker on the piers of Philadelphia. The year is 1793. As you are unloading crates of tea and spices from an oceangoing ship, a mosquito bites you on the arm. Unfortunately, this mosquito carries the virus that causes yellow fever, which the mosquito picked up when it bit a sailor who recently returned from Africa. So now you have thousands of yellow fever viruses swarming into your body. In fact, you have become part of an infamous epidemic that will claim the lives of 10 percent of the people in Philadelphia, and all that stands between you and a fatal case of yellow fever is your immune system.

Your immune system is a complex network of cells and organs that evolved to fight off infectious microbes. Much of the immune system's work is carried out by an army of various specialized cells, each type designed to fight disease in a particular way. The invading viruses first run into the vanguard of this army, which includes big, tough, patrolling white blood cells called **macrophages** (literally, "big eaters"). The macrophages grab onto and gobble up as many of the viruses as they can, engulfing them into their blob-like bodies.



A mosquito bite transmits the yellow fever virus to an unsuspecting dock worker. In 1793, a yellow fever epidemic claimed the lives of 10 percent of Philadelphians.

How do the macrophages recognize the yellow fever virus? All cells and microbes wear a “uniform” made up of **molecules** that cover their surfaces. Each of your cells displays marker molecules unique to you. The yellow fever viruses display different marker molecules unique to them. By “feeling” for these markers, the macrophages and other cells of your immune system can distinguish among the cells that are part of your body, harmless bacteria that reside in your body, and harmful invading microbes that need to be destroyed.

The molecules on a microbe that identify it as foreign and stimulate the immune system to attack it are called **antigens**. Every microbe carries its own unique set of antigens. As we will see, these molecules are central to creating vaccines.

Antigens Sound the Alarm

The macrophages digest most parts of the yellow fever viruses but save the antigens and carry them back to the immune system's base camps, also known as **lymph nodes**. Lymph nodes, bean-sized organs scattered throughout your body, are where immune system cells congregate. In these nodes, macrophages sound the alarm by "regurgitating" the antigens, displaying them on their surfaces so other cells can recognize them. In particular, the macrophages show the yellow fever antigens to specialized defensive white blood cells called **lymphocytes**, spurring them to swing into action.

By this time, about 3 days after the mosquito bite, you are feeling feverish and have a headache. You decide to stay home from work.

Lymphocytes: T Cells and B Cells

There are two major kinds of lymphocytes, **T cells** and **B cells**, and they do their own jobs in fighting off your yellow fever. T and B cells head up the two main divisions of the immune system army.

T Cells

T cells function either offensively or defensively. The offensive T cells don't attack the virus directly, but they use chemical weapons to eliminate the cells of your body already infected with the yellow fever virus. (See "How Viruses Work," p. 18) Because they have been "programmed" by their exposure to the virus antigen, these **cytotoxic T cells**, also called killer T cells, can "sense" diseased cells that are harboring the yellow fever virus. The killer T cells latch onto these cells and release chemicals that destroy the infected cells and the viruses inside. The defensive T cells, also called **helper T cells**, defend the body by secreting chemical signals that direct the activity of other immune system cells. Helper T cells assist in activating killer T cells, and helper T cells also stimulate and work closely with B cells.

The work done by T cells is called your cellular or **cell-mediated immune response**.

B Cells

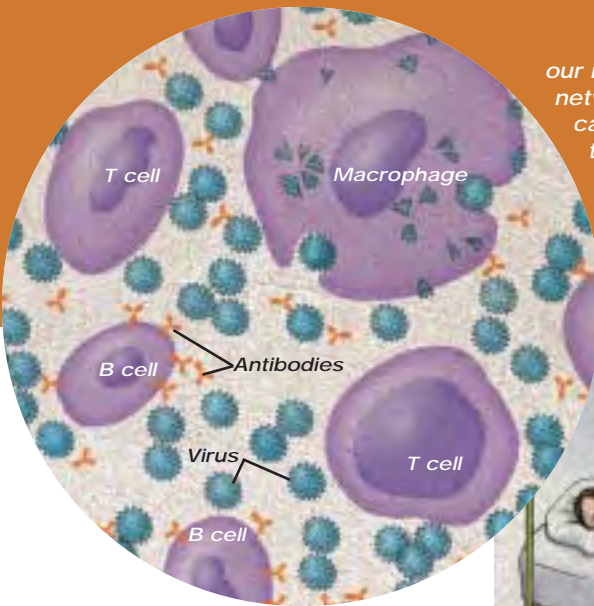
B cells are like weapons factories. They secrete extremely important molecular weapons called **antibodies**. Antibodies usually work by sticking to and coating microbes, and antibodies use the microbe's antigens to grip them. Antibody molecules fit with antigen molecules like pieces of a jigsaw puzzle fit together—if their shapes are compatible, they bind to each other.

Each antibody can usually fit with only one antigen. So your immune system keeps a supply of millions and possibly billions of different antibodies on hand to be prepared for any foreign invader. Your immune system does this by constantly creating millions of new B cells. About 50 million B cells circulate in each teaspoonful of your blood, and almost every B cell—through random genetic shuffling—produces a unique antibody that it displays on its surface.

Before you contracted yellow fever, somewhere in your body B cells were probably circulating with antibodies that, purely by chance, matched antigens from the yellow fever virus. When these B cells came into contact with their matching yellow fever antigen, they were stimulated to divide into many larger cells called **plasma cells** that secreted mass quantities of antibodies to yellow fever virus.

Antibodies in Action

The antibodies secreted by B cells circulate throughout your body until they run into the yellow fever virus. Antibodies attack the viruses that have not yet infected a cell but are lurking in the blood or the spaces between cells. When antibodies gather on the surface of a microbe, it is bad news for the microbe. The microbe becomes generally bogged down, gummed up, and unable to function. Antibodies also signal macrophages and other defensive cells to come eat the microbe. Antibodies are like big, bright signs stuck to a microbe saying, “*Hey, get rid of this!*” Antibodies also work with other defensive molecules that circulate in the blood, called **complement proteins**, to destroy microbes.



our immune system is a complex network of cells and organs. Cells called macrophages gobble up the invading virus and sound the alarm by showing pieces of the invader to T cells and B cells. B cells produce defensive molecules called antibodies that "stick" to the virus.

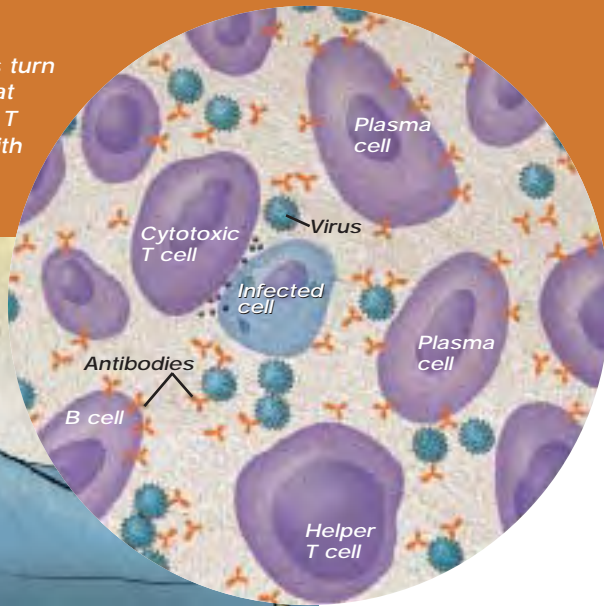


The work of B cells is called the **humoral immune response**, or simply the antibody response. The goal of most vaccines is to stimulate this response. In fact, many infectious microbes can be defeated by antibodies alone, without any help from killer T cells.

Clearing the Infection: Memory Cells and Natural Immunity

While your immune system works to rid your body of yellow fever, you are feeling awful. You lie in bed, too dizzy and weak even to sit up. During the next several days, your skin becomes yellow (or jaundiced) and covered with purple spots. You vomit blood. Your doctor looks grim and tired: He knows that as many as 20 percent of people who contract yellow fever die, and the epidemic is spreading fast through the city.

To overcome the virus, B cells turn into plasma cell “factories” that produce antibodies. Cytotoxic T cells eliminate cells infected with the virus; helper T cells direct the action with chemical signals.



After about a week, however, your immune system gains the upper hand. Your T cells and antibodies begin to eliminate the virus faster than it can reproduce. Gradually, the virus disappears from your body, and you feel better. You get out of bed. Eventually, you go back to working the docks.

If you are bitten by another yellow-fever-infested mosquito, you won't get the disease again. You won't even feel slightly sick. You have become immune to yellow fever because of another kind of immune system cell: **memory cells**. After your body eliminated the disease, some of your yellow-fever-fighting B cells and T cells converted into memory cells. These cells will circulate through your body for the rest of your life, ever watchful for a return of their enemy. Memory B cells can quickly divide into plasma cells and make more yellow fever antibody if needed. Memory T cells can divide and grow into a yellow-fever-fighting army. If that virus shows up in your body again, your immune system will act swiftly to stop the infection.

How Vaccines Mimic Infection

Vaccines teach your immune system by mimicking a natural infection. To show how, let's jump ahead to the 21st century. Yellow fever is no longer a problem in the United States, but you are a relief worker stationed in a part of the world where the disease still occurs, and the Centers for Disease Control and Prevention (CDC) recommends vaccination prior to your departure.

The yellow fever vaccine, first widely used in 1938, contains a weakened form of the virus that doesn't cause disease or reproduce very well. (More on how vaccine makers do that a little later.) This vaccine is injected into your arm. Your macrophages can't tell the vaccine viruses are duds. The macrophages gobble up the viruses as if they were dangerous and, in the lymph nodes, present yellow fever antigen to T and B cells. The alarm is sounded, and your immune system swings into action. Yellow-fever-specific T cells rush out to meet the foe. B cells secrete yellow fever antibodies. But the battle is over quickly. The weakened viruses in the vaccine can't put up much of a fight. The mock infection is cleared, and you are left with a supply of memory T and B cells to protect you against yellow fever, should a mosquito carrying the virus ever bite you.

Next, we'll take a closer look at different types of vaccines—not all of them employ killed or weakened microbes—and learn how each type works.

How Viruses Work

Viruses such as the yellow fever virus are tiny microbes made up of a small number of genes encased in a membrane or protein shell. If you were the size of a cell, a virus would look like a burr attached to your pants leg—a small, round object covered with tiny bristles.

Like burrs, viruses stick to cells. Then they inject their genetic material inside the cells. Once inside, the virus genes take over the cells' resources and molecular machinery, forcing the cells to make more viruses. The newly formed viruses “bud” or are released from the surface of the cells and drift off to infect new cells. Cells infected with viruses can't function properly and usually die. Many are eliminated by killer T cells.

Different Types of Vaccines

Imagine that a new infectious disease emerges from some obscure part of the world and begins to spread across the globe. The infectious agent jumps easily from person to person through the air, and it attacks the lungs, causing terrible coughing, fever, pneumonia, and sometimes paralysis of the respiratory system. Scientists quickly determine that disease *X* is caused by a new species of toxic bacterium. They call it “bacterium *X*.” Unfortunately, bacterium *X* is difficult to fight because it resists most antibiotics.

Everyone agrees a vaccine against bacterium *X* is needed, but how would scientists go about creating one?

First, they would carefully study bacterium *X*. They would figure out what nutrients it requires. They would examine how it damages lung tissue. Geneticists would analyze *X*’s genes. Immunologists would explore how the immune system responds to bacterium *X* and why the body sometimes fails to fight off this microbe. They would identify antigens from *X* that best stimulate the immune system. Other scientists would discover the toxin secreted by bacterium *X*.

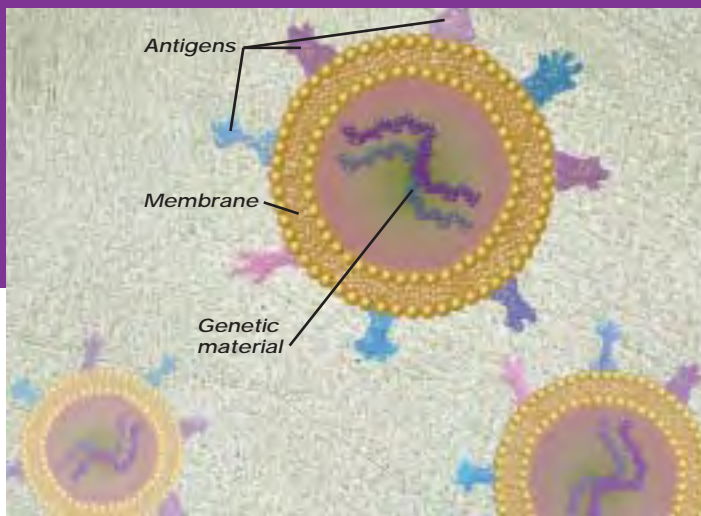
Once scientists had some basic information about *X*, they could begin designing vaccines that might work against it. Following are some of the options that researchers might pursue. They will give you an idea of the main types of vaccine strategies.

Live, Attenuated Vaccines

Some scientists might explore the possibility of a **live, attenuated vaccine** against X. These vaccines contain a version of the living microbe that has been weakened in the lab so it can't cause disease. This weakening of the organism is called **attenuation**. Because a live, attenuated vaccine is the closest thing to an actual infection, these vaccines are good “teachers” of the immune system: They elicit strong cellular and antibody responses, and often confer lifelong immunity with only one or two doses.

Despite the advantages of live, attenuated vaccines, there is a downside. It is the nature of living things to change, or **mutate**, and the organisms used in live, attenuated vaccines are no different. The remote possibility exists that the attenuated bacteria X in the vaccine could revert to a virulent form and cause disease. For their own protection, people with compromised immune systems—such as people with cancer or people infected with the human immunodeficiency virus (HIV)—usually are not given live vaccines.

Live, attenuated vaccines are relatively easy to create for viruses. Viruses are simple microbes containing a small number of genes, and scientists can therefore more readily control their characteristics. Viruses often are attenuated by growing generations of them in specific types of cells that make it hard for the virus to reproduce. This hostile environment takes the fight out of viruses: As they evolve to adapt to their new environment, they become weaker with respect to their natural host, human beings.



Live, attenuated vaccines use a weakened version of the microbe that has been changed to reduce or eliminate its potential to cause disease. This image shows the live microbe's antigens, membrane, and genetic material.

Live, attenuated vaccines are more difficult to create for bacteria. Bacteria have thousands of genes and thus are much harder to control. However, scientists working on a live vaccine for bacterium X might be able to use **recombinant DNA technology** to remove several key genes from X that allow it to grow and cause disease, thereby creating an attenuated X that could be used in a live vaccine. This has been done for the bacterium that causes cholera, *Vibrio cholerae*, although the live cholera vaccine has not been licensed in the United States.

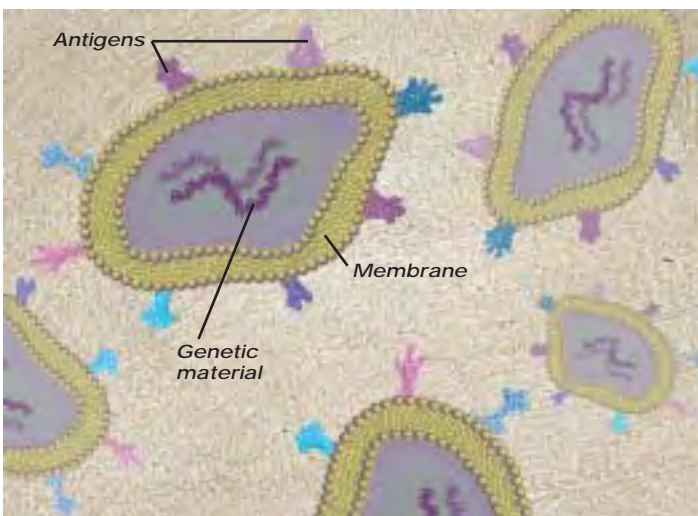
Live, attenuated vaccines usually need to be refrigerated to stay potent. If the X vaccine needs to be shipped overseas and stored by health care workers in developing countries that lack widespread refrigeration, a live vaccine may not be the best choice.

Inactivated or “Killed” Vaccines

An **inactivated vaccine** might be better for bacterium X. Scientists produce inactivated vaccines by killing the disease-causing microbe with chemicals, heat, or radiation. Such vaccines are more stable and safer than live vaccines: The dead microbes can’t mutate back to their disease-causing state. Inactivated vaccines usually don’t require refrigeration, and they can be easily stored and transported in a freeze-dried form, which makes them accessible to people in developing countries.

Most inactivated vaccines, however, stimulate a weaker immune system response than do live vaccines. So it would likely take several additional doses, so-called **booster shots**, to maintain a person’s immunity to bacterium X. This quality could be a drawback in areas where people don’t have regular access to health care and can’t get their shots on time.

Inactivated or “killed” vaccines contain microbes that have been inactivated with chemicals, heat, or radiation. The microbe’s antigens, membrane, and genetic material are still present.



Subunit Vaccines

Scientists would certainly look into the possibility of a **subunit vaccine** for *X*. Subunit vaccines dispense with the entire microbe and use just the important parts of it: the antigens that best stimulate the immune system. In some cases, these vaccines use epitopes—the very specific parts of the antigen that antibodies or T cells recognize and bind to. Because subunit vaccines contain only the essential antigens and not all the other molecules that make up the microbe, the chances of adverse reactions to the vaccine are lower.

Subunit vaccines can contain anywhere from 1 to 20 or more antigens. Of course, identifying which antigens from bacterium *X* best stimulate the immune system would be a tricky, time-consuming process. Once scientists did that, however, they could make subunit vaccines against *X* in one of two ways. They could grow bacterium *X* in cultures, then use chemicals to break it apart and gather the important antigens.

Subunit vaccines contain just the antigens of the microbe that best stimulate the immune system. This image depicts antigens that have been separated from the body of the microbe for use in a subunit vaccine.

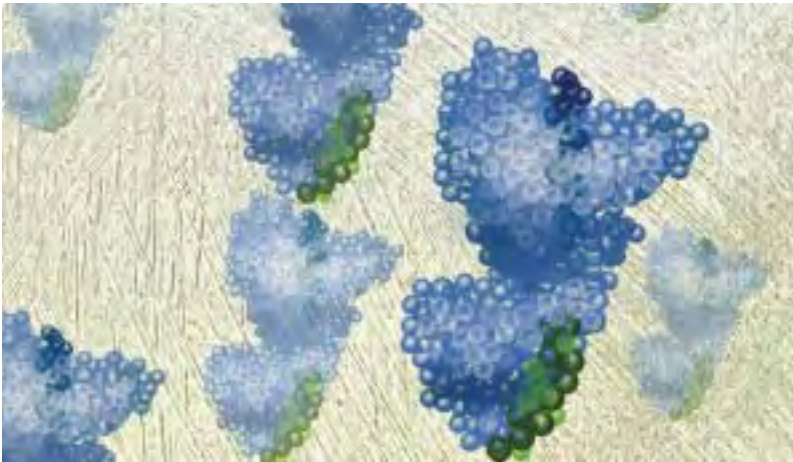


They also could manufacture the antigen molecules from *X* using recombinant DNA technology. Vaccines produced this way are called **recombinant subunit vaccines**. Such a vaccine has been made for the hepatitis B virus. Scientists inserted hepatitis B genes that code for important antigens into common baker's yeast. The yeast then produced the antigens, which the scientists collected and purified for use in the vaccine.

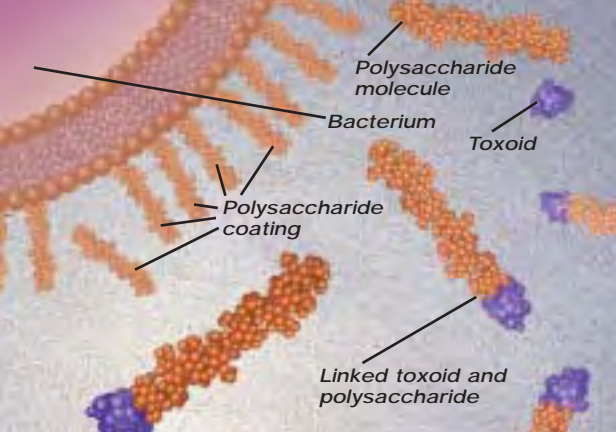
Toxoid Vaccines

Because our imaginary bacterium *X* secretes a toxin, or harmful chemical, a **toxoid vaccine** might work against it. These vaccines are used when a bacterial toxin is the main cause of illness. Scientists have found they can inactivate toxins by treating them with **formalin**, a solution of formaldehyde and sterilized water. Such “detoxified” toxins, called **toxoids**, are safe for use in vaccines.

When the immune system receives a vaccine containing a harmless toxoid, it learns how to fight off the natural toxin. The immune system produces antibodies that lock on to and block the toxin.



Harmless toxoid molecules (artist's representation) are used in toxoid vaccines to immunize and protect people against harmful toxins secreted by some microbes.



Conjugate vaccines link antigens or toxoids to the polysaccharide or sugar molecules that certain bacteria use as a protective coating, thereby allowing the immune system to recognize and attack these “disguised” bacteria. A conjugate vaccine contains the molecules shown in the foreground. The bacterium, part of which is shown in the upper left background, is not part of the vaccine.

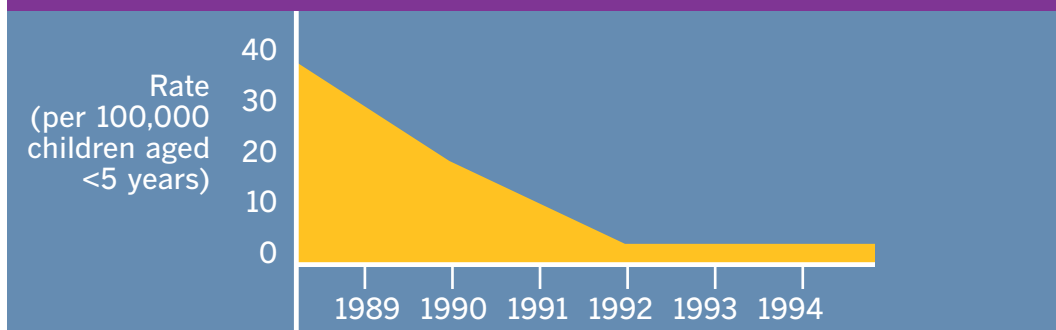
Conjugate Vaccines

If bacterium *X* possessed an outer coating of sugar molecules called **polysaccharides**, as many harmful bacteria do, researchers would try making a **conjugate vaccine** for *X*. Polysaccharide coatings disguise a bacterium’s antigens so that the immature immune systems of infants and younger children can’t recognize or respond to them. Conjugate vaccines, a special type of subunit vaccine, get around this problem.

When making a conjugate vaccine, scientists link antigens or toxoids from a microbe that an infant’s immune system can recognize to the polysaccharides. The linkage helps the immature immune system react to polysaccharide coatings and defend against the disease-causing bacterium.

The vaccine that protects against Hib is a conjugate vaccine.

Incidence rate of invasive *Haemophilus influenzae* type b (Hib) disease among children aged <5 years, United States, 1989-1994



Source: Summary of Notifiable Diseases, United States, 1995. CDC Morbidity and Mortality Weekly Report.

DNA Vaccines

Once the genes from bacterium *X* had been analyzed, scientists could attempt to create a **DNA vaccine** against it.

Still in the experimental stages, these vaccines show great promise, and several types are being tested in humans. DNA vaccines take immunization to a new technological level. These vaccines dispense with both the whole organism and its parts and get right down to the essentials: the microbe's genetic material. In particular, DNA vaccines use the genes that code for those all-important antigens.

