Educational model to illustrate HIV infection cycle

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Abstract

Human immunodeficiency virus (HIV) is a deadly virus and its impact on the functions of the body are misunderstood and overlooked by many people. The goal of this design project is to create a three dimensional educational tool that visually depicts the irreversibility of HIV infection and what makes HIV more harmful than a normal virus. Currently there are no educational tools that are apt for conveying this message in a simplistic manner. This model will be created to highlight the important aspects of the HIV infection process and allow it to be understood by students with minimal biological knowledge. This final product uses an interactive three dimensional model that portrays the larger picture of HIV influence on the immune system as well as the cellular level mechanisms of binding, injection, and replication.

Background and Motivation

HIV attacks the helper T cells of the immune system by binding to CD4 receptors. The virus is then injected into the cell and replicated by reverse transcriptase, which is an error prone process resulting in many mutated strands of HIV. The cell then lyses, releasing the mutated strands of HIV into the body while killing the helper T cell to which it bound. The mutated HIV attack and outnumber the remaining helper T cells which normally send the signal to activate the immune system to fight against viruses and other foreign pathogens. Thus if the immune system is not able to be activated, it is not able to fight off other opportunistic diseases such as pneumonia. HIV causes this disease known as acquired immunodeficiency syndrome (AIDS) for which there is currently no cure and can lead to death.

HIV is spread through contact with infected bodily fluids, most often during sexual contact. The best way to stop AIDS is to prevent the spread of the virus by educating people about methods of personal protection against HIV. The widespread education about HIV and the resulting condition of AIDS is an ongoing effort of doctors, nurses, and volunteers worldwide. Some of the major problems faced by educators are getting people to grasp the concept that once HIV enters a person's cells there is no way to stop replication and prevent HIV from taking over the body. Most people also do not understand why HIV is more deadly than other viruses that one's body is able to fight against. A teaching aid would be beneficial in explaining the severity of HIV and its effects on the body.

Problem Statement

Our client, Marge Sutinen of the UW School of Medicine and Public Health, works to educate students on the permanent effects of HIV in her Contemporary Issues in HIV/AIDS Prevention course. She has asked our team to develop a three dimensional model that captivates the attention of a class of undergraduates and visually illustrates the HIV attachment to CD4 receptors on helper T cells, the permanent effect it has on the body, as well as the differences between HIV and other viruses. This model will be used as an aid in demonstrating the irreversibility of contracting the HIV virus to persuade students to use preventative measures to protect themselves.

Client Requirements

Our client needs a color-coded, three-dimensional teaching aid that will give an overview of the steps of HIV infection and emphasize how HIV is different than any other virus. The model will be used in a class of approximately 30 students, so it must be easily visible from about 6 meters. The intended audience consists of primarily non-science majors, so the advanced biological details of HIV infection do not need to be illustrated.

The model will focus on three main steps of HIV infection: (1) binding, (2) injection and replication, and (3) lysis and release of new HIV viruses. The progression from step to step will be manually controlled by the client, to give time for explanations between each step.

(1) In the binding step, a separate HIV structure that securely binds to the cell will be needed to show the permanent binding to CD4 receptors of the helper T cell. In addition, the CD4 receptor binding sites should differentiate between HIV and other pathogens. Other, non-compatible receptors will be present on the model to show this.

(2) The replication step shows how HIV takes over the host cell's nucleus and controls the production of new HIV particles. These new HIV particles will need to be similar to the initial attacking HIV, but some will be a different color, showing the possibility of mutations of the virus.

(3) In the cell lysis step, the main goal is to show the host cell's DNA, infected with HIV RNA, reproducing new HIV infected cells instead of carrying out

normal cell activities. This step should illustrate the death of the helper T cell and release of new (original and mutated) HIV particles from the host cell.

This model will only be used for one lecture per semester, so it must be able to withstand long periods of storage between uses. It must be lightweight and be easily transported to and from the classroom. The amount of loose pieces should be minimized and the model must be simple to operate with only one person. The model should captivate the audience so they remember the seriousness of HIV. The final product must also contain a PDF explanation of each step of the HIV process that is demonstrated by the model.

Existing Devices

There are currently no models that effectively convey the message, in a simple form, that once HIV enters a cell there is no way to stop infection. Models that are available include posters, computer simulations, and a model produced by Merck and Company Inc.

Figure 1 is an example of a current poster model that depicts the HIV lifecycle. It was produced by the National Institute of Allergy and Infectious Diseases. It has very small captions that are difficult to see and the material is hard to understand without prior knowledge of cell biology. It also does not show the permanency of HIV taking over a cell.

