Case Teaching Notes

for

"Resistance Is Futile ... *or Is It?* The Immunity System and HIV Infection"

by

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Introduction / Background

While the majority of people are prone to HIV infection, some individuals remain uninfected despite repeated exposure. This case study uses the results of the landmark paper by Paxton and his colleagues (Paxton et al., 1996) that offered the first breakthrough in understanding why some people are protected against HIV infection. The case study uses an interrupted progressive disclosure format during which students make hypotheses, predict the outcome of experiments, and compare their predictions with real data. I am aware of another case study developed using Paxton's paper (Rediscovering Biology, 1997–2009a). While the aims, activities, and topics covered by that case are different to this one, I recommend that instructors review the other case given the excellent multimedia and introductory level literature (Rediscovering Biology, 1997–2009b) that accompanies it.

This case was developed for a first-year, non-science-majors course in molecular biology. The case was introduced during a module on the immune system. Students had read introductory-level information about the immune system, viruses, and bacteria, and about the HIV virus in particular. They were also given a 30-minute overview lecture on this topic. The case takes approximately three hours to complete and can be abbreviated for shorter periods. It introduces students to some of the information known about the mechanisms of protection against HIV infection; students should be encouraged to research specific mechanisms in more detail in follow-up assignments.

Objectives

Upon completion of this case study, students should be able to:

- Formulate testable hypotheses given preliminary data;
- Suggest tests to evaluate hypotheses;
- Predict results of experiments that would confirm each hypothesis;
- Interpret data and compare to predicted outcomes;
- Describe cellular and humoral immunity;
- Draw the HIV virus structure and describe the function of each component;
- Describe the interaction of the HIV virus with the immune system;
- Differentiate between resistance and immunity as mechanisms of protection against a foreign particle;
- Debate the pros and cons of personal knowledge of HIV resistance and immunity.

Classroom Management

This case was developed for a three-hour class. Students arrive to class having read a chapter in their first year biology textbook that provides an overview of the functioning of the immune system. They also have done reading on HIV and AIDS. I typically assign them Unit 6: HIV and AIDS available free of charge on the Rediscovering Biology website (Rediscovering Biology, 1997–2009b). When they arrive to class, there is a brief quiz to cover the readings to ensure that each student has come to class prepared. I then provide a 30-minute overview (review and clarification of readings) on the immune system, HIV, and the interaction between HIV and the immune system. Students then break into groups of three to four students. I distribute Part I of the case and give students a pre-set amount of time for reading and group discussion (the time allotted for each section varies—see below for details). This is followed by class discussion to combine input from the student groups and to ensure everyone is on the right track. We then proceed with the next section of the case, reiterating these steps.

For this case, it would be helpful to have either an overhead projector, white or black boards, and pens.

Part I: HIV and the Immune System (30 min)

Part I introduces the case by reviewing necessary background knowledge. It contains information on the immune system, HIV, and HIV infection. Students are asked questions that assess their understanding of the materials. The first few questions check for basic understanding, but further questions ask students to speculate how the immune system interacts with HIV (in a way that they have not been told, but based on their understanding). Following small-group discussion, it is important to review all these questions as a whole group to ensure that everyone is starting with a similar background. This information is crucial in understanding the rest of the case.

The most important question is Question 4, which asks students to consider where viral infection could be prevented. Students must formulate hypotheses that could explain, using what they now know, why some people are protected against HIV infection. I usually visit each student group individually to make sure they understand this question. I ask them to review the life cycle of HIV, and tell me where the virus could be stopped. I then direct them to consider what could be different in the host's genetic makeup that could engender such a barrier to viral replication. I challenge each group to come up with at least three to four possibilities. During the whole-class discussion, I ask each team for one or two hypotheses and write all ideas on the whiteboard for the class to consider as the case proceeds.

Part II: Paxton's Hypotheses about HIV-Protected Individuals (15 min)

Part II of the case asks students to consider how they might investigate their proposed hypotheses. Most teams will come up with correlative studies (e.g., compare the CD4 proteins of normal people and of resistant individuals). Remind students that correlative studies do not have the conclusive powers of controlled experiments.

This part of the case also presents two of the possible reasons that certain individuals are protected against infection: they have a particularly active immune system, or they have T helper cells that resist infection. There are many possible mechanisms by which each of these could occur, and students are encouraged to recognize and classify how their proposed hypotheses fit into each major category. There is the possibility that some students will hypothesize that someone has particularly good B cells that quickly produce HIV-antibodies, preventing infection. This possibility would not fall into either of the categories mentioned by Paxton (but, as we will see later, might indeed be a reason why some individuals have increased protection

against HIV). Instructors should recognize that hypothesis as having merit, but separate from the ones proposed and investigated by Paxton's team. For the whole-class discussion, I usually draw a circle around the hypotheses that were written on the board during the previous section in one color for the "Super T Helper Cells" Hypothesis and in another color for the "Super Cytotoxic T Cells" Hypothesis.

Part III: Predictions from Paxton's Two Hypotheses (20 min)

Part III introduces the experimental design adopted by Paxton' team, and challenges students to predict the outcome of the experiment. Students must think through what each component added to the test tube is doing, and how they interact. When answering Questions 2 and 3 of this part, students should be able to describe *qualitatively* what happens in the test tubes (e.g., HIV infects T_H cells, which then become HIV-producing factories, and the amount of virus (and p24) augments as time goes on).