Researchers have found that when the genes for a microbe's antigens are introduced into the body, some cells will take up that DNA. The DNA then instructs those cells to make the antigen molecules. The cells secrete the antigens and display them on their surfaces. In other words, the body's own cells become vaccine-making factories, creating the antigens necessary to simulate the immune system.

A DNA vaccine against *X* would evoke a strong antibody response to the free-floating *X* antigen secreted by cells, and the vaccine also would stimulate a strong cellular response against the *X* antigens displayed on cell surfaces. The DNA vaccine couldn't cause the disease because it wouldn't contain bacterium *X*, just copies of a few of its genes. In addition, DNA vaccines are relatively easy and inexpensive to design and produce.

So-called “**naked DNA vaccines**” inject the DNA directly into the body. These vaccines can be administered with a needle and syringe or with a needleless device that uses high-pressure gas to shoot microscopic gold particles coated with DNA directly into cells. Sometimes, the DNA is mixed with molecules that facilitate its uptake by the body's cells. Naked DNA vaccines being tested in humans include those against malaria, influenza, herpes, and HIV.

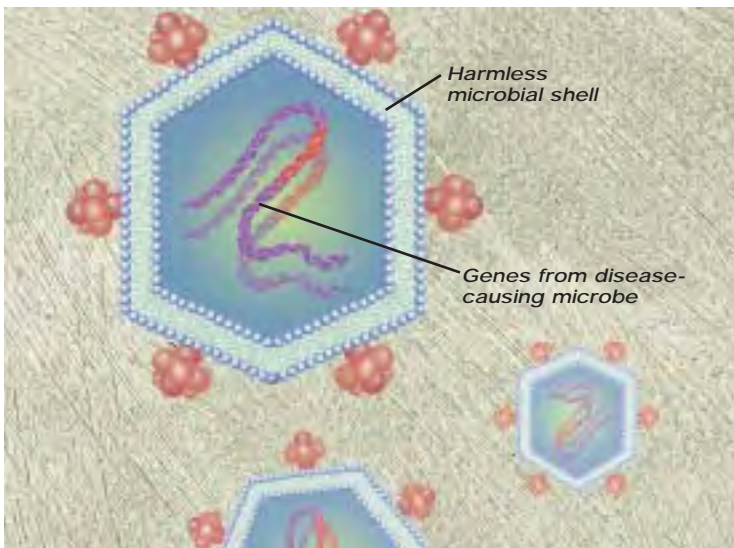


DNA vaccines use a microbe's genetic material; in particular, the genes that code for important antigens. The DNA in these vaccines is a circular form known as a plasmid.

Recombinant Vector Vaccines

Recombinant vector vaccines could be another possible strategy against bacterium X. These experimental vaccines are similar to DNA vaccines, but they use an attenuated virus or bacterium to introduce microbial DNA to cells of the body. “**Vector**” refers to the virus or bacterium used as the carrier.

In nature, viruses latch on to cells and inject their genetic material into them (see “How Viruses Work”). In the lab, scientists have taken advantage of this process. They have figured out how to take the roomy **genomes** of certain benign or attenuated viruses and insert portions of the genetic material from other microbes into them. The carrier viruses then ferry that microbial DNA to cells. Recombinant vector vaccines closely mimic a natural infection and therefore do a good job of stimulating the immune system.



Recombinant vector vaccines use the harmless shell of one microbe to deliver genetic material of a disease-causing microbe. The genetic material contains the code for making vaccine antigen inside some of the body's cells, using those cells as “factories.”

Attenuated bacteria also can be used as vectors. . In this case, the inserted genetic material causes the bacteria to display the antigens of other microbes on its surface. In effect, the harmless bacterium mimics a harmful microbe, provoking an immune response. .

Researchers are working on both bacterial- and viral-based recombinant vector vaccines for HIV,. rabies, and measles.

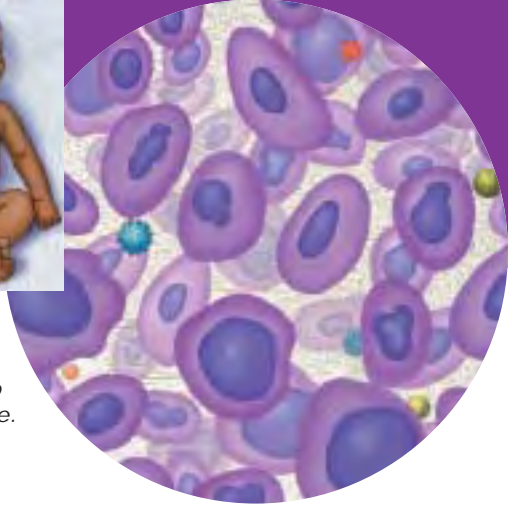
Many Vaccines Against Bacterium X?

The search for a vaccine against bacterium X would likely result in several promising . candidate vaccines. (Researchers working on an . HIV vaccine, for example, have developed dozens. of experimental vaccines at various stages of testing,. including subunit vaccines, DNA vaccines, and recombinant vector vaccines.) But because of the . rigorous research and testing each vaccine must go through, it would take years, probably decades,. before an X vaccine was approved for use in the United States. In the next section, we'll take a closer look at how vaccines are tested and regulated.

Combination Vaccines



An infant's immune system contains billions of circulating B and T cells capable of responding to millions of different antigens at once.



Some vaccines come in combinations. Most of us are familiar with the DTP (diphtheria, tetanus, pertussis) and the MMR (measles, mumps, rubella) vaccines children in the United States receive.

Combination vaccines reduce visits to the doctor, saving time and money and sparing children extra needlesticks. Without combination vaccines, parents would have to bring their children in for each vaccination and all its boosters, and the chances would be greater that kids would miss their shots. Missed shots put children, as well as their communities, at risk.

Concerned parents have wondered whether combination vaccines might overwhelm or weaken a child's immune system, but the immune system contains billions of circulating B and T cells capable of responding to millions of different antigens at once. Because the body constantly replenishes these cells, a healthy immune system cannot be "used up" or weakened by a vaccine. According to one published estimate, infants could easily handle 10,000 vaccines at once.

For more sources of information on this topic, see "Vaccine Concerns, Myths, and Safety Issues on the Web."

Adjuvants and Other Vaccine Ingredients

Adjuvants are ingredients added to a vaccine to improve the immune response it produces. Researchers are studying many types of adjuvants, but the only type licensed for human use in the United States so far are the so-called “alum” adjuvants, which are composed of aluminum salts. These compounds bind to the antigens in the vaccine, help retain antigens at the site of injection, and help deliver antigens to the lymph nodes, where immune responses to the antigens are initiated. The slowed release of antigens to tissue around the injection site and the improved delivery of antigens to the lymph nodes can produce a stronger antibody response than can the antigen alone. Alum adjuvants are also taken up by cells such as macrophages and help these cells better present antigens to lymphocytes.

In addition to adjuvants, vaccines may contain antibiotics to prevent bacterial contamination during manufacturing, preservatives to keep multi-dose vials of vaccine sterile after they are opened, or stabilizers to maintain a vaccine’s potency at less-than-optimal temperatures.

Some Vaccine Types and Diseases They Protect Against

Vaccine Type	Disease
	Live, attenuated vaccines Measles, mumps, rubella, polio (Sabin vaccine), yellow fever
	Inactivated or "killed" vaccines Cholera, flu, hepatitis A, Japanese encephalitis, plague, polio (Salk vaccine), rabies
	Toxoid vaccine Diphtheria, tetanus
	Subunit vaccines Hepatitis B, pertussis, pneumonia caused by <i>Streptococcus pneumoniae</i>
	Conjugate vaccines <i>Haemophilus influenzae</i> type B, pneumonia caused by <i>Streptococcus pneumoniae</i>
	DNA vaccines In clinical testing
	Recombinant vector vaccines In clinical testing

Advantages

Produce a strong immune response

Often give lifelong immunity with one or two doses

Safer and more stable than live vaccines

Don't require refrigeration: more easily stored and transported

Teaches the immune system to fight off bacterial toxins

Targeted to very specific parts of the microbe

Fewer antigens, so lower chance of adverse reactions

Allow infant immune systems to recognize certain bacteria

Produce a strong antibody and cellular immune response

Relatively easy and inexpensive to produce

Closely mimic a natural infection, stimulating a strong immune response

Disadvantages

Remote possibility that the live microbe could mutate back to a virulent form

Must be refrigerated to stay potent

Produce a weaker immune response than live vaccines

Usually require additional doses, or booster shots

When developing a new vaccine, identifying the best antigens can be difficult and time consuming

Still in experimental stages

Still in experimental stages

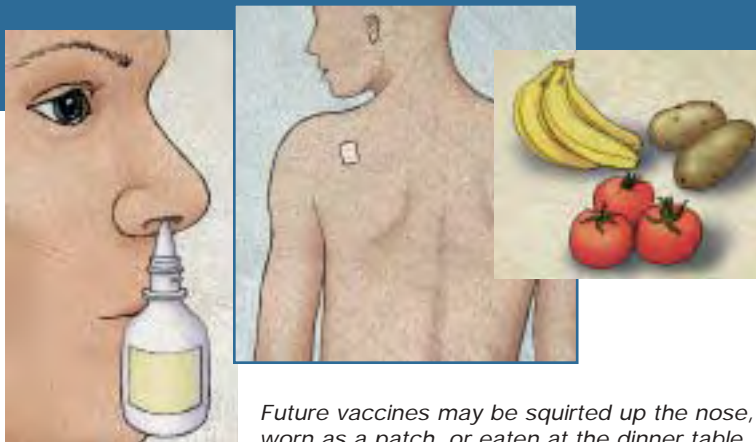
Vaccines of the Future

One day, vaccines may be eaten at the dinner table, applied via a skin patch, or squirted up your nose rather than administered as a shot in the arm—or elsewhere.

Scientists have shown that potatoes genetically engineered to produce an *Escherichia coli* antigen safely triggered an immune response to this bacterium in people who ate small pieces of the potatoes. Similarly, some researchers are modifying bananas to protect against Norwalk virus, a common cause of diarrhea, while other scientists are developing tomatoes containing a vaccine against hepatitis B. Researchers have even engineered a mouse that secretes an experimental malaria vaccine in its milk, and they hope to repeat the experiment with a goat.

Although still a long way off, **edible vaccines** such as these would make it cheaper and easier to immunize people against diseases, especially in developing countries where storing and administering vaccines is often difficult.

The same would be true of vaccines given through a skin patch. Recent tests have shown that a tetanus toxoid administered to mice through a skin patch produces a strong antibody response that protects mice against a lethal dose of the tetanus bacterium. Preliminary tests in humans have established that a skin patch vaccine induces a robust antibody response against *E. coli*, with no serious adverse reactions.



Future vaccines may be squirted up the nose, worn as a patch, or eaten at the dinner table.

A promising live, attenuated flu vaccine might eventually do away with the old flu shot. This vaccine is squirted from a spray bottle into one's nose. This method not only eliminates the needle—making it easier to administer to children—it also closely mimics how the flu virus actually enters your body, which may produce a better immune response. The vaccine, created with NIAID support, has been extensively tested in people and has been shown to work well. In June 2003, the **Food and Drug Administration (FDA)** licensed this vaccine for use in healthy adults and children ages 5 through 49. (For more on the vaccine approval process, see “Making Safe Vaccines,” p. 36)

Making Safe Vaccines

No vaccine is perfectly safe or effective. Each person's immune system works differently, so occasionally a person will not respond to a vaccine. Very rarely, a person may have a serious adverse reaction to a vaccine, such as an allergic reaction that causes hives or difficulty breathing. But serious reactions are reported so infrequently—on the order of 1 in 100,000 vaccinations—that they can be difficult to detect and confirm. More commonly, people will experience temporary side effects such as fever, soreness, or redness at the injection site. These side effects are, of course, much preferable to coming down with the illness.

To make vaccines as safe as possible, FDA requires extensive research and testing before allowing a vaccine to be licensed for general use. The time between discovery of a disease agent and production of a widely available vaccine has been as long as 50 years. Today, with improved technology and research methods, the length of time from basic research to availability of a licensed vaccine can sometimes be reduced. If a vaccine is approved, FDA and other government agencies continue to monitor it for safety. Following are some of the key measures taken to ensure vaccines are safe.

Lab and Animal Testing

Also known as **preclinical testing**, this testing is required before the vaccine can be given to people. Researchers test candidate vaccines in cell cultures and in animals such as mice, rabbits, guinea pigs, or monkeys. If the vaccine appears promising in these preclinical experiments, it may go on to be carefully tested in people.



This vaccine researcher uses a multi-channel pipetter to quickly prepare many biological samples for analysis.

Investigational New Drug Application

Before any vaccine candidate can be tested—much less widely used—in people, its sponsors must submit an Investigational New Drug (IND) application to FDA. This application must explain how the vaccine works, describe how it is manufactured, present all preclinical safety data, and propose a plan for human testing. The IND must also demonstrate the vaccine has passed a series of tests for purity and safety.

Studies in Humans

Once vaccine developers have FDA approval for testing their construct in human volunteers, they begin cautiously, starting with a very small **clinical trial** and progressing through three phases of ever-larger studies. (See “Volunteering for a Clinical Study,” p. 39) Phase I studies enroll 20 or fewer people and primarily test for safety. Phase II studies involve 50 to several hundred people.

These studies continue to test for safety as well as try to determine the best dosage and to gather preliminary data on a vaccine's effectiveness. Phase III studies, designed for thorough testing of the vaccine's power to protect against illness, include thousands of people.

FDA License

The application to FDA for a license to market a vaccine is called a Biologics License Application, (BLA). This application must provide the results of all relevant human studies, describe all manufacturing and testing methods, and show the results of safety and purity tests on batches of the vaccine intended for public use. A BLA must also demonstrate that the vaccine manufacturers comply with all government standards, including those for production facilities, personnel, equipment, packaging, and record-keeping. At this stage, FDA also inspects the manufacturing facility.

The BLA is reviewed first by a team of FDA experts, then by an advisory committee made up of scientists, physicians, statisticians, and consumer representatives. The committee votes on whether or not to recommend that FDA approve the vaccine.

Follow-up Surveillance

Once a vaccine is on the market, FDA continues to monitor its safety. FDA periodically inspects the manufacturing facility, and it tests samples of the vaccine for potency, safety, and purity for as long as the vaccine is made. The manufacturer must also safety test each batch, or lot, of the vaccine.

In addition, most licensed vaccines continue to be evaluated with very large studies that look at tens of thousands of people who have received the vaccine. These **Phase IV** studies try to pick up rare or delayed adverse reactions that might not have been apparent in the smaller studies that led to licensure.

Finally, FDA and CDC gather information on licensed vaccines through the **Vaccine Adverse Events Reporting System (VAERS)**. Anyone—doctors, patients, parents—can report adverse vaccine reactions to VAERS. FDA reviews weekly VAERS reports for each lot of vaccine in use, searching for anything unusual.

Volunteering for a Clinical Study

Clinical trials rely entirely on volunteers—people who contribute their time and energy for the advancement of science and improved health care for all. Tens of thousands of volunteers of all ages and walks of life have participated in these trials.

Typically, a volunteer in a vaccine study agrees to be given the vaccine (or a look-alike placebo), visits a clinic frequently for evaluation, undergoes medical tests, and provides blood samples that researchers will use to assess the vaccine. Because no one knows yet how well the vaccine works, participants should not expect the experimental vaccine to protect them against disease.

Volunteers are fully informed about how the study will be conducted, its potential risks and benefits, and measures taken to ensure their safety and privacy. To find out more about clinical studies, visit **www.clinicaltrials.gov**.

NIAID Vaccine Research

We still need new or improved vaccines to protect against many important disease-causing microbes. Some of these microbes, such as the parasites that cause malaria, have been around forever but have so far eluded scientists' best efforts. Others are newly emerged microbes that researchers are still learning about, such as HIV or West Nile virus. Malaria, HIV/AIDS, and other diseases such as tuberculosis cause immense suffering, especially in developing countries. For this reason, NIAID has made finding vaccines for these diseases a top priority. Another NIAID priority is creating vaccines against the most dangerous potential agents of bioterrorism. Following are some of the vaccine research efforts conducted or supported by NIAID.

Vaccine and Treatment Evaluation Units

NIAID revolutionized the cumbersome, piecemeal approach to vaccine studies by establishing a network of Vaccine and Treatment Evaluation Units (VTEUs) in 1962. These testing sites are based at leading university medical research centers, public health departments, and community clinics across the country. The network can rapidly recruit volunteers for clinical studies, and it played a major role in the studies that led to the licensing of vaccines for Hib and for a new subunit pertussis vaccine. VTEU investigators have also tested and advanced vaccines for pneumonia, influenza, cholera, whooping cough, malaria, and tuberculosis. More recently, they have been called upon to conduct critical studies of smallpox vaccines.

Vaccine Concerns, Myths, and Safety Issues on the Web

Now that vaccines have virtually eliminated many once-feared diseases, the possibility of vaccine side effects or adverse reactions loom larger in some people's minds than the diseases that vaccines prevent, especially now that children routinely receive 11 vaccines by age 2. Most parents today have never seen a case of diphtheria or measles, and some wonder why their children must receive so many shots. Rumors and misinformation about vaccine safety abound. For example, many parents are concerned that multiple vaccines may weaken or overwhelm an infant's immune system or that certain vaccines may cause autism, multiple sclerosis, or diabetes.

For more information on vaccine concerns, myths, and safety issues, try the following sources, which offer current information on these issues.

CDC National Immunization Program

www.cdc.gov/nip

1-800-232-2522

American Council on Science and Health

www.acsh.org

212-362-7044

Immunization Safety Review Committee of the Institute of Medicine

www.iom.edu/imsafety

202-334-1342

Johns Hopkins University Institute of Vaccine Safety

www.vaccinesafety.edu

National Network for Immunization Information

www.immunizationinfo.org

1-877-341-6644

National Partnership for Immunization

www.partnersforimmunization.org

703-836-6110 or 301-656-0003

Vaccine Education Center at The Children's Hospital of Philadelphia

www.vaccine.chop.edu

215-590-9990

HIV Vaccine Trials Network

In 1988, the first HIV vaccine trial in the world began at NIH. That same year, NIAID established the AIDS Vaccine Evaluation Group (AVEG), a network of testing centers at leading universities in the United States devoted exclusively to HIV vaccines. In 1999, NIAID built upon AVEG by creating the HIV Vaccine Trials Network (HVTN), a web of sites in the United States and abroad that test candidate HIV vaccines in clinical trials. The HVTN includes sites in Africa, Asia, South America, and the Caribbean. The international sites allow for studies that examine differences in genetic makeup, nutrition, access to health care, and HIV subtypes in various populations, crucial factors to creating a vaccine that is effective worldwide.

With millions of new HIV infections and deaths from HIV/AIDS occurring worldwide each year—an estimated 5.3 million new infections and 21.8 million deaths in 2000, for example—researchers are working fervently to find a vaccine. A vaccine will be the best tool for halting the spread of HIV infection.

Vaccine Research Center

In 2000, NIAID established the Dale and Betty Bumpers Vaccine Research Center (VRC) on its campus in Bethesda, Maryland, where researchers are working on vaccines against microbes such as HIV, smallpox virus, and Ebola virus. With a roster of about 150 scientists and support staff, the VRC is designed to be a facility where vaccines can be developed from initial concept to final product. The center conducts basic research on microbes and the immune system's response to them, designs candidate vaccines, and tests them in preclinical and clinical trials. VRC scientists also collaborate with researchers around the world in academic, clinical, and industrial laboratories.

Biodefense Vaccines

NIAID is working on new and improved vaccines against possible agents of bioterrorism. To protect citizens from bioterrorist attacks, these vaccines must be safe, easy to administer, and fast-acting—even to the point of providing immunity shortly *after* exposure to the microbe. Researchers supported by NIAID are developing improved vaccines against smallpox, anthrax, plague, and many other possible agents of bioterrorism.

Intramural Vaccine Research

More than 120 scientists at NIAID laboratories in Bethesda, Maryland, and Hamilton, Montana, are studying infectious microbes and the human immune response to them. Many of these scientists are directly involved in vaccine research and have been instrumental in developing currently licensed vaccines, including those for hepatitis A and B. To give just a few examples of intramural vaccine research, the Malaria Vaccine Development Unit, part of the Laboratory of Parasitic Diseases, has been studying the malaria parasite to identify possible antigens for vaccines, and the unit has tested experimental vaccines in Phase I trials. In addition, researchers in the Laboratory of Viral Diseases are working on candidate HIV vaccines.

Conclusion

Vaccines are crucial to maintaining public health: They are a safe, cost-effective, and efficient way to prevent sickness and death from infectious diseases. Vaccines have led to some of the greatest public health triumphs ever, including the eradication of naturally occurring smallpox from the globe and the near-eradication of polio.

In recent years, researchers have increased their understanding of the immune system and how it fights off harmful microbes. Scientists working on vaccines also have advanced technology to draw on, including recombinant DNA technology and the ability to “read” and analyze the genomes of disease-causing organisms. This new knowledge and technology promises to usher in a renaissance in the already vital field of vaccinology. Scientists are hard at work creating improved vaccines, designing new vaccine strategies, and identifying new vaccines candidates to prevent diseases for which no vaccines currently exist.

Glossary

adjuvants—substances sometimes included in a vaccine formulation to enhance the immune-stimulating properties of a vaccine.

antibodies—molecules produced by a B cell in response to an antigen. When an antibody attaches to an antigen, it helps destroy the microbe bearing the antigen.

antigen—a molecule on a microbe that identifies it as foreign to the immune system and stimulates the immune system to attack it.

artificially acquired immunity—immunity provided by vaccines, as opposed to naturally acquired immunity, which is acquired from exposure to a disease-causing organism.

attenuation—the weakening of a microbe so that it can be used in a live vaccine.

B cells—white blood cells crucial to the immune defenses. Also known as B lymphocytes, they come from bone marrow and develop into blood cells called plasma cells, which are the source of antibodies.

bacteria—microscopic organisms composed of a single cell and lacking a defined nucleus and membrane-enclosed internal compartments.

booster shots—supplementary doses of a vaccine, usually smaller than the first dose, that are given to maintain immunity.

cell-mediated immune response (also called cellular immune response)—immune protection provided by the direct action of immune cells (as distinct from that provided by molecules such as antibodies).

clinical trial—an experiment that tests the safety and effectiveness of a vaccine or drug in humans.

complement proteins—molecules that circulate in the blood whose actions “complement” the work of antibodies. Complement proteins destroy antibody-coated microbes.

conjugate vaccine—a vaccine in which proteins that are easily recognizable to the immune system are linked to the molecules that form the outer coat of disease-causing bacteria to promote an immune response. Conjugate vaccines are designed primarily for very young children because their immune systems can not recognize the outer coats of certain bacteria.

contagious—able to transmit disease to other people.

cytotoxic T cells (also called killer T cells)—a subset of T cells that destroy body cells infected by viruses or bacteria.

DNA vaccine (also called naked DNA vaccine)—a vaccine that uses a microbe’s genetic material, rather than the whole organism or its parts, to simulate an immune response.

edible vaccines—foods genetically engineered to produce antigens to specific microbes and safely trigger an immune response to them.

Food and Drug Administration (FDA)—the Federal agency that approves and licenses vaccines and drugs.

formalin—a solution of water and formaldehyde, used in toxoid vaccines to inactivate bacterial toxins.

genetic material—molecules of deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) that carry the directions that cells or viruses use to perform a specific function, such as making a particular protein molecule.

genomes—all of an organism's genetic material. A genome is organized into specific functional units called genes.