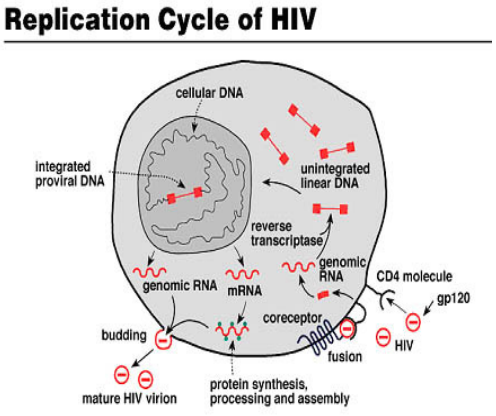


Figure 1 Photo courtesy of NIAID

Computer simulations are widely available on the Internet. Figure 2 is taken from a computer simulation video clip that shows HIV entering a white blood cell. These videos are simulations of HIV entering the host cell. They are very detailed and anatomically correct, but do not include explanations.

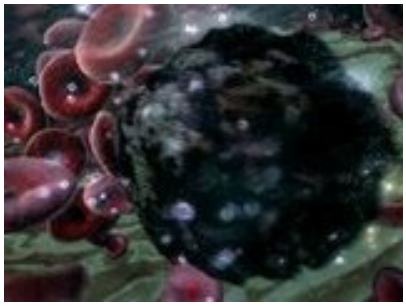


Figure 2: Photo courtesy of gettyimages.com

Computer models are very beneficial if one can identify all of the model's parts and be able to distinguish what is represented in the model. Computer simulations are hard to manually control in order to add additional explanations if students do not fully understand a specific point.

The most pertinent model to our current project is the model manufactured by Merck and Company Inc. It is a three-dimensional model that displays a very detailed and complex explanation of the process of HIV entering a host cell. The host cell is able to be split in half and contains three-dimensional interactive moving parts, diagrams and an accompanying explanation on a CD-ROM. The model itself is hard to see in the back of the classroom because the compact size that makes the model portable. The text is difficult to see from far away and the detailed steps of diagrams and processes are hard to distinguish. Also the descriptions of the process are too in depth.

Figure 3: Model manufactured by Merck and Company Inc,

All three of these devices provide an explanation of how HIV functions and how it affects the cells that it attacks. However, they are overly scientific and for students without a lot of science knowledge they can be overwhelming.

Design Proposal Overview

The process of the binding of HIV particles to CD4 receptors and its subsequent infection is very long and complex. The purpose of this model is to condense the process in such a way that students who do not have full knowledge of the specific cell parts and processes can grasp it. In order to simplify this process, we broke it down into three steps: binding of the HIV particle to CD4 receptors on the helper T cell, integration of the viral DNA into host cell DNA, and replication of the HIV virus resulting in cell lysis. In addition, the model will allow the user to show the devastating effect of HIV on the immune system and demonstrate how the effects of HIV are unique compared to all other viruses.

Initial Design Options

The binding stage needs to demonstrate the permanent attachment of HIV to CD4 receptors. The three options were a locking device, magnets and Velcro (see Design Matrix 1 below). While the locking device would not be as easy to attach as magnets or Velcro, it does demonstrate the permanent binding of HIV to the host cell most effectively. This permanent binding is the most important aspect of the design and therefore the most highly weighted category is teaching effectiveness. The locking mechanism would also be the most inexpensive to manufacture because a soda bottle top

would be sufficient in creating this device. Even though Velcro would be easier to manufacture, and magnets would be the easiest to use, the locking device proved to be the best design option with a total of 88 out of 100.

Binding Design Matrix

Design	Ease of Use (30)	Cost (10)	Manufacturability (20)	Teaching Effectiveness (30)	Consistancy (10)	Total (100)
Locking Device	25	10	15	29	9	88
Magnets	27	6	17	20	8	78
Velcro	22	8	18	13	6	57

Figure 4 – Design matrix for binding step

The injection stage is important to show how viral RNA is transcribed into DNA and then integrated into host cell DNA. The other part of this step is the replication and mutation of the virus inside the host cell. The three options for demonstrating injection and replication are: a syringe/tube combination, a squeeze bottle to fill the nucleus, and a marble/tube combination (see Design Matrix 2 below). The squeeze bottle has the advantage of being extremely easy to use during demonstration, but the liquid would need to be cleaned out after each use. The marble and tube combination would avoid any clean up, but does not show viral DNA integration as effectively as either of the other two options. Overall, it was determined that a combination of a syringe and tube would be the best design. Along with being the least expensive option, the tube could also be

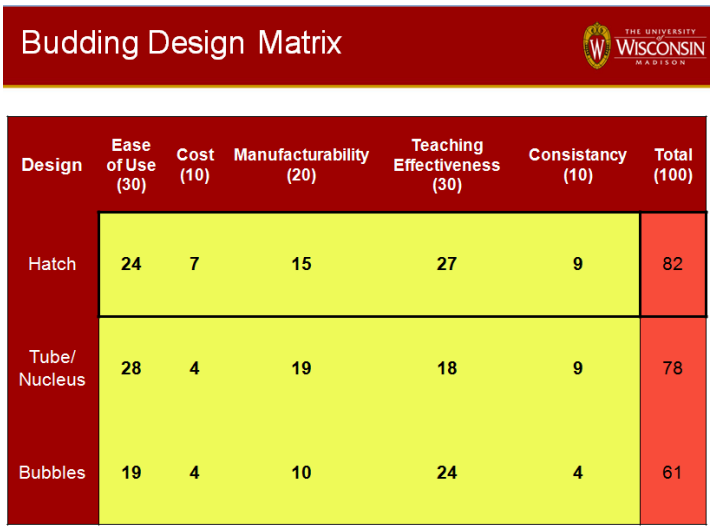
wrapped in the shape of a double helix, showing DNA integration most effectively. Also, the liquid would be fully contained in the system during the demonstration making it minimally error prone.