For the graphing Question 5, instructors should guide students to first predict the results obtained if control cells were used. Remind students that there are two conditions for this experiment (HIV+ T_H, and HIV+T_H+T_C), and hence there should be two lines for every graph. Then ask students to reconsider the outcome of the same experiment if cells from protected individuals were used *and* the cytotoxic T cells were particularly active at recognizing and destroying HIV-infected cells (i.e., if the "Super Cytotoxic T Cells" Hypothesis is correct). Once they have traced the two lines on their graphs, ask students to repeat this thought experiment, but this time assuming that the cells from protected individuals are particularly good at preventing the initial HIV infection (i.e., the "Super T Helper Cells" Hypothesis is correct). One of the most common mistakes that students make is to first increase the amount of virus of p24, and then decrease it over time. Remind them that this experiment is occurring in a test tube, and therefore once formed, any virus produced is "not going anywhere," but rather accumulates in the test tube.

During the class discussion, I typically put three blank graphs in front of the class, ask for three volunteers (from three different teams), and ask each one to draw the predictions of their group for one graph and explain their reasoning.

Part IV: Paxton's Results (10 min)

In Part IV, students compare the results obtained by Paxton with their own predictions. One aspect of the graph representation to point out to students is that the Y axis (amount of p24 viral protein in test tube) is shown on an exponential scale (so small differences between the two curves on the Y axis mean a large difference).

Part V: The "Super T Helper Cell" Mechanism (20 min)

Students are provided with the details of another experiment and asked to predict the outcome. This experiment would ultimately uncover the mechanism by which some people have innate resistance to HIV, through a "Super T Helper Cell" mechanism. Interestingly, the full meaning and implications of this experiment were not understood by Paxton and his team at the time of publication. Publications of results from other teams, which occurred in the same year, provided some information necessary to interpret Paxton's graphs and infer the mechanism of resistance by "Super T Helper Cells." Thus, students are able to re-examine Paxton's results and reach conclusions that the original research team could not. This aspect of science could be discussed with your students. It could be used as a spring board to discuss why it is important to publish data even when the full implications are not apparent, or the collaborative aspect of science (how science progresses in pieces and parts contributed by many research teams).

After students have had a chance to read this section of the case, I typically interrupt the groups to provide some instructions. I draw the six charts on the whiteboard and explain how the experiments that represent each of them differ. I answer questions if they arise, and direct the groups to work on completing each graph. This section typically requires the instructor to visit each team to direct their graphing efforts. Encourage students to graph the controls first, and then repeat the thinking, but this time using cells from protected individuals. You may have to point out on the case hand-out the difference between an M-tropic and a T-tropic strain.

As with Part III, I typically request three volunteers to graph their groups' answer on the whiteboard. Each volunteer draws his or her answer for one hypothesis (e.g., CD_4 is different in the resistant individuals), and explain their reasoning.

Part VI: Why Some People are Protected against HIV (15 min)

Here students analyze the results of Paxton's second experiment, using their predictions as a guide. From this, they can infer the molecular mechanism by which some people are protected against HIV infection. They also consider how robust this resistance really is.

Part VII: Societal Implications of HIV Protection (30 min, optional, possible assignment)

This section is optional. It provides more up-to-date information on the three currently known mechanisms of HIV protection. It is used to launch a discussion on the implications of this knowledge for our society. It could also be used to initiate projects that students must research and present or write about at a later time. In other words, this section could serve to assess student learning and encourage independent research.

Protection against a virus can come from one of two ways: resistance or immunity. The differences between these two terms are problematic for non-major biology students. This case presents people who are protected against HIV by the two different mechanisms. Some people are *resistant* because they have a preexisting CCR5 mutation. Others seem *immune* because they have a more aggressive immune system, and despite repeated exposure to the HIV virus they remain seronegative. Having reviewed both types of protection, students can now begin a discussion of the two ways that one could be protected from HIV/AIDS and the difference between the terms "resistance" and "immunity."

Answer Key

Answers to the questions posed in the case study are provided in a separate answer key to the case. Those answers are password-protected. To access the answers for this case, go to **the key**. You will be prompted for a username and password. If you have not yet registered with us, you can see whether you are eligible for an account by reviewing our password policy and then **apply online** or write to **answerkey@sciencecases.org**.

Follow-up / Extensions

The activities listed below may be used to supplement the case study. Students could be asked to:

- Write an in-class individual paper summarizing what they have learned about the mechanism of resistance and immunity to HIV.
- Write an individual response paper to one of the questions posed in Part VII of the case which explores the societal implications of this knowledge
- Work with their group to research one of the three mechanisms of protection against HIV described in the last section and present it to the class at a later date (students could also produce a research paper of their findings).

- Write a short paper describing why it is believed that the CCR5Δ32 mutation has only occurred once in human history, if your students have some knowledge of evolution.
- Investigate the mechanism of action of the anti-HIV drug AZT and to produce a short report of their findings; they may also speculate how other anti-HIV drugs might work (i.e. what could they do to interfere with viral replication).

Suggestions for Shortening the Case

To shorten the case for use in a single one-hour class period, instructors can give Part I to students ahead of time. Collect the answers to Questions 1–4 at the start of class and then jump into a class discussion of the answers without allowing small group discussion first. Alternatively, if students have prior knowledge of immunity and HIV, Part I can be abbreviated such that only Question 4 is covered. Part III can be abbreviated by only answering Question 4 of this part. Skip Part VII, or assign it as homework.

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