***Haemophilus influenzae* type b (Hib)**—a bacterium found in the respiratory tract that causes acute respiratory infections, including pneumonia, and other diseases such as meningitis.

helper T cells—a subset of T cells that function as messengers. They are essential for turning on antibody production, activating cytotoxic T cells, and initiating many other immune functions.

herd immunity (also called community immunity)—the resistance to a particular disease gained by a community when a critical number of people are vaccinated against that disease.

humoral immune response (also called antibody response)—immune protection provided by B cells, which secrete antibodies in response to antigen (as distinct from that provided by the direct action of immune cells, or the cellular immune response).

immune—having a high degree of resistance to or protection from a disease.

immune system—a collection of specialized cells and organs that protect the body against infectious diseases.

inactivated vaccine (also called “killed” vaccine)—a vaccine made from a whole viruses or bacteria that has been inactivated with chemicals or heat.

live, attenuated vaccine—a vaccine made from microbes that have been weakened in the laboratory so that they can’t cause disease. (See **attenuation**.)

lymph nodes—small bean-shaped organs of the immune system, distributed widely throughout the body and linked by lymphatic vessels. Lymph nodes are gathering sites of B, T, and other immune cells.

lymphocytes—white blood cells that are central to the immune system’s response to foreign microbes. B cells and T cells are lymphocytes.

macrophages—large and versatile immune cells that devour and kill invading microbes and other intruders. Macrophages stimulate other immune cells by presenting them with small pieces of the invaders.

memory cells—a subset of T cells and B cells that have been exposed to antigens and can then respond more readily and rapidly when the immune system encounters the same antigens again.

microbe—a microscopic organism. Microbes include bacteria, viruses, fungi, and single-celled plants and animals.

molecules—the building blocks of a cell. Some examples are proteins, fats, and carbohydrates.

mutate—to change a gene or unit of hereditary material that results in a new inheritable characteristic.

naked DNA vaccines—(See **DNA vaccines**.)

naturally acquired immunity—immunity produced by antibodies passed from mother to fetus (passive), or by the body's own antibody and cellular immune response to a disease-causing organism (active).

pertussis (also called whooping cough)—a respiratory infection caused by the toxic bacterium *Bordetella pertussis*. The wracking coughs characteristic of this disease are sometimes so intense the victims, usually infants, vomit or turn blue from lack of air.

Phase IV studies—very large clinical studies that look at tens of thousands of people who have received a licensed vaccine. These studies try to pick up rare or delayed adverse reactions that might not have been apparent in the smaller Phase I, II, and III studies that preceded licensure.

plasma cells—cells produced by dividing B cells that are entirely devoted to producing and secreting antibodies.

polysaccharides—long, chain-like molecules made up of linked sugar molecules. The outer coats of some bacteria are made of polysaccharides.

preclinical testing—required laboratory testing of a vaccine before it can be given to people in clinical trials. Preclinical testing is done in cell cultures and in animals.

recombinant DNA technology—the technique by which genetic material from one organism is inserted into a foreign cell or another organism in order to mass-produce the protein encoded by the inserted genes.

recombinant subunit vaccines—vaccines made using recombinant DNA technology to engineer the antigen molecules of the particular microbe. (See **subunit vaccine**.)

recombinant vector vaccines—vaccines that use modified viruses or bacteria to deliver genes that code for microbial antigens to cells of the body.

rubella (also called German measles)—a viral disease often affecting children and spread through the air by coughs or sneezes. Symptoms include a characteristic rash, low-grade fever, aching joints, runny nose, and reddened eyes. If a pregnant woman gets rubella during her first three months of pregnancy, her baby is at risk of having serious birth defects or dying.

subunit vaccine—a vaccine that uses one or more components of a disease-causing organism, rather than the whole, to stimulate an immune response.

T cells—white blood cells (also known as T lymphocytes) that direct or participate in immune defenses. (See **cytotoxic T cells** and **helper T cells**.)

toxin—agent produced by plants and bacteria, normally very damaging to cells.

toxoids (also called inactivated toxins)—toxins, such as those produced by certain bacteria, that have been treated by chemical means, heat, or irradiation and are no longer capable of causing disease.

toxoid vaccine—a vaccine containing a toxoid, used to protect against toxins produced by certain bacteria.

Vaccine Adverse Events Reporting System (VAERS)—a follow-up surveillance system that gathers information on adverse reactions associated with licensed vaccines. VAERS is a joint effort of FDA and CDC, and anyone—doctors, patients, or parents—can report adverse reactions to VAERS.

vector—in vaccine technology, a bacterium or virus that cannot cause disease in humans and is used in genetically engineered vaccines to transport genes coding for antigens into the body to induce an immune response.

virulent—toxic, causing disease.

viruses—very small microbes that do not consist of cells but are made up of a small amount of genetic material surrounded by a membrane or protein shell. Viruses cannot reproduce by themselves. In order to reproduce, viruses must infect a cell and use the cell's resources and molecular machinery to make more viruses.



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Lesson

4

Case Studies and Human Research Ethics

OVERVIEW

Purpose

The purpose of this lesson is to help students understand ethical considerations related to testing vaccines in humans. Students will examine historical cases that have influenced research guidelines for human research participants. This will prepare students to later apply their understanding of ethical guidelines to their own research proposals.

Essential Understandings

- The methods of scientific inquiry and research using human subjects must be followed, paying close consideration to ethical principles based upon past historical practices and current guidelines and regulations.
- Selection of human subjects for experimental research must be done carefully based on the goals of research and consideration of risk and benefits to specific individuals and participant populations.
- Examining the ethics of research with human participants encourages the use of critical and logical thinking to form positions and viewpoints.

Learning Objectives

- Students will formulate a set of 'rules' that should guide the use of humans in research, compare that list against current internationally used principles, and summarize key ethical principles.
- Students will analyze and discuss the ethical use of human participants in historical research cases, select the principle that was most violated, and defend their choice.

Key Concepts

The analysis of case histories provides insight into the development of the following concepts: informed consent, vulnerable populations, undue pressure and influence. The Belmont Report provides basic principles for use of human subjects in research: respect for persons, beneficence, and justice.

Prior Knowledge Needed

Ethical Theories (helpful but not necessary)

Research process including animal studies through clinical trials (helpful but not necessary)

Materials

PowerPoint Slides (HIV 101 – slides 16-21) – see

<http://www.nwabr.org/education/hiv/HIVVaccines.ppt>

Student Handouts:

Activity 4.2 Rules for Using Humans in Research

Historical Case Studies #1 - #5

Activity 4.3 Historical Case Studies for Human Research—
Guiding Questions

Activity 4.4 Basic Principles for Using Humans in Research

Activity 4.6 Historical Overview of Guidelines for Using
Humans in Research (optional)

Activity 4.8 Ethical Considerations of AIDS Vaccine Trials

Research Ethics Training Curriculum (optional)—Family Health International has training materials which include slides and discussion focusing on the three basic ethical principles of Respect, Beneficence and Justice. The training materials for Community Representatives work well in the classroom. The pdf version can be downloaded from the FHI site: <http://www.fhi.org/en/RH/Training/trainmat/ethicscurr/RETCCREn/index.htm>. The 11 slides begin here: <http://www.fhi.org/en/RH/Training/trainmat/ethicscurr/RETCCREn/ss/Contents/SectionIV/index.htm>

Prep Time

Time needed to copy Student Handouts and review background materials

Class Time

1-2 days depending upon the depth of discussions, as facilitated by the teacher

Timeline

- If desired, order one of the suggested videos ahead of time
- Prepare overheads (if needed) and student handouts

Extensions

- Present Historical Overview of Guidelines Handout. Relate to previous case studies and the use or abuse of existing guidelines (e.g. Reich Circular 1931 as compared to Nazi experiments, Nuremberg Codes established during PHS Syphilis study).
- Give the specific names of those involved in the case studies and have them research the details, ethical documents and results of each case.
- Explore the use of animals, especially Rhesus macaques, in HIV vaccine development.
- Use one of the following videos to enhance student learning:
 - Ethics in Biomedical Research, Howard Hughes Medical Institute, 2005. This 80 minute DVD includes a helpful 28 minute overview of ethics in research. FREE of charge, www.hhmi.org/bioethics.
 - Susceptible to Kindness: Miss Evers' Boys and the Tuskegee Syphilis Study, 1994, 45 minutes, Cornell University, Media Services Resources Center. Telephone 607-255-2090
 - Documentary of the Public Health Service Syphilis Study -Deadly Deception, 1993, PBS Nova, <http://shop.wgbh.org/>
 - In the Shadow of the Reich: Nazi Medicine, 54 minutes, First Run Features. Telephone 800-229-8575

Adaptations

- IEP/ELL: Have the entire class focus on one case together.

Assessment Suggestions

- Informal assessments as students work in groups to complete Case Study Activity
- Monitor answers on handout and during discussion
- Evaluate homework paragraphs

Common Misconceptions

- Scientists are always ethical and do the right thing
- Scientists are always truthful and objective
- Scientists don't have to follow guidelines when developing research protocols.
- No one is monitoring research to make sure that protocol and safety guidelines are followed.
- People are commonly mistreated while participating in clinical trials.

ADDITIONAL RESOURCES






- **Articles for background reading:**
 - “Infectious Diseases”, The Lancet, Vol 4 July 2004, pages 385-413
 - “Vaccines at Retrovirus 2004”, www.iavireport.org/Issues/0404/VaccinesatRetrovirus2004.asp
 - “Ethical Considerations in HIV preventive vaccine research”. UNAIDS guidance document <http://www.aidsinfo.nih.gov/other/whatisvac.asp>
- **Research Guidelines:**
 - The Belmont Report: <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>
 - The Nuremberg Code: <http://ohsr.od.nih.gov/guidelines/nuremberg.html>
 - Declaration of Helsinki: <http://www.wma.net/e/policy/b3.htm>
 - Nuffield Council on Bioethics: <http://nuffieldbioethics.org/home/index.asp>
 - Office of Human Subjects Research: <http://ohsr.od.nih.gov/info/sheet3.html>
 - The Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects: http://www.cioms.ch/frame_guidelines_nov_2002.htm
 - UNAIDS Guidance Document link: Ethical Considerations of HIV Preventative Vaccine Research http://data.unaids.org/Publications/IRC-pub01/JC072-EthicalCons_en.pdf
- *The use of human subjects in research has a controversial history. Over time, researchers and ethicists have developed guidelines for the recruitment and use of human subjects in studies with potential benefits and risks to those participants. The Public Health Service study of Syphilis in Tuskegee is one of the most famous examples. It is important to stress to students that research provides many health benefits, but that there are also risks associated with using human participants in research.*

Lesson 4 Activities

SUMMARY

- 4.1 *Invitation to Learn*
- 4.2 *Student Brainstorm: What should rules be when doing research trials on human participants?*
- 4.3 *Review of Historical Case Studies*
- 4.4 *Comparison of Student-Derived 'Rules' to Existing Guidelines*
- 4.5 *Selection of Principle Most Violated in Case*
- 4.6 *Debrief and Discussion*
- 4.7 *Human Subjects Expository Paragraphs*
- 4.8 *Ethical Considerations of AIDS Vaccine Trials*

Symbols

-  — video
-  — discussion
-  — hands-on
-  — on-line or web based
-  — homework

4.1 Invitation to Learn

Pose the question, “Why have scientists not been able to come up with a vaccine for HIV after 20+ years of research?”

This question provides a transition from the previous two days and the homework assignment. Many factors are relevant, focus on the following where there is a,

- High mutation rate of HIV, resulting in:
 - High variability of HIV within an individual as well as between individuals
 - High variability of HIV between global regions
- Infection of the same cells that would be involved in a normal immune response
- Difficulty of finding parts of HIV virus that are ‘antigenic’ (would invoke a strong immune response), due to the many carbohydrates coating the virus, the fact that virus buds from human cells, and the fact that many such ‘antigenic’ parts are not exposed until binding occurs.

Introduce vaccine development using the Powerpoint presentation, focusing on slides 16-21, and especially on the parameters of Phase I trials. These slides can be found at: <http://www.nwabr.org/education/hiv/HIVVaccines.ppt>. They may take a number of minutes to download.

Explain to students that the next steps in vaccine development would be animal trials, followed by human trials. This lesson will focus on the ethical guidelines surrounding human participation in scientific research trials. This information will be helpful when considering how they will structure their own Phase I trial in the final assessment.

4.2 Student Brainstorm: What Should the Rules Be?

Put students into five groups (one for each case study). Have each group brainstorm what they think the rules should be when doing research trials on human participants, using the ‘Rules for Using Humans in Research’ Handout.

4.3 Review of Historical Case Studies

Provide one case study to each group. Large classes may have more than one group working on a case study. Each group should have a recorder, a reader, and a reporter, and all students should participate in discussion of case study.

Give each group a case study and the case study guiding questions. Explain to students that after they have read the case study, they need to discuss the ethical use of human participants in their case.

Everyone in the group should contribute to answering the guiding questions thoughtfully and completely.

Once students have completed the questions, the student acting as reporter will summarize the case and explain to the class the findings/opinions of the group.

Record the main ideas concerning human participants on the board or overhead as groups report out. *Modification: Use a “jigsaw” method with case studies so students are exposed to each of the case studies in smaller groups. Then have class discussion where students report out general ideas about ethical use of human subjects in research.*

Before introducing the case studies to the class, teachers should stress the positive role clinical trials have played over time in the advancement of health care.

4.4 Comparison of Student-Derived ‘Rules’ to Existing Guidelines

Introduce the principles using the ‘Basic Principles of Research’ handout.

Students should revise their ‘rules’ as previously selected on their ‘Rules Handout’ as necessary.

Discuss, using the following questions as guides;

- What was included on both your rules and the Basic Principles? Does that indicate how important you see it as an issue?
- What wasn’t included on your list? Is that an oversight on your part (e.g. it didn’t come to mind), or do you feel that it isn’t as important of an issue?
- Are there additional rules that you included? What are the important reasons you included them?
- Is there an important reason why something is on the “Basic Principles” sheet that you didn’t have?

4.5 Selection of Principle Most Violated in Case.

Students select the principle that was most violated in their study.

Note: there are many ways to interpret these cases in light of the principles. This part of the lesson helps students become familiar with the principles, and asks them to justify their selection of principles. Which principle they settle on is not as important as their rationale for selecting it!

4.6 Debrief and Discussion

Review each of the cases, informing students that each of these cases is based on a real event. Give identifying information about each case. Summarize main concepts associated with the case and ethical regulations / guidelines developed as a result of each case.

Case Study #1 Walter Reed and Yellow Fever in Cuba: early case of written use of “informed consent”.

Concepts: Respect for persons: informed consent, Justice: undue pressure and influence (money)

Case Study #2 Nazi Experiments on Concentration Camp Victims: resulted in the Nuremberg Trials that set up the Nuremberg Codes 1946-47.

Concepts: Respect for persons: informed consent, Beneficence: minimizing harms, Justice: vulnerable population

Case Study #3 Public Health Service Syphilis Study 1932-1972: resulted in the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which subsequently issued the Belmont Report.

Concepts: Respect for persons: informed consent, Justice: vulnerable population, undue pressure and influence

Case Study #4 AZT and Pregnant Women in Africa: World Medical Association clarified the use of placebos in the absence of existing proven therapy. (<http://www.wma.net/e/policy/b3.htm>)

Concepts: Justice: vulnerable/target populations

Case Study #5 New York Study using young boys to study effects of fenfluramine on behavior. New York Times 1998, April 15, B3, Hiltz.

Concepts: Respect for persons: informed consent, Justice: vulnerable/target populations, treating patients without symptoms based on characteristics of relatives

4.7 Homework: Human Subjects Expository Paragraphs



Have students write 1 paragraph on each of the following:

- What are the basic principles that guide research with human subjects?
- Why would these principles be important to consider in a trial of an HIV vaccine?

4.8 Ethical Considerations of AIDS Vaccine Trials



Students read an article which raises a number of ethical issues surrounding AIDS vaccine trials. Using the student handout, students provide examples from the article pertaining to the principles of Justice, Beneficence, and Respect for Persons. The New York Times article used for this lesson can be found before student handout 4.8, or at: http://www.michaelspecter.com/times/1998/1998_10_01_nyt_aids.html

Student Handout Activity 4.2

NAME _____ Date _____ Period _____

What do you consider to be the most important “Rules for Using Humans in Research Studies”? You and your group should come up with 5 to 10 rules that would be applicable to most or all human research studies.

RULES FOR USING HUMANS IN RESEARCH

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.
- 8.
- 9.
- 10.

Yellow Fever in Cuba

Following the Spanish-American War, American soldiers took control of the island of Cuba. They, like all other newcomers to Cuba, were confronted with a range of tropical diseases-typhoid, malaria, yellow fever, dengue fever-toward which they had no natural immunity. For every one soldier who died in the war, hundreds quickly died of disease. Cubans typically contracted yellow fever early in life and either died or developed life-long protection. About 30% of people who contracted yellow fever died.

In 1900, researchers began work to combat the disease. One major barrier for studying the disease was that it only affected people. With no animal model to use, the researchers were obliged to do all their experiments on people. Little was known at the time about the cause or transmission of yellow fever, but mosquitoes were suspect. Could a mosquito that bit a sick person then transmit the disease by biting someone who was well?

The experiments were crude but direct. A test tube containing a mosquito was inverted onto the arm of someone who was sick. The mosquito sank its proboscis into the flesh, found a vein or artery, and drank a blood meal. After two weeks, the test tube containing the mosquito was inverted onto the arm of a healthy subject. Researcher and subject then watched as the mosquito once again sank its proboscis through the flesh and into the bloodstream. There, it once again exchanged fluids with its host, injecting salivary juices and the viruses that caused yellow fever into the blood stream while drinking another blood meal.

Researchers created a written “informed consent”^{*} document, which outlined the risks of the experiments and their possible benefits. Those who agreed to be subjects in the experiments had to sign the forms. The American military governor of Cuba provided funds to set up a proper research laboratory-seven tents and a flagpole flying an American flag-and funds were also available to pay volunteers. The American soldiers who participated did not get paid but the Spanish immigrants who volunteered each received \$100 in gold to participate and \$100 more if they got sick. For volunteers, the risks of the yellow fever experiments even seemed worth taking, because, being new to the island, they were likely to contract the disease in any case. At least in an experiment, they would get rapid and decent medical treatments.

All told, 29 people contracted the disease while participating in the commission’s experiments and five died. After mosquitoes were implicated in the transmission of the disease, a thorough mosquito eradication program began, and yellow fever was wiped out in Cuba.

Modified from Kennedy Institute of Ethics

http://www.georgetown.edu/research/nrcbl/hsbioethics/alumni/unit3_i.htm

^{*} The term ‘informed consent’ did not enter into common usage until the 1960s.

Prisoner Experiments

During World War II, several experiments involving human subjects were conducted using prisoners in concentration camps. Some of these experiments focused on the human tolerance to extreme temperatures. These experiments are summarized below.

Freezing / Hypothermia

The freezing experiments were divided into two parts. Part One established how long it would take to lower the body temperature until death occurred, and Part Two determined how to best resuscitate the frozen prisoner

The two main methods used to freeze the prisoner were to put the person in a icy vat of water or to put the prisoner outside naked in sub-zero temperatures.

The icy vat method proved to be the fastest way to drop the body temperature. Prisoners were usually stripped naked and prepared for the experiment.

A insulated probe which measured the drop in the body temperature was inserted into the rectum. The probe was held in place by a expandable metal ring which was adjusted to open inside the rectum to hold the probe firmly in place. The prisoner was then placed in the vat of cold water and started to freeze. It was learned that most prisoners lost consciousness and died when the body temperature dropped to 25 C (77 degrees Fahrenheit).

Sun Lamp

The prisoners were placed under sun lamps which were so hot they would burn the skin. One young prisoner was repeatedly cooled to unconsciousness then revived with lamps until he was pouring sweat. He died one evening after several test sessions.

Internal Irrigation

The frozen prisoner would have water heated to a near blistering temperature forcefully irrigated into the stomach, bladder, and intestines. All prisoners appeared to have died from the treatment.

Hot Bath

The prisoner was placed in warm water and the temperature was slowly increased. This method proved to be the best. Many prisoners died due to shock if they were warmed up too quickly.

Modified from http://nazi_medical.tripod.com/experiments.html

Syphilis in African American Men

In 1932, six hundred poor African American farmers and sharecroppers were subjects in a study run by the federal government to watch what happens when syphilis is left untreated. At the time, there was no reliable cure for syphilis. When a safe and effective treatment for syphilis—the antibiotic penicillin—became widely available in the early 1940s, the study continued and the men were actively prevented from receiving treatment for the disease.

In the study, 399 men with syphilis were followed along with 201 men of the same age who did not have syphilis. The standard treatment for syphilis in the early 1930s was 25-30 applications of mercury. The Alabama Health Officer agreed to the study under the condition that the men receive some treatment. Initially the researchers gave the men treatment. However, money ran out for the treatments, and the researchers decided to continue on with the study anyway. They hoped that funding would be restored for treatment, but felt that there was still value in a ‘natural history’ study that could potentially show the disease was the same in African Americans and Caucasians. The amount of treatment was clearly inadequate according to the standards of the day, but the researchers felt justified in leaving the men untreated. The researchers wanted to observe how the disease progressed in untreated individuals and compare it to an earlier study of Norwegian men who had not received treatment (because the Norwegian study occurred before 1910, only very toxic treatments were available to those patients at that time).

The researchers used the general term ‘bad blood’ when describing the patients’ condition. None of the subjects knew that their ‘bad blood’ was actually syphilis. The men received painful spinal taps, which they believed were treatments because they received a letter from the government saying that they should come receive this ‘special treatment’. The incentives for submitting to the taps and other evaluations were warm meals, a free burial, and free medical care for other diseases, as long as the treatment was not penicillin. The researchers worked with the local draft board to prevent the subjects of the study from being drafted for World War II. Had they entered the army, the men would have been tested for syphilis and given penicillin if they had the disease.

Over the years, more than a dozen articles about the study were published in medical journals. The study did not end until 1972 after the story was brought to public attention by a researcher from the Center for Disease Control shared his concern with a news reporter. During those forty years, over 100 men died. The survivors filed a suit against the US government in 1973, eventually settling out of court for \$37,500 each and a life time of medical care.

Modified from Kennedy Institute of Ethics

http://www.georgetown.edu/research/nrcbl/hsbioethics/alumni/unit3_i.htm.

AZT and Pregnant women in Developing Countries

Newborns whose mothers are infected with HIV can acquire the infection from their mothers at the moment of birth. In some developing countries with HIV/AIDS epidemics, more than 30% of pregnant women who are examined at prenatal clinics are infected with the AIDS virus.

Clinical trials in 1994 showed that, if a pregnant woman took the drug AZT in pills during the last 12 weeks of pregnancy and as an injection during labor and if the baby received AZT during the first six weeks of life, the baby had a much-reduced chance of becoming infected with the virus. Since that time, in the United States, pregnant women infected with HIV are advised to use this “076 regimen” of AZT.

In 1997, researchers gave a placebo, rather than AZT, as a control to pregnant women in a developing country who were infected with HIV and were participating in clinical trials. The “standard” treatments for AIDS for these women were no treatments at all. (The 076 regimen, for example, was simply too expensive for women and governments in poor countries, costing between \$800-\$1000 per person.) The researchers were evaluating lower and fewer doses of AZT in the studies to see if low doses might be effective. Such doses might be affordable and accessible for poor women around the world.

Women involved in the study did not know whether they received the 076 regimen or the placebo. In addition, women were not told what dose- the lower experimental dose- or the standard amount of AZT they would receive during the trial.

Modified from Kennedy Institute of Ethics

http://www.georgetown.edu/research/nrcbl/hsbioethics/alumni/unit3_i.htm

Behavior in Young Boys

One hundred boys in New York, ranging in age from six to ten, participated in three research projects to find out whether the levels of the brain chemical serotonin could be correlated with aggressive behavior.

The boys were chosen for the study not because they had shown aggressive behavior but because their brothers had. Each boy had an older brother who was in jail or a mother who was considered by the researchers to be doing a poor job rearing her sons. All came from poor families; 44% were African American, 56% were Hispanic, and none were white.

The studies took place at a New York State Psychiatric Institute between 1993 and 1996. Each boy received a single dose of the drug fenfluramine, which increases serotonin levels. The drug is one component of fen-phen, which was recalled as a diet pill in 1997, because it seemed to cause heart valve defects. Experts on the use of fenfluramine consider it unlikely that the boys in the experiments suffered any harm from the drug, as they were given only a single small dose. Those with heart damage used the drug in larger doses over a period of months. However the drug has side effects such as nausea, headache, dizziness, anxiety, and irritability.

Each boy had to stay in the hospital bed for 5 hours, during which time numerous blood samples were taken. He could not eat for 17 hours. At the end of the study, each family received a gift certificate for \$125 to spend at a local toy store.

Modified from Kennedy Institute of Ethics

http://www.georgetown.edu/research/nrcbl/hsbioethics/alumni/unit3_i.htm

**Historical Case Studies for Human Research –
Guiding Questions**

As a group, discuss the answers to the questions below as they relate to your case study. One person in your group should record your answers to be shared with the class.

1. What possible benefits came from the study?

2. What possible harms came from the study?

3. Were the human participants able to consent to their involvement in the study?
If so, what factors would influence their participation?

4. How were the subjects for the study chosen? Do you think they were chosen fairly?

5. What are the differences between participating in a study giving a treatment and participating in a study where a treatment is withheld?

6. How should rules related to human participants research be enforced?

7. Was the treatment of humans in this case ethical? Explain your answer.

Student Handout Activity 4.4

NAME _____ Date _____ Period _____

Basic Principles for using humans in research

Basic Principle	Respect for Persons	Beneficence	Justice
Description	Respect the autonomy of individuals; obtain informed consent	Minimize all potential harm(s) and maximize potential benefit(s) to the subject as well as potential benefit to society	Be fair in the distribution of the benefits and in bearing the burden of research
Applications	<ul style="list-style-type: none"> -Acknowledge a person's right to make choices, to hold views, and to take actions based on personal values and beliefs. -Identify prospective subjects without violating their right to privacy. -Utilize a continuous, on-going consent process in consideration of the nature and duration of the research. -Obtain informed consent from subjects using the "reasonable volunteer standard" in an environment conducive to rational decision making. -Ensure the subject understands <u>all</u> the elements of consent necessary to make an informed decision. -Involve the subject's relatives and counselors in the consent process, with the subject's permission. -Minimize any risk that the subject may develop a therapeutic misconception about the research. -Obtain assent to the degree possible from persons with diminished autonomy and developing autonomy. -Honor a cognitively impaired person's dissent to participate in research, except under compelling clinical circumstances. -Honor a child's dissent to participate in research, except under compelling clinical circumstances in consideration of the age and cognitive ability of the child. -Treat subject with dignity and respect. 	<ul style="list-style-type: none"> -Minimize all potential harm(s) to the greatest extent possible -Maximize the potential benefit(s) of the research by ensuring there is a sound research design, protocol compliance, and timely publication of results. -Ensure that the risk(s) of the research are outweighed, or balanced, by potential benefit(s) to the subjects and/or to society. -Ensure there is a favorable risk(s)/benefit(s) relationship of the research compared with the available alternative(s) which offer the subject the prospect of direct benefit(s). -Ensure that the rights and welfare of the subject always take precedence over the needs of science 	<ul style="list-style-type: none"> -Don't target, or exclude, a subject population based upon convenience or availability. -Don't use vulnerable subjects in research without direct benefit before using less vulnerable subjects. -Guard against positional influence (e.g., physician and patient) during recruitment. -Avoid potential or real financial and other conflicts of interest (e.g. finder's fees, recruitment bonuses, gifts from sponsors)

Student Handout Activity 4.6

NAME _____ Date _____ Period _____

HIPPOCRATES (460 BC)

PERCIVAL (1803)

BEAUMONT (1785-1853)

BERNARD (1813-1878)

HISTORICAL OVERVIEW OF GUIDELINES FOR USING HUMANS IN RESEARCH

REICH CIRCULAR (1931)

- The investigator is responsible for the life and health of the human subject.
- Experimentation is prohibited without consent from the human subject.
- Animal studies should be conducted prior to human studies.
- Human experimentation should be avoided if replacement is possible by use of animals.
- Experiments involving children are prohibited if they are endangered.
- Experiments involving dying subjects are prohibited.
- Academic training courses should stress the physician's responsibilities during experimentation.

THE NUREMBURG CODE (1947)

- Voluntary consent
- Yield fruitful results otherwise unobtainable
- Human Trials should be based on successful animal experiments
- Avoid physical and mental suffering
- Not done if injury expected
- Risk less than importance of problem
- Conducted by qualified people
- Participation can be terminated by the subject at any time
- An investigator may find reasons to also terminate the participation of a subject

DECLARATION OF HELSINKI (1964; REVISED 1975, 1983, 1989, 1996, 2000)

Basic Principles

- Human research should be based on animal experiments
- Studies should be conducted by qualified persons
- Importance of research proportionate to risk
- Risks and benefits should be assessed beforehand
- Effects of drugs on personality considered

Notable revisions of the Basic Principles of Helsinki

- 1975 Independent Committee Review; informed consent emphasized
- 1983 Obtainment of a minor's "consent" when possible
- 1989 Independent Committee Review clarified; statement of compliance with Helsinki
- 2000 32 Basic Principles; Research with cognitively impaired expanded;
- Best proven therapy criteria

THE BELMONT REPORT (1978)

Basic principles

1. **Respect for persons:** Respect the autonomy of individuals by obtaining their informed consent or, in the case of persons with diminished or developing autonomy, obtain proxy consent from their legally authorized representative.
2. **Beneficence:** Minimize all risks (i.e., potential harms) and maximize potential benefit(s) to the subject which are associated with research participation as well as potential benefit to society.
3. **Justice:** fairness in distribution of the benefits and in bearing the burden of research.

the New York Times

Urgency Tempers Ethics Concerns in Uganda Trial of AIDS Vaccine

October 1, 1998 by Michael Specter

KAMPALA, Uganda—Raphael Nawiro got up extra early one steamy morning this summer. He walked a mile from his home, then took two long bus rides until he reached Uganda's principal medical complex, the aging, overburdened Old Mulago Hospital.

He went directly to the office of Dr. Roy Mugerwa, who will run an AIDS vaccine trial that is about to begin here.

"I want to enroll in the study," he told the secretary, eager to take part in a promising and ethically contentious experiment. "I want to help find a cure for what's killing us all."

The secretary nodded gravely and told him where to go to fill out forms. "I can't promise a thing," she said.

Nawiro, a schoolteacher, is under no illusions that the test of any vaccine will prevent him from becoming infected with HIV, the virus that causes AIDS. But at the age of 32 he has lost five members of his family to this plague, and he is weary of the endless death that has come to rule his country.

"It's time to do something serious about this disease," he said quietly as he rushed off to work. "Isn't a vaccine really the only hope we have?"

On this continent the answer to that dark question is a ringing, undeniable yes. People infected with HIV in rich countries now have access to drug combinations that extend their lives. But in Africa, where AIDS threatens to destroy an entire generation, there is no such reason for optimism. And unless somebody comes up with a vaccine, that is unlikely to change before millions more die.

In the past, ethical guidelines have made clear that vaccines should be tested in developed countries—where health care is excellent—before they are used in places without a safety net, like Uganda. With AIDS, for the first time, the international medical community has done away with that necessity.

"It has to be this way," said Mugerwa, medical professor at Makerere University who is the principal investigator for the vaccine trial scheduled to begin in October.

"Nobody is going to do it first anywhere else," he said, "and I don't blame them. We are the people with the problem. Why should Americans undertake risky research on themselves for a problem they don't really have? That would make them the guinea pigs. The risk belongs here, where the people are dying."

In Uganda, a country struggling valiantly to cope with an epidemic that has infected 20 percent of its population, the questions surrounding the trial have become deafening.

Who will take part in the first round, and what will happen if people become infected and sick after they have volunteered, given that Uganda spends about \$6 per person annually on health care? Will they receive the best medical care that money can buy, as they would in America or France, two other countries that are testing AIDS vaccines? If they do, who will pay? If not, will they be treated like any other Africans—given aspirin, good wishes and no hope?

What if, as is often the case with vaccines, this trial shows that it may not prevent an AIDS infection but it may make the disease less deadly? Should the test be stopped immediately so that the vaccine can be given to people right away, before scientists can find out the answers to how good the vaccine might ultimately be or how best to use it? Or should the test go on, with some people receiving a useless placebo, so that researchers can learn the full potential of any possible vaccine?

And, although most scientific experts say there will be no useful AIDS vaccine for at least a decade, what will happen if that vaccine is eventually produced thanks to the help of the eager, fragile and desperate people of Uganda?

What guarantee will there be, after helping to solve one of modern medicine's most frightening and complex problems, that any proven AIDS vaccine would be available here or in similar countries, where most basic medicines are too expensive to buy?

Drug companies will want to recoup their enormous investments, and that means selling a vaccine to people who can pay for it. Few effective vaccines, even the one for hepatitis B, which was developed only after long testing in Senegal, have been made routinely available in Africa.

They just cost too much.

“Everybody is worried that we will use Africa, develop a vaccine there, say thanks and then take it back to Europe and America,” said Dr. Peter Piot, the executive director of the United Nations AIDS

Program, who has worked to focus more attention on the scope of the epidemic in the developing world. “I don’t believe that will happen. But we are in a terrible position. The process is perilous. It is unfair. And it is filled with inequities—because the world is filled with inequities.

“What is our choice? In Africa they need a vaccine. Should we just tell them we have too many ethical problems to help them find one?”

A walk across the campus of the Old Mulago, this giant hospital complex that has served as ground zero in Africa’s gruesome fight with AIDS, answers that question in about five minutes.

There are no waiting rooms, but every landing on every floor overflows with sick people. Mothers in bright cotton robes sit quietly nursing their infants; old men wheeze in the stairwell. Hundreds of men and women sit in eerie silence, coughing and waiting for a number to be called. Some wait for days, sleeping when they can, eating if there is food. There is probably no hospital on earth—and possibly no country—more besieged by the AIDS epidemic. Every pair of eyes seems to spell the word despair.

So despite a rancorous debate in the West, where critics say Africans will be misused in any test here because the highest standards of care and of informed consent are impossible to attain, Uganda is about to begin its trial. And it is hard to find anybody in this country who thinks that’s a bad idea.

Forty healthy volunteers will be selected. Half will receive a placebo that would have no effect on an HIV infection. The other half will receive a vaccine into which some genes responsible for producing important HIV proteins, some building blocks of the virus, have been inserted. There will be no actual virus in the vaccine. It is an initial test and its purpose is to see whether it is safe and whether it has any effect.

If the vaccine stimulates the body’s defenses—and the placebo does not—that will mean that the vaccine should undergo further tests on a larger group of people.

There are different strains of HIV, known as clades, and the predominant strains from Africa are different from those usually seen in the West. Still, one of the critical questions about any vaccine is how widely it can be used, and the hope is that at least the basic building blocks of any vaccine that work on one strain would also work on the others.

Because the vaccine may reduce the amount of HIV in people who have already become infected, it cannot really be tested broadly in the United States. Americans who are diagnosed with HIV now immediately start a drug treatment regimen aimed at cutting down the amount of the virus in their bloodstream.

Anything less would be considered unethical. But if people in a vaccine trial are also on these new drugs, researchers would have no way to judge whether a vaccine is reducing the virus, or whether the medicine was doing it.

Since people in Uganda cannot hope to afford such drug treatment, which can cost more than \$15,000 a year, they are perfect subjects for such a vaccine test.

“The question arises are we basically exporting our risky scientific research, from which we would benefit, to the third world?” said Thomas M. Murray, director of Case Western Reserve University’s Center for Biomedical Ethics, speaking at a forum on the vaccine trials this year. Case Western, which for years has had a relationship with Makerere University Medical School, is one of the vaccine trial sponsors.

“This is a far more morally complicated issue than critics of the research have ever made it out to be,” Murray said.

That’s because it has become clear to many people that there are practical and cultural barriers to applying the same standards of ethics in America and Africa. In the United States, for example, informed consent is required for people who take part in drug tests. They need to know what the test will do, what the risks are and what the rewards are. In Africa, such consent is often given by husbands or doctors or tribal leaders and many health officials say the country simply doesn’t have enough trained doctors to inform everyone about complicated programs like the AIDS vaccine trials. Informing a representative of a village would never be considered

enough in America, but in Uganda who should decide what is enough?

Most experts, in Africa and in the West, say that every participant always deserves to understand the risks and possibilities of trials. And most specialists believe that informed consent is not only possible in Africa, but essential if trials are to work. Still, there is simply not enough time or money in most cases to make certain that each potential risk or reward is understood.

“Things seem so simple in a rich country,” said Dr. Peter Mugenyi, the director of Uganda’s Joint Clinical Research Center, which will administer the AIDS vaccine trials here in conjunction with a consortium of groups that include the National Institutes of Health and Pasteur-Merieux, the French company that has developed the vaccine and will provide it for the study.

“They sometimes talk about this in America like it’s the Tuskegee experiment and we are simple, ignorant dupes,” he said. In the Tuskegee experiment, one of medicine’s most notorious abuses of research subjects, poor black men in Alabama were denied affordable, effective and widely available treatment for syphilis. They were not informed of their rights in the research or told what was happening to them. And they were allowed to get sick when penicillin could have cured them all.

“It’s terribly insulting to us and to the Western agencies and individuals who have worked with us,” said Mugenyi, who presides over a state-of-the-art research center staffed with highly trained scientists from Uganda, Europe and America. “Sure there are some questions that are hard to address, like how will these people be cared for if they become sick. But let’s also look at the world and tell the truth. In the history of medicine the only things that have really worked to stop diseases in the third world have been vaccines. Drugs won’t work for us. Prevention has obviously failed.

“Education is almost impossible. Without a vaccine we are going to keep on losing and we are going to lose a lot.”

More than a million people in Uganda have already died of AIDS. The country’s leadership is easily the most open in Africa about the issue—the

president and other leaders mention the disease in nearly every speech. It is only rare families where at least one member has not fallen ill.

Mugerwa and his colleagues are aware that in the past, when vaccines have been developed in Africa, they disappear as soon as they become worth money. That is why Uganda decided to be in on every level of testing.

“We are participating in the trials,” he said, “not just with our citizens, but with our brains. We have demanded a role in the research and we have sent our best people abroad to help develop the drugs. When this vaccine becomes effective—in a year or 10 years or two generations—we want to be able to say that we have a central interest in this product and you owe us for it.”

That will help but it won’t solve the problem. Representatives from Pasteur-Merieux have said that it is now impossible to guess how much a vaccine would cost since it does not yet exist. They have also said, repeatedly, that foundations, international relief agencies, pharmaceutical companies and governments will all have to band together to come up with enough money to buy vaccines for poor countries. The message is clear: First let’s get a vaccine, then we will figure out how to get it to you.

“If you are a student of history, it’s not all that comforting to see how Africa has been treated in the past,” said Dr. Edward Mbiddle, chief of Makerere University’s Cancer Institute. “But you know what? If we are going to have a future, we can’t afford to live in history.”

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Student Handout Activity 4.8

NAME _____ Date _____ Period _____

What is this article about?

This article raises a number of ethical issues surrounding AIDS vaccines trials. Provide some examples related to the following ethical principles:

Respect for Persons

Beneficence (“doing good”)

Justice

KEY Activity 4.8

What is this article about?

A 1998 HIV vaccine trial in Uganda and the ethical issues surrounding it.

This article raises a number of ethical issues surrounding AIDS vaccines trials. Provide some examples related to the following ethical principles:

Respect for Persons

Informed consent issues – consent is given by husbands, doctors, or tribal leaders. Often there are not enough doctors to fully inform everyone about complex vaccine trials. Is it acceptable to have a village representative give consent for individuals? How can we be sure that risks and rewards have been understood?

Beneficence (“doing good”)

The Africans mentioned in the story are actively interested in participating in an HIV vaccine trial, in order to help find cures for “what’s killing us all”. The benefits (a vaccine that could help millions of Africans) could be very large. This benefit, Dr. Piot argues, leads us to action, rather than lamenting that we have ‘too many ethical problems to help’.

Justice

Justice demands that there be an equitable distribution of burdens and benefits. Will the Africans share in the benefits of a vaccine or will it be too costly? Are they assuming too much risk? The researchers note that the “risk belongs...where the people are dying.”

How will individuals who become infected after volunteering (not because of the vaccine, but because the vaccine is ineffective) be treated? Will they be treated as Americans would, with costly medical care, or by the standards of their country, where \$6/day is spent on health care?



Lesson 5

Global Awareness Activity



Objectives

Students will be able to:

- Identify potential impacts of inequitable resource (educational, wealth, and health) distribution on HIV/AIDS.
- Draw correlations between education, health resources and HIV/AIDS status, and between culture and participation in HIV/AIDS vaccine trials.

Class Time

One class period plus a short time the following period to discuss student homework

Introduction

This activity is designed to demonstrate how differences in culture, resources, and HIV/AIDS in five regions of the world combine to impact work on the HIV/AIDS pandemic. Access to medical care and education, cultural characteristics, and wealth are all issues that will be explored to heighten students' global perspective on how difficult it is to launch an HIV vaccine trial.

Materials






- Yarn or string (preferably in 5 different colors)
- Masking tape
- Ambassador's cards (provided)
- 15 sandwich bags
- Baggie label template to print out on Avery 8660 labels (provided)
- 28 oz. Hershey's Kisses (149 Kisses)
- 129 band aids (or xerox a sheet of band aids and cut them out)
- 400 red beads or beans
- UNAIDS Fact Sheets (optional)

Procedure

Before class:

- Measure out the yarn for each region according to Region Information chart. It may be helpful to have a different color of yarn for each region.
- Count out numbers of Hershey Kisses, band aids, and red beads required for each region and put them in separate labeled bags.
- Read through supporting information and familiarize yourself with the general characteristics of each region. Be sure to understand the connections between education, women's rights, cultural and religious traditions, and wealth.
- Copy and cut ambassador cards.
- Just before the activity begins, arrange the yarn on the floor to represent the regions and tape in place.
- Keep baggies hidden in a larger paper bag but have it nearby to hand to students.
- Make large cards with each region's name to put on the floor. This makes it easier for students to identify the regions.

Symbols

-  — video
-  — discussion
-  — hands-on
-  — on-line or web based
-  — homework

Lesson modified from "Food For Thought" the Population Connection

<http://www.populationconnection.org/education/library/references/dl/10>

Essential Understandings

Pandemics are influenced by global health issues, cultural diversity, environmental contexts, educational levels and socioeconomic conditions. Selection of human subjects for experimental research must be done carefully based upon the goals of the research and consideration of risks and benefits to specific individuals and participating populations

Prior Knowledge Needed

Basic understanding of global geography and HIV, basic understanding of Human Subject Trials and ethical considerations of choosing experimental population

Common Misconceptions

- Health care is available to anyone who is sick
- Poor people don't go to school because they don't care about education
- People in other countries get HIV/AIDS because they are promiscuous
- Women are able to choose whether or not their sex partners use condoms

Student Background

When determining a population to use for clinical trials, many factors must be considered, especially for a global problem like HIV vaccinations affecting a multitude of cultures. Researchers in the US are bound to the Basic Principles of Autonomy, Beneficence, and Justice, both here and internationally but these principles may have different connotations to different cultures.

[For example; in many cultures women have no say about their medical care or whether they would like to participate in a clinical trial. Husbands or senior male members of the family make these decisions for them. This must be considered when obtaining informed consent from female participants. The issue is community and familial consent and right of women to say “no”. While community consent is vital in some cultures, *the US Code of Federal Regulations requires individually signed consent for all trials using US government funds*. One novel way around this in one country was to obtain community consent from the tribal leaders. Potential volunteers were seen individually in private and separate informed consent sought with a signature. When people came out of the room where they were meeting privately with researchers, it was immediately apparent to everyone else in the waiting area if they had agreed to participate, because they had a band aid on their arm where blood was drawn to determine eligibility. That meant that confidentiality was being breached (inadvertently) but also that there was now the possibility of undue influence by others in the community who felt that trial participation was important. Wishing to curtail the problem of social harm and to protect confidentiality, the researchers gave everyone a band aid.]

Homework

Option 1: HIV Vaccine Trials: Global Contexts

Have students write 1 paragraph on each of the following:

- What potential impacts do levels of education, wealth, and health have on the distribution of HIV/AIDS? Use a particular example or examples from the lesson.
- What criteria should scientists use when determining where in the world to conduct an HIV vaccine trial?
- What ethical and cultural considerations must researchers make before choosing populations to conduct such trials? Draw correlations between education, health resources and HIV/AIDS status, and between culture and participation in HIV/AIDS vaccine trials.

Option 2: Comparing the regions: Where Should Vaccine Trials be Conducted?

Have students fill out Student Handout 5-1, with accompanying questions.

Facilitating the Activity

Begin the Global Awareness Activity

Tell students that five regions of the world will be compared in this activity so they can see how the economic, educational, and cultural differences influence how and where clinical trials occur internationally.

Appoint 5 students to be the “ambassadors” for the world regions. Have them stand in their yarn region.

Populate the regions with the rest of the students, according to the chart (or the World Ambassador card). Note: If you have too few students, you can use chairs to substitute for the missing citizens. If you have too many students, appoint the extra students to a “United Nations Advisory Committee.” Instruct the members of the Committee to pay close attention, as you will be calling on them for their opinions as a neutral party later in the activity. They should be thinking in terms of whether the inequities in each region’s share of population/health care/income are problems, and if so, what policies could lead to solutions. This committee can be funded with a small amount of kisses and band aids to use as they see fit during the discussion time.

Identify each region for the class.

Explain that the dimensions of their regions are to scale, and the number of students within each region is proportional to its actual population; the idea is to give an accurate sense of the population density in each area. Note that, according to UN definitions, Mexico is part of Latin America.

Read the Demographic statistics (A-C) from the World Ambassador card. Have each ambassador read A-C on his or her card. Some discussion questions:

What are some reasons for the differences in the number of children born per woman in each region?

What do indicators like short life expectancy say about the standard of living in a region? How would this influence a person’s decision in participating in a clinical trial?

Read the Quality of Life statistics (D-F) from the World Ambassador card. Have each ambassador read D-F on his or her card.

Which regions have more localized populations? How would this affect HIV/AIDS research and the recruitment of human subjects for clinical trials? Would certain segments of the population be easier or harder to recruit and follow through the trial?

What is the difference between the number of boys in school and the number of girls in school? How does education contribute to the societal and self worth of a person? How does the percentage of school age children enrolled in school reflect the importance or availability of education in your region?

Is there a correlation between the percentage of people living in urban/rural areas, and the average number of children a woman has? Based on B and D, what can you infer about the desire for large families in some regions?

Read the HIV statistics (G-H) on the World Ambassador card. Have each ambassador read G-H on his or her card. Be sure to highlight that the statistics for H (percentage of adults infected with HIV/AIDS in 2003) are from *one country* within that ambassador's region.

What is the population of your community, town, or region? How does this compare with the number of AIDS-related deaths for the different regions of the world?

What percentage of adults are HIV+? What happens to a country that loses a large segment of its adult working/ child caring population? Who cares for children? Who supports the families? How does this affect the stability of the country?

Note that the percentage of people living with HIV/AIDS can vary widely between countries within a region. For example, in Asia, 1.5% of adults in Thailand are infected, and <1% in the Philippines. In Africa, 37.3% of adults in Botswana are infected, and 4.1% in Uganda.

Give out the baggies with the red beads (each red bead = 100,000 people with HIV/AIDS). Have the ambassador read the statistics labeled on the bag. For all of the visual aids, start with the region that has the fewest items (beads, band aids or candies) and continue to the region with the most.

How does the number of red beads compare with the population of that region? Which region has the highest percentage of people living with HIV/AIDS?

Give out the baggies containing band aids (each band aid = \$40 spent on health care). Read the statistics for each region.

How much money is spent per capita (explain this means average per person) on health care? Compare this statistic to the life expectancy in that region.

Give out the baggies containing the Hershey's kisses (each candy = \$350 per capita Gross National Income). Read the statistics for each region.

How does the need for HIV/AIDS care in each region compare with the amount of beads, band aids and Hershey's Kisses in their bags?

	<p>What options do those regions with few resources have when evaluating solutions to their HIV/AIDS epidemic? How might countries in these regions react to US researchers wanting to implement HIV vaccine trials with their population?</p> <p>What ethical considerations must US researchers make before choosing populations to conduct such trials? What are some issues of Justice that might arise? Beneficence? How might Respect for Persons be honored? (The Student Handout from Activity 4.4 might be useful for this discussion).</p> <p>Why do many international organizations, such as the HIV Vaccine Trials Network, find it so important to partner with a local group in the country receiving resources? What might that local group provide?</p>
<p>More about the Lesson:</p>	<p>Extensions</p> <p>Have students research countries in more depth. The movie <i>A Closer Walk</i> provides insight into HIV in different areas of the world. Find out more information in the form of the Director's Journals found on their website: http://www.acloserwalk.org/about_the_director/directors_journals.php</p> <p>Additional information on specific countries can also be found at: http://www.pbs.org/wgbh/pages/frontline/aids/atlas/world.html</p> <p>Have students conduct web-based searches using the phrase "medical care in (country)"</p> <p>Another excellent global simulation called <i>Unfair Race</i> was created for the PBS series <i>Rx For Survival</i>. The activity can be found at: http://www.pbs.org/wgbh/rxforsurvival/campaign/givetime/pdf/Rx_Unfair_Race.pdf</p> <p>Adaptations</p> <p>Simplify the information on the cards, and present more of the information orally.</p> <p>Assessment Suggestions</p> <ul style="list-style-type: none"> • Assess participation of students in class discussion • Students address learning objectives through written homework requirement • Embedded discussion questions could be written out for groups/individuals to answer

Sources

- The World Health Report 2003
<http://www.who.int/whr/2003/en/>
- 2005 World Population Sheet
http://www.prb.org/pdf05/05WorldDataSheet_Eng.pdf
- UNAIDS/WHO AIDS Epidemic Update: December 2005
http://www.unaids.org/epi/2005/doc/report_pdf.asp
- 2004 Report on the Global AIDS Epidemic - Tables of Countries Specific HIV/AIDS Estimates and Data
www.unaids.org/bangkok2004/GAR2004_html/GAR2004_14_en.htm
- Lesson modified from “Food For Thought” the Population Connection <http://www.populationconnection.org/education/library/references/dl/10>

Region Information Chart

	North America	Latin America	Europe	Africa	Asia
Yarn Length -feet (meters) 65 Participants 26 Participants	35 (10.7) 25 (7.6)	36 (11) 25 (7.6)	38 (11.6) 27 (8.2)	43 (13.1) 30 (9.1)	44 (13.4) 31 (9.4)
2006 Population in millions With 65 Participants (1 = 100 million) With 26 Participants (1 = 250 million)	332 3 1	566 6 2	732 7 3	924 9 4	3,968 40 16
Region's Percent of World Land Area	15	16	18	24	25
Per Capita Annual Health Care Costs (US \$) 1 Band Aid = \$40	\$3525 88 band aids	\$217 5 band aids	\$1287 32 band aids	\$116 3 band aids	\$43 1 band aid
Per Capita GNI PPP* 1 Hershey's Kiss = \$500	\$41,285 83 kisses	\$4,496 9 kisses	\$23,987 48 kisses	\$1,030 2 kisses	\$2,119 4 kisses
Number of people with HIV/AIDS (1 red bead= 100,000)	1.2 million 12 beads	2.1 million 21 beads	720,000 7 beads	26.3 million 263 beads	9.9 million 99 beads

Sources:

Population Reference Bureau, "2006 World Population Data Sheet." PRB, Washington, DC.

www.prb.org

The World Bank, World Development Indicators 2006. The World Bank, 2004.

www.worldbank.org

UNAIDS, "AIDS Epidemic Update: December 2005." UNAIDS/WHO.

Specific Country Figures (2005)

<http://www.cia.gov/cia/publications/factbook/geos/br.html>

*GNI PPP=Per capita Gross National Income adjusted for the "purchasing power parity". It standardizes the value of the money across the globe in terms of what it can actually buy.

Comparing the Regions: Where Should Vaccine Trials be Conducted?

REGION	Reasons FOR conducting a trial in this area	Reasons for CONCERN if a trial were conducted in this area
North America		
Latin/ South America		
Europe		
Africa		
Asia		

Which region do you think is most suitable for a vaccine trial?

Why?

What special concerns must be addressed for that region?

Region and Country Cards

World Ambassador Card/Facilitator Card Suggested order for reading statistics (and number of students per region) in a class of 24 students: World → North America (1) → Latin America (2) → Europe (3) → Africa (3) → Asia (15)	
Demographics	I am the World Ambassador. Here are some statistics that shape the world. A. World population is estimated at: 6 billion, 300 million B. The world's women bear an average of: 2.8 children C. Our life expectancy at birth is: 67 years.
Quality of Life	D. The percentage of the world's people living in urban areas is: 47% E. Of the world's 12-17 year olds, 63% of the boys and 55% of the girls are enrolled in school. F. On average, there is one medical doctor per 688 people
HIV/AIDS statistics + visual aids	G. Number of AIDS-related deaths in 2005: 3.1 million H. Percentage of the world's adults (ages 15-49) infected with HIV/AIDS: 1.2% *I. Number of people with HIV/AIDS in each region: each red bead = 100,000 people *J. Per capita spent on health care in 2001: each band aid = \$40 *K. Per capita Gross National Income: each candy = \$350 *This information is not included on the other Ambassador cards, and there are no "world" statistics. When handing out the bags of beans, band aids and candy, start with the region with the least amount and continue to greatest.

North American Ambassador Card I am the North American Ambassador. Here are some statistics that shape my region of the world:	
	A. North America's population is estimated at: 323 million B. North American women bear an average of: 2.0 children C. Our life expectancy at birth is: 77 years
	D. The percentage of our people living in urban areas is: 79% E. Of our 12-17 year olds, 99% of the boys and 98% of the girls are enrolled in school. F. On average, there is one medical doctor per 374 people.
	G. Number of AIDS-related deaths in North America in 2005: 18,000 H. Percentage of adults (ages 15-49) from the United States infected with HIV/AIDS in 2003: .6%

Latin/South American Ambassador Card

I am the Latin and South American Ambassador.

Here are some statistics that shape my region of the world:

- A. Latin and South America's population is estimated at: 540 million
- B. Latin and South American women bear an average of: 2.7 children
- C. Our life expectancy at birth is: 71 years
- D. The percentage of our people living in urban areas is: 75%
- E. Of our 12-17 year olds, 51% of the boys and 58% of the girls are enrolled in school.
- F. On average, there is one medical doctor per 576 people.
- G. Number of AIDS-related deaths in 2005: 90,000
- H. Percentage of adults (ages 15-49) from **Brazil** infected with HIV/AIDS in 2003: .7%

European Ambassador Card

I am the European Ambassador.

Here are some statistics that shape my region of the world:

- A. Europe's population is estimated at: 727 million
- B. European women bear an average of: 1.4 children
- C. Our life expectancy at birth is: 74 years
- D. The percentage of our people living in urban areas is: 73%
- E. Of our 12-17 year olds, 97% of the boys and 100% of the girls are enrolled in school.
- F. On average, there is one medical doctor per 285 people.
- G. Number of AIDS-related deaths in 2005: 12,000
- H. Percentage of adults (ages 15-49) from **France** infected with HIV/AIDS in 2003: .4%

African Ambassador Card

I am the African Ambassador.

Here are some statistics that shape my region of the world:

- A. Africa's population is estimated at: 861 million
- B. African women bear an average of: 5.2 children
- C. Our life expectancy at birth is: 52 years
- D. The percentage of our people living in urban areas is: 33%
- E. Of our 12-17 year olds, 38% of the boys and 33% of the girls are enrolled in school.
- F. On average, there is one medical doctor per 1,742 people.
- G. Number of AIDS-related deaths in 2005: 2.5 million
- H. Percentage of adults (ages 15-49) in **Zimbabwe** infected with HIV/AIDS in 2003: 24.6%

Asian Ambassador Card

I am the Asian Ambassador.

Here are some statistics that shape my region of the world:

- A. Asia's population is estimated at: 3 billion, 830 million
- B. Asian women bear an average of: 2.6 children
- C. Our life expectancy at birth is: 67 years
- D. The percentage of our people living in urban areas is: 38%
- E. Of our 12-17 year olds, 62% of the boys and 53% of the girls are enrolled in school.
- F. On average, there is one medical doctor per 923 people
- G. Number of AIDS-related deaths in 2005: 583,000
- H. Percentage of adults (ages 15-49) in **Thailand** infected with HIV/AIDS in 2003: 1.5%

*Information for data cards taken from 2003 World Population Data Sheet, The World Health Report 2003, and 2004 Report on the Global AIDS Epidemic (Table of Country-Specific HIV/AIDS Estimates and Data, end 2003)

Extension to Activity 5

North American Region

United States

Adults & Children with HIV:	950,000
Adults (ages 15-49) with HIV:	940,000
Women (ages 15-49) with HIV:	240,000
Children ages 0-14 with HIV:	10,000
Percentage of adults (ages 15-49) infected:	0.6
AIDS-related deaths in 2003:	14,000
Per Capita spent on health care in 2001:	\$4887

all data in 2003 unless noted

North American Region

Canada

Adults & Children with HIV:	56,000
Adults (ages 15-49) with HIV:	55,000
Women (ages 15-49) with HIV:	13,000
Children ages 0-14 with HIV:	1,000
Percentage of adults (ages 15-49) infected:	0.3
AIDS-related deaths in 2003:	1,500
Per Capita spent on health care in 2001:	\$2163

all data in 2003 unless noted

Latin/South American Region

Brazil

Adults & Children with HIV:	660,000
Adults (ages 15-49) with HIV:	650,000
Women (ages 15-49) with HIV:	240,000
Children ages 0-14 with HIV:	10,000
Percentage of adults (ages 15-49) infected:	0.7
AIDS-related deaths in 2003:	15,000
Per Capita spent on health care in 2001:	\$222

all data in 2003 unless noted

Latin/South American Region

Mexico

Adults & Children with HIV:	160,000
Adults (ages 15-49) with HIV:	160,000
Women (ages 15-49) with HIV:	53,000
Children ages 0-14 with HIV:	n/a
Percentage of adults (ages 15-49) infected:	0.3
AIDS-related deaths in 2003:	5,000
Per Capita spent on health care in 2001:	\$370

all data in 2003 unless noted

Latin/South American Region

Honduras

Adults & Children with HIV:	63,000
Adults (ages 15-49) with HIV:	59,000
Women (ages 15-49) with HIV:	33,000
Children ages 0-14 with HIV:	3,900
Percentage of adults (ages 15-49) infected:	1.8
AIDS-related deaths in 2003:	4,100
Per Capita spent on health care in 2001:	\$59

all data in 2003 unless noted

European Region

United Kingdom

Adults & Children with HIV:	51,000
Adults (ages 15-49) with HIV:	47,000
Women (ages 15-49) with HIV:	14,000
Children ages 0-14 with HIV:	4,000
Percentage of adults (ages 15-49) infected:	0.2
AIDS-related deaths in 2003:	<500
Per Capita spent on health care in 2001:	\$1835

all data in 2003 unless noted

European Region

France

Adults & Children with HIV:	120,000
Adults (ages 15-49) with HIV:	120,000
Women (ages 15-49) with HIV:	32,000
Children ages 0-14 with HIV:	n/a
Percentage of adults (ages 15-49) infected:	0.4
AIDS-related deaths in 2003:	<1,000
Per Capita spent on health care in 2001:	\$2109

all data in 2003 unless noted

European Region

Spain

Adults & Children with HIV:	140,000
Adults (ages 15-49) with HIV:	130,000
Women (ages 15-49) with HIV:	27,000
Children ages 0-14 with HIV:	10,000
Percentage of adults (ages 15-49) infected:	0.7
AIDS-related deaths in 2003:	<1,000
Per Capita spent on health care in 2001:	\$1088

all data in 2003 unless noted

These country statistics can be used to further explore the differences between individual countries within a region.

European Region

Russia

Adults & Children with HIV:	860,000
Adults (ages 15-49) with HIV:	860,000
Women (ages 15-49) with HIV:	290,000
Children ages 0-14 with HIV:	n/a
Percentage of adults (ages 15-49) infected:	1.1
AIDS-related deaths in 2003:	9,000
Per Capita spent on health care in 2001:	\$115

all data in 2003 unless noted

African Region

Uganda

Adults & Children with HIV:	530,000
Adults (ages 15-49) with HIV:	450,000
Women (ages 15-49) with HIV:	270,000
Children ages 0-14 with HIV:	84,000
Percentage of adults (ages 15-49) infected:	4.1
AIDS-related deaths in 2003:	78,000
Per Capita spent on health care in 2001:	\$14

all data in 2003 unless noted

African Region

Namibia

Adults & Children with HIV:	210,000
Adults (ages 15-49) with HIV:	200,000
Women (ages 15-49) with HIV:	110,000
Children ages 0-14 with HIV:	15,000
Percentage of adults (ages 15-49) infected:	21.3
AIDS-related deaths in 2003:	16,000
Per Capita spent on health care in 2001:	\$110

all data in 2003 unless noted

African Region

Botswana

Adults & Children with HIV:	350,000
Adults (ages 15-49) with HIV:	330,000
Women (ages 15-49) with HIV:	190,000
Children ages 0-14 with HIV:	25,000
Percentage of adults (ages 15-49) infected:	37.3
AIDS-related deaths in 2003:	33,000
Per Capita spent on health care in 2001:	\$190

all data in 2003 unless noted

African Region

Zimbabwe

Adults & Children with HIV:	1,800,000
Adults (ages 15-49) with HIV:	1,600,000
Women (ages 15-49) with HIV:	930,000
Children ages 0-14 with HIV:	120,000
Percentage of adults (ages 15-49) infected:	24.6
AIDS-related deaths in 2003:	170,000
Per Capita spent on health care in 2001:	\$45

all data in 2003 unless noted

African Region

South Africa

Adults & Children with HIV:	5,300,000
Adults (ages 15-49) with HIV:	5,100,000
Women (ages 15-49) with HIV:	2,900,000
Children ages 0-14 with HIV:	230,000
Percentage of adults (ages 15-49) infected:	21.5
AIDS-related deaths in 2003:	70,000
Per Capita spent on health care in 2001:	\$222

all data in 2003 unless noted

Asian Region

India

Adults & Children with HIV:	5,100,000
Adults (ages 15-49) with HIV:	5,000,000
Women (ages 15-49) with HIV:	1,900,000
Children ages 0-14 with HIV:	120,000
Percentage of adults (ages 15-49) infected:	0.9
AIDS-related deaths in 2003:	n/a
Per Capita spent on health care in 2001:	\$24

all data in 2003 unless noted

Asian Region

Thailand

Adults & Children with HIV:	570,000
Adults (ages 15-49) with HIV:	560,000
Women (ages 15-49) with HIV:	200,000
Children ages 0-14 with HIV:	12,000
Percentage of adults (ages 15-49) infected:	1.5
AIDS-related deaths in 2003:	58,000
Per Capita spent on health care in 2001:	\$69

all data in 2003 unless noted

Asian Region

China

Adults & Children with HIV:	840,000
Adults (ages 15-49) with HIV:	830,000
Women (ages 15-49) with HIV:	190,000
Children ages 0-14 with HIV:	n/a
Percentage of adults (ages 15-49) infected:	0.1
AIDS-related deaths in 2003:	44,000
Per Capita spent on health care in 2001:	\$49

all data in 2003 unless noted

Asian Region

Philippines

Adults & Children with HIV:	9,000
Adults (ages 15-49) with HIV:	8,900
Women (ages 15-49) with HIV:	2,000
Children ages 0-14 with HIV:	n/a
Percentage of adults (ages 15-49) infected:	<0.1
AIDS-related deaths in 2003:	<500
Per Capita spent on health care in 2001:	\$30

all data in 2003 unless noted

*Information for data cards taken from 2003 World Population Data Sheet, The World Health Report 2003, and 2004 Report on the Global AIDS Epidemic (Table of Country-Specific HIV/AIDS Estimates and Data, end 2003)

Baggie Labels

Copy and attach to baggies
or print onto Avery 8660 labels

ASIA

$\$43 = 1$ band aid
Per Capita Annual Health Care Costs
1 band aid = \$40

EUROPE

$\$1,287 = 32$ band aids
Per Capita Annual Health Care Costs
1 band aid = \$40

AFRICA

$\$116 = 3$ band aids
Per Capita Annual Health Care Costs
1 band aid = \$40

LATIN AMERICA

$\$217 = 5$ band aids
Per Capita Annual Health Care Costs
1 band aid = \$40

NORTH AMERICA

$\$3,525 = 88$ band aids
Per Capita Annual Health Care Costs
1 band aid = \$40

ASIA

$\$2,119 = 4$ kisses
Per Capita Gross National Product
1 Hershey's Kiss = \$500

EUROPE

$\$23,987 = 48$ kisses
Per Capita Gross National Product
1 Hershey's Kiss = \$500

AFRICA

$\$1,030 = 2$ kisses
Per Capita Gross National Product
1 Hershey's Kiss = \$500

LATIN AMERICA

$\$4,496 = 9$ kisses
Per Capita Gross National Product
1 Hershey's Kiss = \$500

NORTH AMERICA

$\$41,285 = 83$ kisses
Per Capita Gross National Product
1 Hershey's Kiss = \$500

ASIA

9.9 million = 99 beads
Number of people with HIV/AIDS
1 red bead = 100,000

EUROPE

720,000 = 7 beads
Number of people with HIV/AIDS
1 red bead = 100,000

AFRICA

26.3 million = 263 beads
Number of people with HIV/AIDS
1 red bead = 100,000

LATIN AMERICA

2.1 million = 21 beads
Number of people with HIV/AIDS
1 red bead = 100,000

NORTH AMERICA

1.2 million = 12 beads
Number of people with HIV/AIDS
1 red bead = 100,000

Culminating Assessments

OVERVIEW

Three different culminating assessments are offered:

Option A – Individual Essay

Students are asked to combine the paragraphs they have written for homework over the course of the unit into one essay.

Two handouts accompany Option A:

- A framework for the student to use in writing his or her essay. The backbone of the essay will be the paragraphs students have been writing for homework throughout the unit.
- A grading rubric for both teachers and students to use.

Option B – Group Research Proposal Presentation

Students complete a ‘Research Proposal’ in small groups, and present the proposal to an Institutional Review Board (IRB) – either their classmates or other reviewers. The IRB will recommend the best proposal using the criteria for evaluation.

Two handouts accompany Option B:

- A guide to help student groups create a fundable research proposal.
- A presentation/grading rubric for both teachers and students to use.

Option C – Research Proposal Review as a member of an Institutional Review Board

Working either individually or as a group, students review a mock research proposal seeking to gain IRB approval. The IRB evaluates whether or not the research proposed should proceed.

Four handouts accompany Option C:

- A guide with questions to help students review the provided research proposal.
- A mock research proposal.
- A grading rubric for both teachers and students to use.
- An answer key for assessing student responses to the questions posed in handout 1.

The Science and Ethics of HIV Vaccine Testing Essay

Over the course of this unit, you have been asked to provide summaries of the lessons presented. This assignment asks you to combine them all into one paper. You have done most of the writing already, so this should be a matter of adding some introductory remarks, transitions between paragraphs, and conclusion.

Introduction: Provide a brief introduction describing the content of the paper (information about HIV biology, vaccines, ethics of research with humans, and the global contexts of HIV/AIDS).

Body: The summary paragraphs that you should include are:

(Note: you may combine some of the material in these paragraphs in order for your essay to flow more smoothly).

- Describe the structure and life cycle of HIV.
- What are possible targets for interrupting the HIV life cycle?
- What are the different types of vaccines currently available or in research that are most promising for preventing HIV infection?
- What are the challenges associated with creating an HIV vaccine?
- What are the basic principles that guide research with human subjects?
- Why would these principles be important to consider in a trial of an HIV vaccine?
- What potential impacts do levels of education, wealth, and health have on the distribution of HIV/AIDS? Use a particular example or examples from the lesson.
- What criteria should scientists use when determining where in the world to conduct an HIV vaccine trial?
- What ethical and cultural considerations must US researchers make before choosing populations to conduct such trials? Draw correlations between education, health resources and HIV/AIDS status, and between culture and participation in HIV/AIDS vaccine trials.

Conclusion: What conclusions can you draw from this unit? What are the implications for the future?

Reflection: Provide a brief reflection on a separate page describing whether this unit has changed your thinking about medical research, HIV/AIDS, and human trials, and if so, how. Would you change your answer to the first scenario about volunteering for a vaccine study? Please explain why or why not.

Essay: Science and Ethics of HIV Vaccine Testing

CATEGORY	4 Exemplary	3 Proficient	2 Partially Proficient	1 Developing
Introduction (Organization)	"The introduction is inviting, states the main topic and previews the structure of the paper."	"The introduction clearly states the main topic and previews the structure of the paper, but is not particularly inviting to the reader."	"The introduction states the main topic, but does not adequately preview the structure of the paper nor is it particularly inviting to the reader."	There is no clear introduction of the main topic or structure of the paper.
Transitions (Organization)	A variety of thoughtful transitions are used. They clearly show how ideas are connected.	"Transitions clearly show how ideas are connected, but there is little variety."	Some transitions work well; but connections between other ideas are fuzzy.	The transitions between ideas are unclear or nonexistent.
Sequencing (Organization)	Details are placed in a logical order and the way they are presented effectively keeps the interest of the reader.	"Details are placed in a logical order, but the way in which they are presented/introduced sometimes makes the writing less interesting."	"Some details are not in a logical or expected order, and this distracts the reader."	Many details are not in a logical or expected order. There is little sense that the writing is organized.
Accuracy of Facts (Content)	All supportive facts are reported accurately.	Almost all supportive facts are reported accurately.	Most supportive facts are reported accurately.	NO facts are reported OR most are inaccurately reported.
Support for Topic (Content)	"Relevant, telling, quality details give the reader important information that goes beyond the obvious or predictable."	"Supporting details and information are relevant, but some key content is absent"	"Supporting details and information are relevant, but several key pieces of content are absent"	Supporting details and information are typically unclear or not related to the topic.
Required Paragraphs Included (Content)	Draws in supplementary materials beyond what was covered in class. All required paragraphs present	All required paragraphs present.	"The majority of required paragraphs are present, some are missing."	The majority of required paragraphs are incomplete or missing.
Conclusion (Organization)	The conclusion is strong and thoughtfully addresses implications for the future	Conclusions are drawn from the unit and implications for the future are mentioned.	The conclusion and implications for the future are partially developed.	The conclusion and statement of implications is unclear or missing.
Reflection (Content)	Unusually thoughtful and thorough, uses several specific examples	Reflects on how learning has impacted them, uses specific examples	Reflects on learning but may not use examples	Reflection missing or incomplete

Group Research Proposal Presentation

Your research team has developed a vaccine for HIV that has produced promising results in laboratory and animal studies. You are now ready to proceed with Phase I vaccine testing in humans. Your task is to create a proposal to be reviewed by an Institutional Review Board (IRB). Once approved by the IRB, you may receive funding. However, since funding is limited only group will be able to conduct their trial. The funder (teacher!) will look to the recommendations of the IRB in deciding whether or not to fund your trial (in order for one group to receive extra credit)!

Use the questions below and your materials from the unit as guides as you create your proposal.

The presentation should focus on three main areas of understanding:

- **The structure of HIV and HIV vaccines**
- **The ethics of research with human participants**
- **The global context of conducting the trial**

For each area listed above, you will be expected to present the following information:

The structure of HIV and HIV vaccines

- Accurately explain where and how your vaccine will interrupt the HIV life cycle.
- Explain what part of the virus is used in the vaccine.
- Clearly identify the type of vaccine (subunit, DNA, etc.), and describe why you chose that type.
- How will you ensure that participants do not contract HIV from your vaccine?

The ethics of research with human participants

- Provide information about study participants (age, gender, size of study).
- Describe how many people are in a Phase I study and what its primary purpose is.
- Define *respect for persons* and how explain how your study honors respect for persons (autonomy, informed consent). Explain how you will deal with patient fears misconceptions about the vaccine trial (for example, fears of contracting HIV).
- Define *beneficence* and explain how study honors beneficence Do the benefits outweigh the risks for participants? How have you minimized the risks to the patients? Will the participants benefit directly from the study? How are the participants receiving the best care possible?
- Define *justice* and explain how the study honors justice. What basic healthcare and education about HIV do you owe the participants? How will the population be recruited and selected? Is a vulnerable population being used? How is the selection fair? Why should these participants bear the burden of the risks when the larger global population will reap the benefits of a successful trial?

The global context of conducting the trial

- Identify your study location and explain why you chose it.
How does the local trial population relate to the global population?
- What cultural considerations do you need to address in your recruitment and in how you conduct the trial?

In addition, you will be evaluated on the presentation itself:

You should have at least one visual aid to support your presentation, speak clearly, and make the presentation interesting for the audience. Your presentation should reflect thorough preparation.

Presentation Rubric

Science and Ethics of HIV Vaccine Trials

Student Name: _____

CATEGORY	Exemplary	Proficient	Partially Proficient	Developing	Not Enough to Evaluate
Structure of HIV and HIV Vaccine Strategies					
HIV Life Cycle Interruption	<ul style="list-style-type: none"> Accurately explains where and how vaccine will interrupt HIV life cycle Provides rationale for why this is the most effective strategy 	<ul style="list-style-type: none"> Accurately explains where and how vaccine will interrupt HIV life cycle 	<ul style="list-style-type: none"> Explains where and how vaccine will interrupt HIV life cycle with little support or some errors 	<ul style="list-style-type: none"> Does not clearly identify interruption of HIV life cycle 	<ul style="list-style-type: none"> Identification of life cycle absent
Type of Experimental Vaccine	<ul style="list-style-type: none"> Type of vaccine accurately correlates to where HIV life cycle is to be interrupted Provides rationale for why this is the most effective type of vaccine to use 	<ul style="list-style-type: none"> Type of vaccine is clearly identified Provides rationale for the type chosen 	<ul style="list-style-type: none"> Both type and rationale are mentioned but not clearly explained Description of type or rationale is complete but the other component is missing 	<ul style="list-style-type: none"> Type of vaccine identified incorrectly Rationale unclear or illogical 	<ul style="list-style-type: none"> Type of vaccine not identified Rationale absent
Safety of Vaccine	<ul style="list-style-type: none"> Explanation of why the vaccine will be effective but not infectious Explanation of why other vaccine types may cause infection or increase risks 	<ul style="list-style-type: none"> Explanation of why the vaccine will be effective but not infectious 	<ul style="list-style-type: none"> Partial explanation of why the vaccine will be effective but not infectious 	<ul style="list-style-type: none"> Explanation incorrect, unclear, or illogical 	<ul style="list-style-type: none"> Explanation absent
Design of Experimental Vaccine	<ul style="list-style-type: none"> Clearly identifies part of the HIV virus used in vaccine and provides rationale for why it is the best choice Makes clear connection to type, life cycle, and safety 	<ul style="list-style-type: none"> Clearly identifies part of HIV virus used in vaccine Makes connection to type, life cycle, and safety 	<ul style="list-style-type: none"> Identifies part of HIV virus used in vaccine Makes some connections to type, life cycle, and/or safety 	<ul style="list-style-type: none"> Incorrectly identifies part of HIV virus used in vaccine Weak connections to type, life cycle, or safety 	<ul style="list-style-type: none"> Identification absent No connections to type, life cycle, or safety

CATEGORY	Exemplary	Proficient	Partially Proficient	Developing	Not Enough to Evaluate
Ethics of Research with Human Participants					
Description of Trial	<ul style="list-style-type: none"> Provides information about study participants (age, gender, size of study) and justification for the use of this particular population Description of trial accurately reflects Phase I parameters and provides explanation of subsequent phases. 	<ul style="list-style-type: none"> Provides information about study participants (age, gender, size of study) Description of trial accurately reflects Phase I parameters 	<ul style="list-style-type: none"> Provides most information about study participants, but is partially incomplete Description of trial partially reflects Phase I parameters 	<ul style="list-style-type: none"> Provides limited information about study participants Description of Phase I trial is incorrect 	<ul style="list-style-type: none"> Information about study participants is absent
Autonomy	<ul style="list-style-type: none"> Defines respect for persons with clear examples Explains how study honors respect for persons with specific examples related to informed consent and autonomy Explains detailed strategies for dealing with patient misconceptions, providing specific examples 	<ul style="list-style-type: none"> Defines respect for persons Explains how study honors respect for persons Explains strategies for dealing with patient misconceptions 	<ul style="list-style-type: none"> Defines respect for persons Explanation of how study honors respect for persons is incomplete Identifies strategies for dealing with patient misconceptions but explanation is incomplete 	<ul style="list-style-type: none"> Inaccurate definition of respect for persons Explanation of how study honors respect for persons is inaccurate Strategies for dealing with patient misconceptions lacking 	<ul style="list-style-type: none"> Definition is absent Explanation is missing Strategies absent
Beneficence	<ul style="list-style-type: none"> Defines beneficence with clear examples Explains how study honors beneficence with specific examples Detailed description of benefits for patients including medical care during study Detailed description of risks to patients including how risks are minimized Rationale explains how benefits outweigh risks and makes connections to individual and societal benefits. 	<ul style="list-style-type: none"> Defines beneficence Explains how study honors beneficence Outlines benefits for patients including medical care during study Outlines risks to patients including how risks are minimized Rationale explains how benefits outweigh risks 	<ul style="list-style-type: none"> Defines beneficence Explanation of how study honors beneficence is incomplete Partially outlines benefits and risks to patients Incomplete explanation of how benefits outweigh risks 	<ul style="list-style-type: none"> Inaccurate definition Explanation of how study honors beneficence is inaccurate Benefits and risks to patients incorrectly identified Incorrect explanation of how benefits outweigh risks 	<ul style="list-style-type: none"> Definition is absent Explanation of how study honors beneficence is missing Benefits and risks not mentioned Explanation of how benefits outweigh risks is missing
Justice	<ul style="list-style-type: none"> Defines justice with clear examples Explains how study honors justice with specific examples Explains how strategies for recruitment do not target or exclude based upon convenience or availability Provides rationale for specific population selected with consideration to influence and conflicts of interest 	<ul style="list-style-type: none"> Defines justice Explains how study honors justice Defines strategies for recruitment Provides rationale for specific population selected with consideration to vulnerability 	<ul style="list-style-type: none"> Defines justice Explanation of how study honors justice is incomplete Defines strategies for recruitment Rationale for specific population selected is unclear 	<ul style="list-style-type: none"> Inaccurate definition Explanation of how study honors justice is inaccurate Strategies for recruitment weak Rationale for specific population selected contains errors Connection between local trial population and global population is illogical 	<ul style="list-style-type: none"> Definition is absent Explanation is missing Strategies absent Rationale is missing

CATEGORY	Exemplary	Proficient	Partially Proficient	Developing	Not Enough to Evaluate
Global Context					
Study Location	<ul style="list-style-type: none"> Identifies study location Provides rationale for choice with explanation for why alternatives were not chosen Provides strong connection between local trial population and global population 	<ul style="list-style-type: none"> Identifies study location Provides rationale for choice Provides connection between local trial population and global population 	<ul style="list-style-type: none"> Identifies study location Rationale for choice incomplete Connection between local trial population and global population weak 	<ul style="list-style-type: none"> Study location unclear Rationale is illogical Connection between local trial population and global population is illogical 	<ul style="list-style-type: none"> Study location absent Rationale is missing Connection is absent
Cultural Considerations	<ul style="list-style-type: none"> Cultural considerations addressed for recruitment with specific examples of for different segments of the society Cultural considerations addressed during trial with specific examples for relationship between patient and doctor/caregiver 	<ul style="list-style-type: none"> Cultural considerations addressed for recruitment Cultural considerations addressed during trial 	<ul style="list-style-type: none"> Cultural considerations for recruitment or during trial mentioned but not clearly explained 	<ul style="list-style-type: none"> Cultural considerations for recruitment or during trial incomplete or illogical 	<ul style="list-style-type: none"> Cultural considerations absent
Presentation					
Presentation	<ul style="list-style-type: none"> Excellent use of visual aid (s) in supporting points Students speak clearly and present information in an engaging manner Presentation demonstrates outstanding level of preparation 	<ul style="list-style-type: none"> Good use of visual aid (s) in supporting points Students speak clearly and present information in an engaging manner Presentation demonstrates good level of preparation 	<ul style="list-style-type: none"> Visual aid(s) present, but may not strongly support points Students speak somewhat clearly, some information is difficult to follow Presentation demonstrates preparation 	<ul style="list-style-type: none"> Visual aid (s) confusing, inaccurate, or incomplete Presentation is somewhat unclear, some information is incomplete or difficult to follow Presentation demonstrates limited preparation 	<ul style="list-style-type: none"> Visual aid (s) lacking Presentation is unclear, most information is incomplete or difficult to follow Evidence for preparation is lacking

NAME _____ Date _____ Period _____

HIV Vaccine Trials and Human Subject Selection

Research Proposal Review as a Member of an Institutional Review Board

1. Your assignment is to become a member of an Institutional Review Board (IRB) and review a proposal for an HIV vaccine trial. The application is attached.
2. Use the basic principles and IRB review handouts from class to review the proposal and answer the following questions.
3. Identify areas of concern (and there are problems!) in the proposal, explain why you are concerned using supporting details from the handouts to back up your viewpoint.
4. Be sure to state the ethical principle(s) being violated for each problem you find.
5. Please type your responses.

Questions:

1. Do the benefits outweigh the risk to the subjects? Will the subjects directly benefit from the study? Are they at risk for serious harm? Is there a way for a subject to get out of the study?
2. Have the researchers minimized the risks? Are the subjects receiving the best care possible?
3. Are the subjects being selected in an equitable way? Has there been any undue influence? Is a vulnerable population being used?
4. Will the methods and results of the study keep the subjects identity and HIV status confidential?
5. Has the researcher assured the subject understands all aspects of the study and provided a way out if they do not wish to participate?
6. How has this unit changed your thinking about medical research, HIV/AIDS and human subject trials?
7. How would you change your answer for the first scenario about your friend having HIV and wanting you to be a volunteer for a vaccine study?

Research Proposal

- I. Date of application:** (Teacher to fill in current date)
- II. Investigator:** National Institute of Allergy and Infectious Diseases (NIAID)
- III. Title of Study:** Safety of an HIV Vaccine in HIV Negative Women
- IV. Time Period:** 6 months
- V. Funding:** National Institutes of Health and Bigmoneydrugs International
- VI. Summary of Research Activities**

A. Background

- i. HIV/AIDS has become a devastating pandemic with developing countries being the most adversely affected.
- ii. There is no cure for this disease with a 98% mortality rate.
- iii. The treatments used are expensive and require access to medical care, medication and monitoring.
- iv. Cultural norms in many of the nations with high infection rates limit the effectiveness of prevention education.
- v. The HIV disease process put people at high risk for infection because the disease may be asymptomatic for several years and the testing for this disease is not readily available worldwide.
- vi. India has a rapidly growing population of HIV positive people. There are 1 billion people; half are sexually active adults. The epidemic has spread to all states and territories, the highest prevalence being in the state of Maharashtra. The most common cause of infection is heterosexual contact.
- vii. The infection rate by gender varies, but there are 2-2.5 times more males infected than females.

B. Research design

- i. Study design sequence and timing
 - 1. The study will span a six month period.
 - 2. The subjects will be screened for general health and negative HIV status.
 - 3. Food will be delivered weekly to each participating family
 - 4. The subject will be injected with the vaccine or placebo in a standard blind study format.
 - 5. Blood will be drawn for antibody testing each month for 6 months.
 - 6. The subjects will not be given HIV prevention information so as to not influence normal cultural practices. This protocol will allow for the natural exposure to occur and thus allow more data to be collected.
 - 7. At the end of the study, results will be reported to the participants and their HIV status will be checked one more time. HIV prevention information will be given to the participants.

-
- ii. How study procedures differ from standard care
 - 1. There is no standard for HIV vaccines at this time.
 - 2. If a subject becomes infected she will be notified and the local health authorities will be notified

C. Controls and Blinding

- i. There will be a placebo used in this trial.
- ii. The researcher in the field will not know what is being administered.
- iii. The subjects will not know if they received the vaccine or the placebo

D. Subjects

- i. Subjects: Females age 15-49
- ii. Special Qualifications: HIV negative, married, and available for 6 months of follow up
- iii. Source Of Subjects: India, State of Maharashtra
- iv. Number of Subjects: Phase I prevention trial – 20-80
- v. Exclusion Criteria
 - 1. HIV positive
 - 2. Pregnant
 - 3. Live attenuated vaccination in the past 120 days
 - 4. Husband objects to wife's participation
- vi. Recruiting subjects
 - 1. Head of villages will be approached and informed of the nature of the study and asked to provide names of potential subjects.
 - 2. Husbands and wives will then be approached and given the information and consent forms, which will be in their native language. An interpreter will be available for questions.
- vii. Payments or free services
 - 1. Subjects will receive a complete physical including HIV screening.
 - 2. The subject and family will receive food during the study to assure adequate nutrition during the study.
 - 3. The village leader will receive compensation for each referral to be negotiated for the benefit of the village.
- viii. Location of study
 - 1. The exams, inoculations and follow up blood draws will be done in the subject's home.

E. Risks and Benefits

- i. Nature and amount of risk
 - 1. Patient may contract HIV from the Vaccine
 - 2. They may contract HIV from unprotected sexual contact if while taking the placebo or if the vaccine is ineffective.
 - 3. There may be unforeseen side effects of the vaccine as this is the first human trial.
 - 4. Infection could develop at the site of inoculation
- ii. Benefits
 - 1. The family will receive better nutrition for the six month trial.
 - 2. The subject may become immune to HIV
 - 3. If successful, a Phase 2 trial will be done extending the services to the village of the subjects
 - 4. If successful, this drug will go through Phase 3 trials and be available for the U.S. market.

F. Adverse Effects

- i. If a subject becomes ill from the vaccination process or contracts HIV during this study, they will receive treatment from the local health care system.
- ii. Compensation for their illness will be in the form of payment for their care.

G. Confidentiality

- i. Data will be published without identifying information.

H. Consent forms will be provided in the native language.

I. Drugs

- i. A recombinant Vaccine for HIV-1
- ii. Toxicity - Not established Phase I trial

NAME _____ Date _____ Period _____

IRB Review Questions

Response	Criteria	Score
Above Standard	Clarity of thought, Complete. Shows understanding of all flaws in the IRB application and clearly identifies the Basic Ethical Principles violated. Describes corrections needed to improve study both scientifically and ethically.	
Standard	Clarity of thought, shows understanding of flaws in the IRB, but did not identify all flaws. Clearly identifies the science and basic ethical principles violated for those flaws identified.	
Below Standard	Completes the assignment, but explanations may be slightly ambiguous or unclear, may contain some incompleteness, inappropriateness, or unclarity in identification of Flaws and/or does not correctly identify ethical principles	
Needs Improvement	Begins successfully, but omits significant parts or fails to complete, may misuse ethical and scientific terms. Information may be incorrect or omitted, incorrect or incomplete in analysis, inferences and conclusions.	
Conventions	Criteria	Score
Standard	Writing style shows organization, grammatical correctness, correct spelling.	
Below Standard	Errors in spelling, grammar, or organization.	

Total Score: _____

Comments: _____

Key for Research Proposal Review

Questions: Students should be citing facts from the Basic Principles handout.

1. Principle = Beneficence

- a. Very few benefits
 - i. Better nutrition
 - ii. Possibility of immunity
- b. Risks-
 - i. Side effects from an unknown medication.,
 - ii. Infection at injection site.
 - iii. Contracting HIV through vaccine or unprotected sex with placebo or ineffective vaccine.
 - iv. There is no opt out option listed in the proposal.
 - v. Study is too short and there is no long term follow up to see if the HIV status of the subject changes. Could pose risks not only for this population, but also for the subjects in the next phase.

2. Principle = Beneficence

- a. It is difficult to minimize risk from drug itself as it has not had human trials yet.
- b. By using a placebo subjects may take more risks in sexual activity thinking they are protected.
- c. The subjects are not being offered the best care (drug cocktails) if they become infected.
- d. If the women become pregnant during the study is there a risk to the fetus.
- e. HIV prevention information is being withheld.

3. Principle = Justice

- a. Women only in the study? Why not men, reasoning not clearly stated.
- b. Women in this part of the world have few rights. The husband or village leader can force or prevent a women's participation. This makes them a vulnerable population
- c. Undue influence is present by negotiating with the village leader, perhaps leading him to force women in his village to participate.
- d. Malnutrition is a huge problem in this area, so women may participate to get more food for their family. Husbands may force their wives to participate for the food and/or to receive favors from the village leader.

4. Principle = Respect for Persons

- a. The village leader will know who is in the trial or who refused allowing undue influenced to be placed on subjects
- b. Families will know as husbands will have the opportunity to object. They may shun their wives if they have complications as a result of the trial
- c. The subjects will be confidential in the reporting of the data in the final publication.
- d. Their health status will be reported to the local health care providers.
- e. The whole

5. Principle = Respect for Persons

- a. The informed consent document is not included.
- b. There is no indication of who the interpreters are. They may have a bias to convince women to join the study.
- c. Limited education and understanding of HIV and the immune system may hamper the subjects ability to understand the purposes and risks of the study
- d. There are many opportunities for undue influence
- e. There is no option for leaving the study after starting listed in the proposal

6. Students own viewpoint with answers backed up by course material

7. Students own view point with answers backed up by course material.



Appendix

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111 Creating an HIV Vaccine

115 Vaccine Challenges

120 The Role of Non-Human Primates

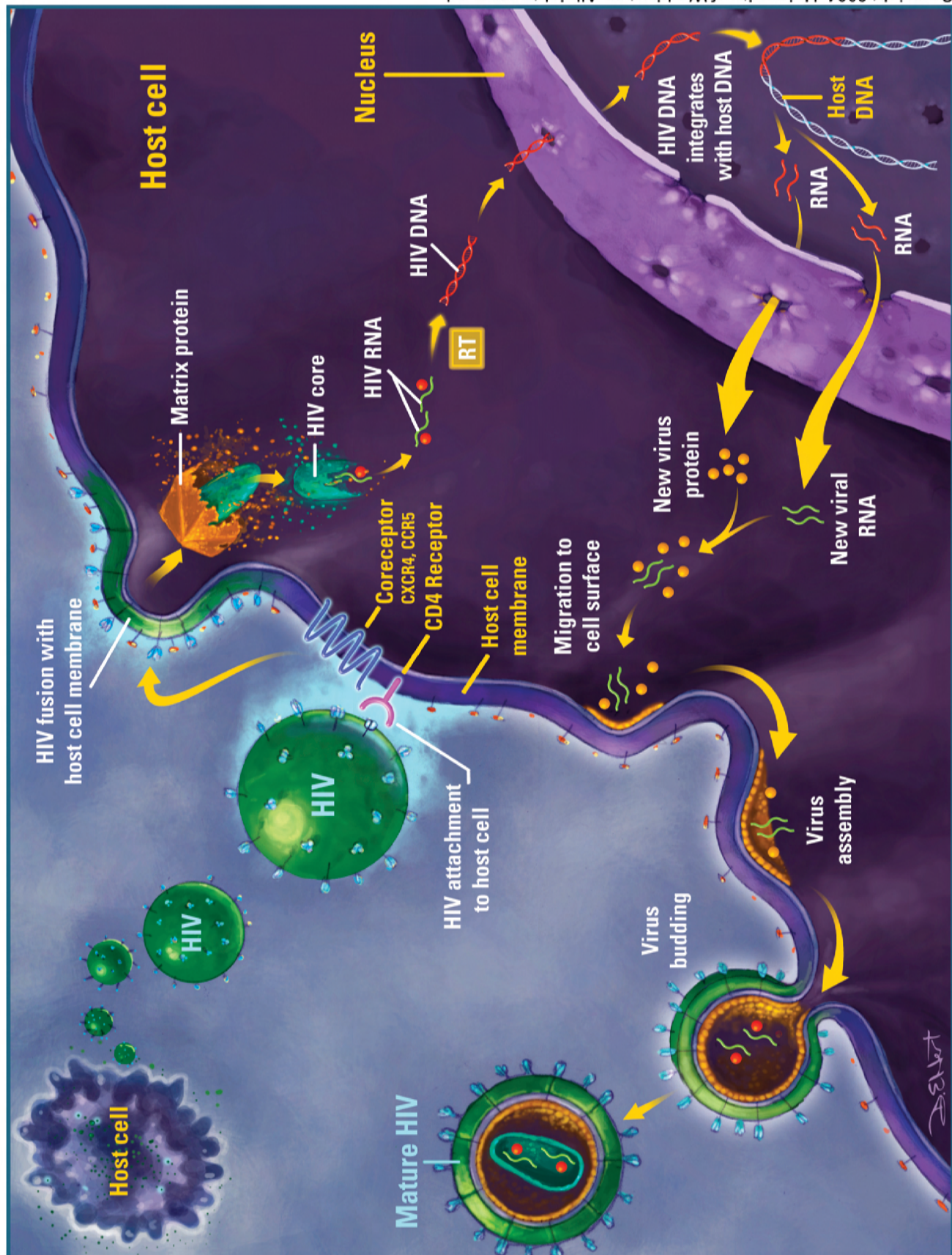
124 Lesson Extensions

126 Resources for the Ethical Considerations for using Human Subjects in Research

- Declaration of Helsinki
- Nuremberg Code

131 Resources for HIV Vaccine Information

Overview of HIV infection



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HIV Background

Viruses: Living Or Non-living?

(Before teaching this section review characteristics of living and non-living cells.)

When a virus is outside a living cell it is crystalline in nature. It produces no energy and performs no life functions since it has no nucleus or cytoplasmic organelles. All living substances grow and reproduce but a virus cannot do that until it enters a living host. A virus is many times smaller than a bacterium and can be seen only by an electron microscope. The HIV virus is so small that if it were the size of a softball, the white blood cell would be about the size of a classroom! It may contain either a single or double strand of DNA or single stranded RNA within a protective protein coat called a capsid. The capsid protects the RNA from harsh environmental conditions.

The RNA Molecule

- A. RNA is similar in structure to DNA, but it is single stranded and uses the sugar ribose. The backbone is made up of ribose and phosphoric acid groups, which alternate. A nitrogenous base side chain is attached to each ribose-phosphoric acid group. The four side chains or bases in RNA are adenine, cytosine, guanine and uracil. Uracil is the base which takes the place of thymine in the DNA model. The combination of one phosphate, a 5 carbon sugar and one of the 4 bases is called a nucleotide.
- B. In a normal cell there are 3 major types of RNA:
 - i. mRNA (messenger RNA)
 - 1. mRNA serves as a temporary «messenger» which makes a complementary copy of DNA genes and carries them from the nucleus to the ribosome in the cytoplasm.
 - ii. tRNA (transfer RNA)
 - 1. As the mRNA attaches to the ribosome, the tRNA acts like a «trucker» with two ends. One end «fits» the mRNA code and the other end carries specific amino acids. As the first end «fits» into the mRNA code each amino acid links to the next amino acid forming a long chain which eventually becomes a protein.
 - iii. rRNA(ribosomal RNA)
 - 1. rRNA, found in the ribosome helps the tRNA to work more efficiently.

The HIV Virus

- A. HIV fuses with the lipid-protein cellular membrane of a T-cell (or other target cell) and sneaks through it to invade the host cytoplasm. Once inside, the viral reverse transcriptase copies the single strand of HIV RNA to make a single strand of DNA. The reverse transcriptase then makes a second complementary strand of DNA. This double stranded DNA is now ready to invade the cell's nucleus.

B. HIV is a retrovirus - the flow of genetic information of the virus is reversed from the usual 'central dogma' of DNA->RNA. In a retrovirus, the information is copied backwards from RNA to make DNA, which is then inserted into the cell's DNA. In translation the DNA then forms mRNA. This method of copying happens in no other living system. When HIV inserts itself directly into the cell's DNA this sequence remains integrated in the host genome. This extra step in replication from RNA to DNA to mRNA results in many mutations in replication. (This high mutation rate causes drug developers to have to play «catch up» when they try to develop new drugs to interfere with the HIV in the viral replicating process.).

HIV Transmission

- A. Transmission: Have students work in pairs and develop a list of how HIV is transmitted and risk behaviors.
- B. Body fluids –
- i. Semen
 - ii. Vaginal fluid
 - iii. Blood
 - iv. Breast milk
- C. Risk behaviors
- i. Unprotected sex
 - ii. IV drug use with needle sharing
 - iii. Infected mother to child
- D. Heterosexual transmission is the most common cause of disease transmission.
- E. Individuals capable of infecting others may not know they have the disease as the initial symptoms may mimic the flu and then the person will be asymptomatic for a fairly long period of time.

HIV Origins

Research based on genetic similarity of the viral genome and proteins indicates that HIV-1 arose through a transmission of SIV (Simian Immunodeficiency Virus) from Chimpanzees to Humans, and HIV-2 arose through transmission from SIV from Sooty Mangabeys to Humans.

In some communities, it is believed that the US government developed HIV as a tool for the genocide of segments of the population (African-American, for example). Although this is not a hypothesis considered by most scientists, it does impact the willingness of certain groups to participate in HIV research.

Immune System – Background

Natural or Innate

- A. relatively nonspecific – only recognizes a limited number of different pathogen characteristics
- B. when activated is called the inflammatory response
- C. born with capacity fully developed, does not change after birth
- D. includes
 - i. physical & chemical barriers that block pathogen entry into body
 - ii. phagocytic cells, (neutrophils & macrophages), attack & engulf pathogens
 - iii. other cells: mast cells, eosinophils, basophils,
 - iv. blood protein systems: complement, coagulation, acute phase, and kinin systems
 - iv. cytokines secreted by inflammatory cells that influence both the innate and the acquired immune responses

Acquired or Adaptive Immune Response

- A. very specific, responds to specific sites on invading pathogens
- B. response is different for each pathogen, even for different types of a given pathogen
- C. when activated is called the immune response
- D. response to a pathogen only develops after an individual encounters a pathogen, therefore continues to develop over a lifetime
- E. includes only lymphocytes (3 kinds) and the antibodies produced by B cells which are one of the types of lymphocyte
 - i. T cells – are three main types,
 - 1. Helper T cells (CD4+),
 - helper T cells are key to the entire immune response
 - activate cytotoxic T cells, B cells & macrophages
 - 2. Cytotoxic T cells (CD8+)
 - effective against intracellular pathogens
 - kills virally infected cells & tumor cells
 - recognizes specific antigens on cells
 - requires activation
 - 3. Natural killer cells
 - a primitive lymphocyte
 - lacks the specificity of a cytotoxic T cell
 - sometimes considered part of innate immunity
 - kills virally infected cells & tumor cells

ii. B cells

- produce antibodies that are specific to pathogen antigens
- are 5 different types of antibody, each with different functions
- 5 types of antibody are IgM, IgA, IgD, IgG, IgE
- effective against extracellular pathogens
- each type of antibody activates a different set of mechanisms that work to destroy or inactivate pathogens

F. once activated a fraction of either T or B cells will become memory cells

- some immune memory is retained for many years and other types are only retained for a period of months.
- we do not understand why there are differences in the duration of immune memory for various pathogens.

G. immunity can be acquired actively via the processes described above or passively via transfer of antibodies as happens when an infant receives antibodies from the mother via breast milk

- can be active or passive

**Artificially
Acquired
Immunity**

Discuss students' experiences with vaccines first – What vaccines have they had?

- Some form of the pathogen is introduced by the vaccine which stimulates the immune response by presenting the antigen

Creating an HIV Vaccine-Background

HIV Life Cycle – Review

- A. Discuss life cycle based on animations shown
- B. Why can't the immune system fight HIV like other viruses?
 - i. attacks cells responsible for mounting immune response
 - ii. high mutation rate
 - iii. many viral regions that immune system could target for response are shielded
 - iv. Inserts itself into the host DNA
 - 1. part of that cell until it dies
 - 2. replicated as part of DNA each time cell divides

Basic Genetic Structure of HIV

- A. Retrovirus
 - i. Composed of single strand of RNA
- B. High Mutation Rate
 - i. Inherent nature of RNA leads to more mistakes than DNA
 - ii. RNA transcriptase has “built-in” mistakes generator
 - iii. 1000s of copies made a day – high chance of variability
 - iv. in 24 hrs 10¹⁰ new virions a day! – averages one mutation per replication
 - v. leads to variations of HIV:
 - 1. within one person
 - 2. can be changes between two people – one who had HIV originally and one who contracted it from them
 - 3. variation throughout the world – different “clades” in different parts of the world (HIV in Africa different from HIV in United States or Thailand). 7-8 major types
- C. Three main genes
 - i. Gag: structural proteins – give rise to main structures such as capsid, general envelope, etc.
 - ii. Pol: enzymes – direct development of reverse transcriptase, protease, and other important enzymes which aid in “hijacking” the host cell and forcing it to make multiple copies of the virus
 - iii. Env: surface proteins - these are the proteins involved in recognition and binding to T cells; they are constructed of a trimer of three ‘ball’ units (gp 120, or glycoprotein 120) attached to three ‘stick’ units (gp 41) that span the viral membrane.

Developing a Vaccine for HIV

A. Desired responses:

- i. Want to create neutralizing antibodies that will be broadly reactive. Neutralizing antibodies bind to the virus and prevent it from infecting cells. Neutralizing antibodies ideally need to attach to, or label, viruses from many different clades of HIV (not just one type)
- ii. Neutralizing antibodies need to target specific protein regions, which are more conserved (not mutated) in HIV. However, these conserved regions are not in readily accessible regions of the protein
- iii. Increase cytotoxic T cell (CTL) response-A vaccine also needs to enable T cells to respond to many variations of HIV env proteins. The CTL response is necessary to keep the HIV infection from overwhelming an individual's immune response, but cannot prevent infection from occurring in the first place.
- iv. The desired immune response needs to somehow allow for, or change with, the many virus variations and escape mutations that occur or vaccine will not be effective for any length of time

B. Focus on Env protein

- i. Exposed regions are largely covered by glycoproteins, which shield regions that might invoke a neutralizing antibody response. Glycoproteins themselves do not elicit a strong antibody response.
- ii. Conserved regions of the Env protein are only exposed when binding with receptor (CD4 on T cells) and co-receptor (CXCR4 or CCR5, depending on the cell). The exposed regions are more prone to changes, and much more common (found on other cells, etc.) and thus a vaccine to exposed regions of the protein is not likely to be effective.

C. Vaccines which have been developed:

- i. AIDSVAX vaccine
 1. being tested by VaxGen and NIAID (National Institutes of Allergy and Infectious Disease)
 2. uses a protein subunit of the virus to stimulate the immune response of a vaccinated individual
 - a. disappointing results – This vaccine was highly immunogenic (people's immune systems really responded well and produced lots of antibodies). However, these antibodies were not effective at neutralizing HIV.

3. contains multiple viral protein sequences to ensure a response to a broad range of HIV strains
4. also being researched in conjunction with another vaccine to boost cytotoxic T cells. Inducing a 'dual response' (both neutralizing antibody and CTL) may prove effective.

ii. HIV-1ΔkURNe vaccine

1. strain of HIV genetically altered in the laboratory to produce a weakened form of the virus
2. large portions of HIV genetic code have been snipped out – cannot produce lethal effect
3. tested in monkeys
 - a. initial trials encouraging – monkeys developed immunity to the virus
 - b. over time the weakened virus mutated back into a deadly form
 - c. vaccinated monkeys developed SIV from the vaccinations!

iii. Many other vaccines in “production”

1. expected that by the end of 2004 more than 30 clinical trials will be underway globally.
2. can show chart of research at this point, or save for later lesson
 - a. Developing an AIDS vaccine, THE LANCET, Infectious Diseases Vol 4 July 2004 – page 408-409

If a Vaccine is Developed...How is it Tested?

- A. Many research models are used before a vaccine can be tested in humans
- B. Scientific Methods Used in Biomedical Research (see table 2.3 from For the Greater Good Curriculum, available from Northwest Association for Biomedical Research, www.nwabr.org)
- C. Primate Models and HIV Research
 - i. Contributions to understanding of HIV
 1. Most Primates DO NOT contract HIV, but they DO contract a similar infection from Simian Immunodeficiency Virus (SIV).

2. Chimpanzees can contract HIV-1 but:
 - a. Disease is very rare
 - b. Takes more than 10 years from contraction to death
 - c. Now on endangered species list
3. Macaques, a species of monkey including pig-tailed macaques
 - a. Contract SIV
 - b. Show a range of pathogenicity – different strains and species (like HIV in humans)
 - c. Death in 6 months – 2 years after infection
 - d. Disease similar to AIDS in people
 - i. CD4+ T-cell decline
 - ii. Wasting
 - iii. Envelope uses the same coreceptors as HIV, but differs in amino acid sequence
 - e. SHIV
 - i. Hybrid of HIV-1 and SIV
 - ii. Contains HIV-1 env in SIV backbone
 - iii. Animal-passaged virus is more pathogenic (Animal-passaged virus is grown/cultivated in an animal and then transferred to another animal, as opposed to being grown in cell culture)
- ii. Vaccine research
 1. can use primates as models
 - a. produce similar vaccine which targets SIV instead of HIV and test in primates
 2. SHIV
 - a. Causes disease in monkeys, like SIV
 - b. Vaccine can contain HIV env gene or protein
 - i. Components of a successful vaccine could move directly into formulations for humans
 3. Can give HIV vaccine to test toxicity, etc. in primate model, but cannot challenge (infect with HIV) so gives incomplete information
- iii. Challenges:
 1. cannot test complete HIV vaccine in primate model

<p>Vaccine Challenges</p>	<p>Overview</p> <p>There are many challenges to finding a vaccine against HIV, yet finding an effective vaccine against HIV may be the only realistic approach to controlling the ever-expanding global HIV epidemic. Worldwide efforts are focused on designing an effective vaccine to prevent infection with HIV, to limit illness if infected or to reduce the amount of virus found in the bloodstream of a person already infected with HIV.</p>
<p>Characteristics of an Ideal HIV Vaccine</p>	<p>An ideal HIV vaccine would have all the characteristics mentioned below. Finding such a vaccine, however, becomes a formidable challenge as we try to balance the effectiveness of the vaccine and the practicality of the vaccine.</p> <p>An ideal HIV vaccine would:</p> <ol style="list-style-type: none"> 1. Be effective in preventing transmission through sexual contact, mother-to-child contact, and through tainted IV drug use. 2. Be very safe, with minimal risk of adverse reactions even in unscreened “real world” populations. 3. Be given in a single dose. 4. Offer long-lived protection many years after vaccination 5. Be low cost, allowing widespread vaccination in developing countries 6. Be easy to transport and administer, even in countries with minimal infrastructure. 7. Work well against different variations of the virus. <p>This ideal vaccine may not be practical or realistic in the face of today’s AIDS epidemic, however. Given the scope of the disease, even an imperfect AIDS vaccine that limits HIV growth in an infected person but does not necessarily prevent infection will result in a significant impact on the spread of the disease. If we could find a vaccine that would slow the progression of HIV in already-infected individuals, this could delay the onset of AIDS, reduce the risk of HIV transmission from those individuals to their sexual partners and from infected mothers to their children. An effective HIV vaccine would therefore slow the spread of HIV in human populations and provide hope of its eventual eradication. However, despite extraordinary advances in knowledge there are still many challenges to developing an HIV vaccine.</p>

Challenges in HIV Vaccine Development

Challenges to HIV vaccine development can be broadly classified into the following categories:

1. **HIV Sequence variation:** HIV continually evolves because of genetic mutation introduced when the viral RNA polymerase makes more copies of HIV genome and recombination between the two strands of the viral RNA genome. Initially, a person is infected with only one or a limited number of HIV variants. Once HIV infection becomes established, however, the virus continually undergoes genetic changes, and many variants may arise within an infected person. Whenever a drug or immune response destroys one variant, a distinct but related resistant variant can emerge. In addition, certain variants may thrive in specific tissues or become dominant in an individual because they replicate faster than others. Any of these changes may yield a virus that can escape identification and attack by (i) neutralizing antibodies (NAbs) that bind the viral variants and prevent the virus from binding and infecting its target cell and (ii) cytotoxic T lymphocytes (CTL) that perform immune surveillance and kill the virus infected cells.

There are two types of HIV, HIV-1 and HIV-2. HIV-1 is primarily responsible for the global pandemic. Using HIV-1 **isolates** obtained from patients around the world, the genes encoding their envelope and core proteins have been analyzed and compared. On this basis, scientists have grouped HIV-1 isolates worldwide into three groups, M, N, and O. The M (Major) group can be further divided into nine **subtypes**, or **clades**. Each subtype within a group is about 30 percent different from any of the others. If an individual is infected with two different subtypes, a new (recombinant) form of virus can develop that contains gene fragments from both parental viruses. Hence, since there are a vast number of HIV variants circulating worldwide, a successful vaccine will need to induce an immune response that protects against a large portion of these variants. In contrast, successful vaccines for other viruses have only had to protect against one or, like polio, a limited number of virus subtypes. Thus, HIV researchers will need to account for strain variation within individuals and among populations when developing HIV vaccines.

Despite HIV changing so much due to genetic mutation and recombination, HIV still needs to preserve certain regions on its viral proteins for efficient function. For example: HIV is coated with viral envelope that helps in the viral binding and entry leading to infection of target cells. The viral envelope glycoprotein changes its outside such that it escapes from powerful neutralizing antibodies (NAbs), but retains the structural integrity of the core that it exposes just before binding to target cells. This core is highly conserved amongst diverse isolates from different clades. In fact, NAbs that recognize the conserved core of the HIV envelope glycoprotein

(broad NAbs) tend to recognize and prevent infection of HIV virus isolates from different clades suggesting that targeting these conserved regions will result in a vaccine that can recognize the wide variety of circulating HIV vaccine. Though these broad NAbs have been shown to prevent infection in animal models of HIV infection, it has been very difficult to develop these exact responses through vaccine approaches in animal models and in infected patients. Notwithstanding, efforts should still focus towards developing an HIV vaccine that incorporates parts that elicit immune responses against the conserved regions of HIV genes.

2. Protective immunity in natural infection not clearly established: Despite advances in our knowledge regarding immune responses against HIV in infection, we are not yet clear on which immune responses are important for the protection against HIV infection. One way to understand this is to study (i) a subset of people who appear to resist HIV infection despite multiple exposures to HIV called “exposed seronegatives” (ii) HIV infected patients who control HIV replication to such low levels that they do not progress to disease for decades and are called “long-term nonprogressors” (iii) monkeys that carry ancestral viruses to HIV that are resistant to disease despite extremely high viral loads.

Studies of “exposed seronegatives” showed that they are not completely virus negative as they carry 100 to million fold lower virus than patients with typical disease progression. But why these people carry such low-levels of virus despite multiple exposures to HIV is unknown. Earlier research studies in this cohort of people indicated that they might have had abortive infection as a result of (i) exposure to lower virus levels from their sexual partner resulting in quick immune control or (ii) increased resistance to infection due to their genetic predisposition. Studies also indicated that these HIV exposed individuals mount strong cytotoxic T lymphocyte responses and antibody responses at the mucosal sites showing that infection may be prevented if immune responses at the mucosal (genital, oral) areas are developed and persist. Such mucosal responses should be a part of future vaccine efforts.

Studies of “long-term nonprogressors” indicated that these HIV infected patients mount very strong (higher quantity and quality), durable and broad immune responses, both cytotoxic T lymphocytes and neutralizing antibodies. CTLs from these patients have been shown to produce more than what is typically produced in an HIV infected patients of a killer protein called “granzyme” that punches holes in the virus infected cells. NAbs that arise in these long-term nonprogressors also tend to be stronger and more potent at preventing HIV virus from infecting cells. In fact, the only “broad NAbs” mentioned in the earlier section were found in

a long-term nonprogressor. To date, no vaccine strategy has predictably induced broadly neutralizing protective antibodies in humans.

Monkeys naturally infected in the wild with viruses closely related and yet distinct from HIV called Simian immunodeficiency virus (SIV) have been shown to support high levels of virus replication without any suffering from disease in contrast to humans. How can these monkeys be seemingly resistant to disease? Again research studies in these macaques show that these monkeys turn a blind eye to the virus replicating in them. An analogy to this phenomenon would be why certain people are allergic to peanuts and pollen, whereas others are not. It is due to the hyperactivation of the immune cells in the allergic individual that results in the allergic reaction. Immune cells in non-allergic individuals turn a blind eye to the same peanuts and pollen allergens resulting in no tissue damage or allergic reactions. Similarly, monkeys naturally infected with SIV do not mount any anti-viral immune responses and inflammatory responses to the virus. Disease in HIV infected humans occurs as a result of widespread damage to tissues and immune cells that traffic to the site of infection from the anti-viral immune responses in the patient attacking infecting cells and cause a cascade of inflammatory events. This tissue damage is lacking in these naturally infected macaques and is thought to be the consequence of millions of years of co-evolution of SIV in these monkeys such that these monkeys have learned to adapt to infection. Since we cannot wait for millions of years for us to co-evolve with HIV, vaccine efforts should target prevention of HIV's direct and indirect damage to tissues and immune cells.

3. HIV Latency: HIV like other retroviruses in its class integrates into the host genome upon entry into the target cell and makes a double stranded DNA copy from its RNA genome. So, once HIV enters and infects the target cell, the cell is permanently infected and can be eradicated only by cytotoxic T lymphocytes. In infected cells, HIV can remain latent from years to decades by not expressing any of the viral proteins on the cell surface thus escaping immune surveillance by CTLs and natural killer cells (NK cells). HIV not only infects CD4+ T helper cells (immune cells that stimulate CTLs

to kill infected cells), but also cells of the innate immune system called macrophages that attack and engulf pathogens. Macrophages present pathogens to T cells comprising of CD4+ T helper cells and CTLs, and B cells that produce antibodies and stimulate the latter into action. It has been shown even after prolonged virus suppression by antiretroviral therapy that upon cessation of treatment, latently infected macrophages can be reactivated leading to productive infection. It is not entirely clear whether virus multiplication and exit occurs differently within macrophages, but it has been recently shown that HIV that is released from macrophages are inherently more resistant to the body's NABs than viruses emerging out of CD4+ T cells. Not only are the viruses from macrophages resistant to NABs, but the macrophages themselves are found to be resistant to killing by virus-specific CTLs, showing that macrophages are specialized compartments for HIV infection. Vaccine efforts should therefore target latent reservoirs of HIV infection such as in macrophages.

4. HIV Transmission is complex: Sexual transmission accounts for nearly 90% of all HIV transmission from one person to another. Sexual transmission and mother-to-child transmission occurs in the mucosal areas (genital, oral mucosa). Our current knowledge of the events that occur during mucosal infection and the immune responses important for defense against mucosal infection is quite limited. Unlike other viruses, HIV can be transmitted and can exist in the body not only as free virus but also within infected cells. While free viruses are found to be resistant to NABs, cell-associated viruses have been found to be resistant to virus-specific CTLs. Viruses found in these mucosal areas have been found to be different from the viruses floating in the blood and thus vaccine strategies should target not just virus infection in the blood but also HIV infection in the genital and oral mucosa, which offer the frontline of defense against HIV and other infectious organisms. Recent data from studies using mucosal vaccines and microbicides (small drug inhibitors that prevent HIV from binding to receptor on target cells) have shown sterilizing immunity in monkey models showing promise of this approach to control HIV transmission in the mucosa.

The Role of Non-Human Primates

Overview

Most of the progress in studying HIV disease pathogenesis and immunity has been possible through studies of Simian immunodeficiency virus (SIV) and related chimeric viruses called Simian/human immunodeficiency virus (SHIV) in non-human primates. The following section will discuss the importance of non-human primates to HIV/AIDS research.

Characteristics of an Ideal Animal Model

Animal models are tools for understanding elements of infection and disease pathogenesis and in the development, and evaluation of potential drug/vaccine strategies before their testing in the human populations. The characteristics of an ideal animal model for HIV would be:

1. Infection/ disease in the animal model is similar to infection in humans
2. The immune system in the animal model is similar to the immune system in humans so that the immunity that develops against the infectious organism can be compared to (though not exactly applicable) what happens in humans.
3. Easy to test potential drug therapies and vaccine strategies, that might be considered unethical in humans.
4. Smaller experimental time-frame of disease
5. Ease of sample collection from the animals, low-cost, easy maintenance

Despite concerted efforts by scientists to develop low-cost, easy to maintain animal models using mice, it has not been possible to obtain a murine model for HIV as mice are resistant to HIV. Cats can only be infected with distantly related Feline immunodeficiency virus (FIV). HIV fails to replicate and cause disease except in humans and chimpanzees, thereby limiting the ability to evaluate drug therapies or vaccines prior to human testing. However, non-human primates (macaques) can be infected with related viruses and have been valuable as adjunct testing systems to prioritize future drug/vaccine strategies.

Viruses and Non-Human Primate Models

One of the first models to be developed to study HIV disease was the experimental infection of chimpanzees (*Pan troglodytes*) with HIV-1. This model was useful in recapitulating the infection process, route of infection, and antiviral immunity that developed after infection. Though disease pathogenesis was similar to that observed in humans, the disease occurrence too was similar to that in humans with occurrence only after 10 yrs of study. In addition, chimpanzees, our closest primate relative, are an endangered species and are extremely expensive and difficult to maintain. Thus for these reasons, the chimpanzee model has been excluded as a suitable animal model for HIV.

In the early 1980s, primate centers in the New England area reported disease in a group of Indian rhesus macaques (*Macaca mulatta*), whose disease profile was similar to AIDS in humans. It was discovered that these macaques were accidentally exposed to SIV from other naturally infected macaques resulting in what is now called as simian (or monkey) AIDS. Since then, these macaque models that simulate HIV pathogenesis in humans have helped in gaining valuable insight into HIV-1 transmission and pathogenesis. The primate lentivirus family includes HIV-1, HIV-2 and SIV, and these viruses infect a variety of non-human primates, endemic in certain species while leading to pathogenesis in others. It has now been documented based on phylogenetic relatedness (similarity in the viral genome and proteins) that HIV-1 arose from zoonotic transmission events of SIV from chimpanzees (SIVcpz) while HIV-2 arose through separate zoonotic transmissions of related SIV from Sooty Mangabeys (SIVsm). These ancestral viruses do not cause disease in the naturally infected macaques in the wild, however, they cause disease (simian AIDS) when transferred to other macaque species. Thus a non-human primate model using macaques was developed to study HIV disease pathogenesis. To further study immune responses directed against HIV envelope, chimeric viruses have been developed where the SIV envelope has been swapped with HIV envelope within the backbone of the SIV genome. The HIV portion of the genome enables studying immune responses to HIV envelope while the SIV portion helps to infect macaques. These viruses are called simian-human immunodeficiency viruses (SHIV) and also cause disease similar to SIV in macaques and HIV in humans. However, disease occurs much faster within 1-3 yrs making it much easier to follow infected macaques, perform experiments and evaluate therapies within a short time-frame.

Importance of Non-human Primate Models

The importance of non-human primate models to our current understanding of HIV disease cannot be stressed enough. SIV or SHIV infection of non-human primates has been instrumental in:

1. Understanding HIV disease in humans in the following ways:
 - a. Helped study the role of individual genes involved in SIV/HIV disease pathogenesis
 - b. Proved that virulence of the virus during SIV infection in macaques (and HIV infection in humans) was dependent on the virus and upon the host, suggesting patients' genetic factors play an important role in controlling infection and disease
 - c. Showed the importance of CD8⁺ T-cells in controlling early acute infection and the importance of B-cells and neutralizing antibodies (NAbs) in controlling disease outcome
 - d. Correlated the human finding that the plasma viral load predicts time to disease, thereby validating the non-human primate model for studying HIV pathogenesis.
2. Evaluating drug/immuno therapies:
 - a. Helped in the study of timing of post-exposure prophylaxis of the anti-HIV drug called D4T. The macaque study showed that short course treatment at very high doses followed by stopping the treatment was effective in controlling virus load and preventing CD4⁺ T cell loss for more than a year after withdrawal of treatment. These studies are important to study if adverse outcomes will arise when an HIV infected patient stops treatment.
 - b. Determined the role of NAbs as pre-exposure or post-exposure therapies. Macaques passively infused with broad NAbs were found to be completely protected against infection (sterilizing immunity) or have delayed disease in infected macaques even against the most pathogenic of SHIVs. This led to further studies on the timing of NAbs treatment, the different combinations of NAb to use, which injection route to use, and dosing of NAbs without risking human lives. These advances have led to the testing of NAbs as therapy for preventing mother-to-child transmission in humans wherein HIV infected mothers or newborn babies will be exposed to these broad NAbs capable of preventing infection in macaques. Stay tuned for results on these clinical trials.

3. Evaluating vaccine strategies:

- a. Have been useful in determining the relative efficacy of different types of vaccines (subunits, live recombinant viral vectors, prime boost and live-attenuated)
- b. Showed that live-attenuated vaccine that is effective in preventing infection in adult macaques actually causes disease in newborn macaques thereby halting the testing of live-attenuated vaccine in humans.
- c. The advantages of using individual and multiple components in the vaccine (eg. One HIV protein or multiple proteins, and which combinations are better)
- d. Advantages of including adjuvants in the vaccine cocktail. Adjuvants help in stimulating the immune system and help in making better immune responses to the vaccine and subsequent to virus infection.
- e. Effects of infection through different routes. Injection through intravenous route simulates injection-drug use exposure and results in infection directly in the blood. Infection in the mucosal areas such as genital, and mouth simulate sexual and mother-to-child transmission and recapitulates the most common mode of transmission.

**Limitations of
Non-human
Primate Model**

Genes of HIV and SIV differ and therefore drug therapies that target certain HIV regulatory proteins may not be fully effective against SIV infection. The rate of disease (1-3 yrs) is faster than in humans (5-20yrs) and it is not entirely clear if such a rapid disease course is representative of HIV-1. No single animal model is likely to be perfect, each with its own advantages and disadvantages. Non-human primate models should be used as adjunct testing grounds of potential antiviral strategies to weed out the not so effective drug/vaccine strategies prior to testing in humans. Any vaccine/drug strategy that is deemed protective in the non-human primate model may then be trial tested in humans. Scientists should bear in mind that while non-human primate models help in the understanding of HIV disease pathogenesis, there is no substitute for information that can be gleaned directly from HIV infected humans.

Audience

9-12, but may be modified for 7-8

Time required

2 x 50 minutes minimum

Materials

Background information on HIV, Overheads/Butcher paper, markers, and other presentation materials

Objective

Students will demonstrate their understanding of process of HIV infection by suggesting potential interventions.

WA State EALRs addressed

1. The student understands and uses scientific concepts and principles.
- 1.2 Recognize the components, structure, and organization of systems and the interconnections within and among them
2. The students knows and applies the skills and processes of science and technology.
- 2.2 Apply science knowledge and skills to solve problems or meet challenges

Outline

1. Divide students into 6 groups, roughly corresponding to steps in HIV infection/replication:
 - Binding/Entry
 - Reverse Transcription
 - Integration and Transcription
 - Translation and Cleaving of Viral Proteins
 - Assembly and Budding
 - Immune System Response
2. Provide a brief overview of steps to the entire class, then provide each group with a written summary of the events that occur during their assigned step.
3. Have students brainstorm possible interventions for their step. Students should focus on the creativity of their solutions.
4. If time permits, have students research their assigned step in more detail and to refine their ideas. The enclosed list of web resources may be helpful. In researching, students may come across strategies that are currently being pursued. Encourage them to explore these also.
5. Allow students to share their ideas with the class, and to discuss as a group the feasibility of their proposals.
6. As a follow-up, comment on some of the recent research strategies.

Assessment

Students synthesize their understanding of the overall infection/replication process and the immune response into a written/graphic summary.

Additional Lesson Plan Ideas:

Secondary School

<http://www.nsta.org/pubs/nstapress/online.htm> — The Science of HIV (also 12 pg update in pdf)

<http://www.pbs.org/newshour/extra/teachers/lessonplans/health/aids/>

http://www.uen.org/utahlink/lp_res/HIVAIDS001.html (HIV testing)

Elementary:

http://www.uen.org/utahlink/lp_res/HIVAIDS001.html

Selected possible interventions

Binding/Entry

siRNA, antisense RNA, ribozymes

antibodies to gp120

soluble CD4 receptors

fusion proteins consisting of part of CD4 and Fc of immunoglobulin

fusion proteins consisting of part of CD4 and toxin

block action of gp41

Reverse Transcription

Reverse Transcriptase Inhibitors

AZT (Zidovudine) and other nucleoside analogues

Nevaripine

siRNA, antisense RNA, ribozymes

Integration and Transcription

siRNA, antisense RNA, ribozymes

RNA decoys

Translation and Cleaving of Viral Proteins

Protease Inhibitors -viral protease, HIV aspartyl protease, cleaves products from pol and gag genes into functional proteins, including structural units and enzymes

Intracellular antibodies and transdominant proteins

Assembly and Budding

Targeting the ‘viral assembly line’

Immune System Response

Vaccine strategies- Stimulate neutralizing antibodies and cytotoxic lymphocytes via vaccine (subunit, vector, peptide, DNA vaccines)

Stimulate natural immune system (interferons, interleukins, actions of adjuvants)

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic Principles For All Medical Research

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort

it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional Principles For Medical Research Combined With Medical Care

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote
3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

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5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Footnote: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Page back to paragraph 29.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

<http://www.wma.net/e/policy/b3.htm>

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Reprinted from Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2, pp. 181-182.. Washington, D.C.: U.S. Government Printing Office, 1949.

<http://ohsr.od.nih.gov/guidelines/nuremberg.html>



HIV VACCINE
TRIALS NETWORK

Resources for HIV Vaccine Information

www.hvtn.org/resources

Agence Nationale de Recherches Sur la Sida (ANRS)

www.anrs.fr/index.php/article/home/16 (en français)

The ANRS, funded by the French government, is one of the principal international actors in the search for a preventive HIV vaccine.

AIDSinfo www.aidsinfo.nih.gov, www.aids.gov

Both are a service of the U.S. Department of Health and Human Services.

AIDS Vaccine Advocacy Coalition (AVAC) www.avac.org

www.aidsvaccineclearinghouse.org/

AVAC is an advocacy group in the U.S. that publishes an annual review of progress in HIV vaccine development.

American Foundation for AIDS Research www.amfar.org

Supports AIDS research, AIDS prevention, treatment education, and the advocacy of sound AIDS-related public policy.

Capitol Area Vaccine Effort www.aidsvaccine.org

Washington D.C. volunteers organized around trial participation.

Centers of Disease Control and Prevention www.cdc.gov/hiv/vaccine.htm

The U.S. government's disease control and prevention agency.

Global Alliance to Immunize Against AIDS (GAIA) www.gaiavaccine.org

GAIA is a non-profit foundation for a global AIDS vaccine.

HIV and Hepatitis.com www.hivandhepatitis.com/hiv_vacc.html

A resource for HIV vaccine news articles.

International AIDS Economics Network (IAEN) www.iaen.org

IAEN focuses on the economics of HIV/AIDS prevention and treatment.

International AIDS Vaccine Initiative (IAVI) www.iavi.org

IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV/AIDS, focusing on developing countries.

International Council of AIDS Service Organizations www.icaso.org

ICASO promotes and supports the work of community AIDS organizations around the world.

National AIDS Trust (NAT) www.nat.org.uk

NAT, a U.K. based organization, aims to promote a wider understanding of HIV and AIDS.

National Institute of Allergy and Infectious Diseases (NIAID) / NIH

www.niaid.nih.gov/daids/vaccine/default.htm

NIAID is the primary agency of the U.S. government devoted to research on HIV/AIDS

South African AIDS Vaccine Initiative (SAAVI) www.saaavi.org.za

SAAVI was established to coordinate the research, development and testing of HIV/AIDS vaccine in South Africa.

UNAIDS www.unaids.org

The Joint United Nations Programme on HIV/AIDS.

University of California at San Francisco (UCSF) <http://hivinsite.ucsf.edu>

UCSF's HIVinsite web page contains extensive information (información en español también)

Vaccine Research Center (VRC) www.vrc.nih.gov/VRC/

The Dale and Betty Bumpers Vaccine Research Center at NIH.

WHO-UNAIDS HIV Vaccine Initiative

www.who.int/vaccine_research/diseases/hiv/en/

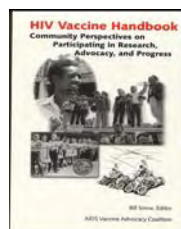
A joint activity of the World Health Organization and the United Nations Programme on HIV/AIDS.

Advocates for Youth

www.advocatesforyouth.org/hivvaccine.htm

HIV vaccines from a youth perspective.

Booklets



HIV Vaccine Handbook Community Perspectives on Participating in Research, Advocacy and Progress.

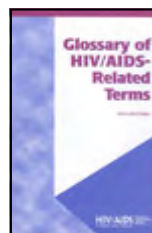
Edited by Bill Snow

AIDS Vaccine Advocacy Coalition

www.avac.org/primer.htm

For your free copy, please call NPIN 1-800-458-5231

Inventory item D305



Glossary of HIV/AIDS-Related Terms

Produced by AIDSinfo

For a free copy, contact AIDSinfo

1-800-448-0440

ContactUs@aidinfo.nih.gov



Understanding Vaccines

Produced by NIH/NIAID

<http://www.niaid.nih.gov/publications/vaccine/pdf/undvacc.pdf>

For a free copy, contact the NIAID

Office of Communications

(301) 496-5717



Getting the Global House in Order

AIDS Vaccine Advocacy Coalition
May 2004

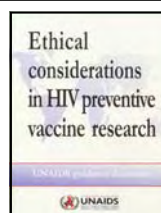
www.avac.org/pdf/reports/2004AVACReport_High.pdf



Developing Vaccines for HIV and AIDS: An Introduction for Community Groups, 2nd Edition.

Produced by the International Council of AIDS Service Organizations (ICASO)

Available in French, English, Spanish at: www.icaso.org/icaso/vaccines.htm



Ethical considerations in HIV preventive vaccine research

UNAIDS Guidance Document

www.unaids.org/publications/documents/vaccines/index.html

Bulletins



VAX Bulletin

Community-focused monthly

Produced by the International AIDS Vaccine Initiative (IAVI)

www.iavi.org

Available in French, Spanish, English, German, and Portuguese.



WHAT IS AN HIV VACCINE?

A preventive HIV vaccine is a substance that teaches the body's immune system to recognize and protect itself against HIV, the virus that causes AIDS. HIV vaccines currently being tested in humans are made from man-made materials that **CANNOT** cause HIV infection.

Scientists believe that an effective HIV vaccine, given before exposure to HIV, could have a number of possible outcomes. These include:

- Preventing infection in most people
- Preventing infection in some people
- Preparing a person's immune system to block continued infection and eliminate the virus (vaccines against measles, mumps and polio work this way)
- Delaying or preventing the onset of illness or AIDS

The long-term goal is to develop a vaccine that is 100 percent effective and protects everyone from infection. However, even if a vaccine only protects some people, it could still have a major impact on controlling the epidemic. A partially effective vaccine could decrease the number of people who get infected with HIV; those people, in turn, would not pass the virus on to others. Even when an HIV vaccine is developed, education and other prevention efforts will be needed so that people continue to practice safe behaviors.

HISTORY OF VACCINES

The value of vaccines was recognized approximately 200 years ago, beginning with a vaccine against smallpox. The smallpox vaccine saved millions of lives, and its success helped people understand that introducing a vaccine into the body can actually trigger a protective immune response, and prevent disease.

Today, there are numerous safe and effective vaccines. Vaccines have been used successfully against many life threatening diseases, including measles, and polio in most of the world.

COMMUNITY PARTICIPATION IN VACCINE RESEARCH

By raising awareness and encouraging study participation, individuals and communities can contribute to the successful development of HIV vaccines. Although tens of thousands of people have already volunteered to take part in HIV vaccine studies, many more will be needed. A large HIV vaccine trial will require thousands more participants of all race/ethnicities, genders and socioeconomic backgrounds to ensure that the vaccine works in all populations.

Therefore, community support is essential in efforts to break down stigma and myths about HIV vaccine research. Developing an effective HIV vaccine depends upon individuals and communities informing, educating and supporting others.

HOW TO HELP

- Let others know you support HIV vaccine research
- Educate others about the need for an HIV vaccine
- Support vaccine trial volunteers and/or volunteer yourself

The National Institute of Allergy and Infectious Diseases (NIAID), at the National Institutes of Health (NIH), supports a comprehensive program of HIV vaccine research.

For more information about HIV vaccines, please visit:
www.niaid.nih.gov/daiids/vaccine
www.hiv.nih.gov
www.addinfo.nih.gov
 or call 1-800-448-0440.

Para información en español sobre las vacunas contra el VIH, llame al:
 1-800-448-0440.



February 2004

NIH Publication No. 04-5279

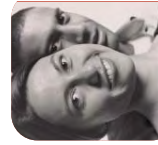


HIV VACCINES EXPLAINED

MAKING HIV
VACCINES
A REALITY



HIV VACCINE RESEARCH
Our best minds. Our best science. Our best hope.



THE NEED FOR AN HIV VACCINE

Despite the availability and success of HIV treatment drugs in the United States, the best long-term hope for controlling the AIDS epidemic worldwide is the development of safe, effective and affordable preventive HIV vaccines. Consider these facts:

- ### HIV/AIDS IN THE UNITED STATES
- Nearly half a million Americans have died of AIDS since the epidemic began.
 - The Centers for Disease Control and Prevention (CDC) estimate that as many as 950,000 Americans are living with HIV, and more than one-third of them do not know it.
 - Each year, over 40,000 people become infected with HIV, a rate that has remained virtually unchanged in recent years. Seventy percent are men and 30 percent are women. Of these, half are younger than 25 years of age.
 - Minority communities are disproportionately affected by the epidemic. More than half of all new HIV infections occur in African Americans, who make up 12 percent of the U.S. population. AIDS is the fifth leading cause of death of Americans aged 25-44, and is the number one cause of death in African American men of all ages. Nineteen percent of new HIV infections occur in Latinos, who make up 13 percent of the population.
- ### HIV/AIDS AROUND THE WORLD
- To date, nearly 25 million men, women and children have died from AIDS worldwide.
 - Currently, 40 million people are estimated to be living with HIV/AIDS and 14,000 new infections occur each day.
 - Today, more than 13 million children under the age of 15 have lost one or both of their parents to AIDS, most in sub-Saharan Africa.



PREVENTIVE VERSUS THERAPEUTIC HIV VACCINES

Preventive HIV vaccines currently under development are given to HIV negative people and are designed to prevent infection and control the spread of HIV, not to cure AIDS.

Multiple HIV vaccines may be necessary to prevent infection or disease in the same way multiple drugs are needed to treat people already infected with HIV.

Researchers are also evaluating therapeutic vaccines to treat people with HIV infection or AIDS. While the same vaccine may be tested for both preventive and therapeutic effects, what works to prevent HIV infection may not necessarily work to treat people who are already infected with HIV.

IS AN HIV VACCINE AVAILABLE NOW?

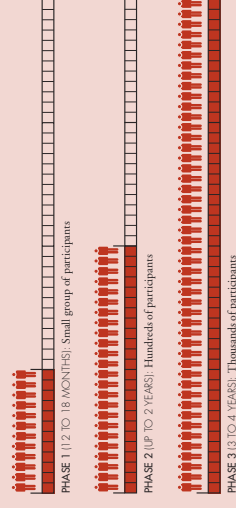
No! Scientists have been studying HIV for over two decades — and continue to make progress. Even when a promising vaccine is discovered, it will take time to test and evaluate its safety and effectiveness.

TESTING HIV VACCINES

Vaccine development requires several years of research in laboratories and animals before testing in humans can begin. A potential vaccine goes through three phases of testing in humans before the Food and Drug Administration (FDA) can consider licensing it for public use. The three phases of preventive HIV vaccine clinical trials are:

- **Phase I** — involves a small number of healthy volunteers (HIV-negative) to test the safety and various doses of the vaccine; usually lasts 12 to 18 months
- **Phase II** — involves hundreds of volunteers (HIV-negative) to test the safety and immune responses of the vaccine; can last up to 2 years
- **Phase III** — involves thousands of volunteers (HIV-negative) to test the safety and effectiveness of the vaccine; can last 3 to 4 years

Throughout all phases of human testing, independent reviewers regularly monitor the study to ensure the safety of the volunteers.



PROTECTING RESEARCH PARTICIPANTS

HIV vaccine clinical trials are voluntary. Researchers are required to obtain the informed consent of all participants to make sure they fully understand the purpose of the study, how the HIV vaccine will be tested, the number of clinical visits required and the possible risks and benefits associated with receiving the vaccine.

So far, few side effects have been associated with experimental HIV vaccines. Those that have occurred generally have been mild to moderate and similar to those of approved vaccines. The most common side effects are soreness at the site of the injection, a low-grade fever, and body aches, which readily disappear on their own. Throughout the study, volunteers are carefully examined to determine if there are any serious side effects associated with the vaccine.

After a volunteer receives an HIV vaccine, it is possible to test positive for HIV antibodies on a standard HIV test (i.e., ELISA) because the vaccine triggers the body to produce antibodies against HIV.

The HIV vaccines being tested in humans do not contain HIV; therefore, they cannot cause HIV infection. Other tests are available at the study sites to determine whether a volunteer is actually infected with HIV. If volunteers engage in behaviors that expose them to HIV, they may still become infected with HIV.

It is rare for volunteers to encounter problems as a result of testing positive for HIV antibodies. Testing antibody positive does not mean the person is infected. However, volunteers could potentially experience problems donating blood, getting insurance, traveling to other countries or getting employment.

All volunteers are offered an identification card to show they are part of the study, and research staff are available to help address any issues that may arise.

HIV Preventive Vaccine

What is a Vaccine?

A vaccine is a substance that stimulates the body's immune response; the goal of vaccination is to prevent or control an infection. There are several different types of vaccines. The types of vaccines that are being studied to prevent HIV/AIDS are subunit vaccines, recombinant vector vaccines, and DNA vaccines. These vaccines contain only some of the many substances that HIV needs to make more copies of itself; the vaccines themselves cannot cause HIV or AIDS.

A given HIV vaccine may be used either alone or in combination with another HIV vaccine. One approach to HIV vaccination is called the prime-boost strategy, which combines two different types of HIV vaccines.

Subunit Vaccines

Subunit vaccines, also known as "component" vaccines, contain only individual proteins or peptides from HIV, rather than the whole virus. Instead of collecting protein or peptide components from the virus itself, they are made in the laboratory using genetic engineering techniques. Most HIV subunit vaccines are based on laboratory-made forms of the HIV envelope proteins that coat the outside of the virus. These envelope proteins can prompt the body to produce an anti-HIV immune response.

Another type of subunit vaccine is called a virus-like particle vaccine (also known as a VLP or pseudovirion vaccine). Virus-like particles are non-infectious HIV look-alikes that contain one or more, but not all, HIV proteins.

Recombinant Vector Vaccines

Recombinant vector vaccines are based on microorganisms such as viruses or bacteria that do not cause disease in humans or have been weakened so as not to cause disease. The viruses or bacteria are used

as vectors, or carriers, to deliver harmless HIV genes into the cells of the body. The body produces proteins from the HIV genes and these proteins stimulate an anti-HIV immune response.

Some of the viral vectors being studied for HIV vaccines include ALVAC (a canarypox virus), MVA (a cowpox variant), and ADV5 (adenovirus 5). A modified version of the bacterium *Salmonella typhi* is also being studied as a vector for HIV vaccines. Most of the recombinant vector vaccines for HIV deliver several HIV genes.

DNA Vaccines

DNA vaccines introduce pieces of laboratory-made HIV DNA into the body. Unlike recombinant vector vaccines, DNA vaccines do not rely on a viral or bacterial vector. Instead, "naked" DNA containing HIV genes is injected directly into the body. Cells take up this DNA and use it to produce HIV proteins. The proteins trigger the body to produce an anti-HIV immune response.

Prime Boost Strategies

A prime-boost strategy is one approach to HIV vaccination. In this approach, administration of one type of HIV vaccine (such as a recombinant vector vaccine) is followed by a second type of HIV vaccine (such as a subunit vaccine). The goal of this approach is to stimulate different kinds of immune responses and enhance the body's overall immune response to HIV.

For more information:

<http://www.niaid.nih.gov/daids/vaccine/>
<http://www.vrc.nih.gov/VRC/>