Injection/ Replication Design Matrix

Design	Ease of Use (30)	Cost (10)	Manufacturability (20)	Teaching Effectiveness (30)	Consistancy (10)	Total (100)
Syringe/ Tube	27	10	16	25	10	88
Squeeze Bottle	19	8	18	20	8	73
Marble/ Tube	16	8	12	13	5	54

Figure 5 – Design matrix for injection/replication step

The final stage of HIV transmission is the release of new HIV viruses from the host cell. Originally, three options were being considered to show budding of new HIV particles: a hatch releasing HIV particles, a tube coming from the nucleus releasing marbles for HIV particles and the use of a bubble gun to show HIV spreading (see Design Matrix 3 below). With these options, it was decided that the hatch option would most effectively show the budding of HIV particles. The particles could be similar in shape and size to the original binding particle and the user could easily be re-attached to similar binding sites on the helper T cell. Also, the budding viruses would be different colors from the original virus showing mutations that would occur during replication of the virus.



Design	Ease of Use (30)	Cost (10)	Manufacturability (20)	Teaching Effectiveness (30)	Consistancy (10)	Total (100)
Hatch	24	7	15	27	9	82
Tube/ Nucleus	28	4	19	18	9	78
Bubbles	19	4	10	24	4	61

Figure 6 – Design matrix for budding step

Additions from Mid-semester Design

Reevaluating our initial design options, we realized that we missed some of the design requirements and criteria we established earlier in the semester. It did not strongly show the difference between HIV and other viruses, which may not show the severity of HIV as well as possible. The main goal of this project is to show the harshness and permanent effect HIV has on the body in order to persuade students to use preventative measures to protect themselves. Because of this, we decided to add more to the previously chosen proposed design.

It was decided that an image of cell lysis and subsequent release of HIV particles would more effectively show how the immune system is compromised. Therefore, a sliding track mechanism was designed so that the two halves of the helper T cell would split releasing mutated HIV.

In addition to showing the mechanism of HIV infection of an individual helper T cell, this model was also designed to allow the user to show the effect of HIV infection

on the immune system. It was decided that a cutout of a human figure covered by a semitransparent sheet, lit from behind by LEDs, would represent the strength of a person's immune system. Two parallel circuits were designed, one allowing for the control of the brightness of white LEDs and the other controlling red LEDs.

Finally the differences between HIV and any other virus are important in understanding the deadliness of this disease. Therefore, another separate somatic cell was incorporated into the design. However, the only step shown on this cell was attachment of a virus. Attachment of a virus to the somatic cell will weaken the immune system, but the body will fight off the infection and regain its health. Any virus can attach to any receptor on the somatic cell, showing the wide variety of viruses that could attack the body and provide a contrast to the selectivity of HIV viruses for CD4 receptors.

The user will have control over the order of attachment and immune system function, so a wide variety of presentations are possible and different topics can be focused on more than others. However, a description of an HIV infection followed by infection by an opportunistic disease will be included with the model. Finally, a simple instruction manual will be included with the model, allowing it to be used easily by anyone, including students in the class.

Final Design

Our final product is an interactive display board that can be used as a teaching tool to explain why HIV is a more deadly than any other virus. The presentation of our project goes through three different scenarios: the binding of a normal virus to a somatic cell, binding of HIV to a helper T cell, and the binding of a normal virus after HIV has infected the body. It then shows how the immune system responds to each of these

scenarios. Each stage of the demonstration is manually controlled to allow the operator to give explanations between each step of the process.

Figure 7: Final Product

Model Construction:

Our project is displayed on two foam display boards. The first board has slots cut into it to secure all of the components and the back board was added to cover the cells and circuit as well as for additional support. Two support stands are attached to the back of the board so it can easily stand independently on a table during the presentation. The helper T cell and somatic cell are created out of crafter's hollow foam hemispheres. They were initially covered with a layer of Activ-Clay. The clay gave a solid base over the foam and a layer of plaster was added for more support. A layer of Mod Podge was then painted over the plaster to act as a sealant and a base coat for the acrylic paint. The cell receptors are constructed out of soda bottle caps which allows it to be screwed on to demonstrate permanent binding. The clay was placed over the bottle to hold the receptors

in place. The viruses and HIV are constructed out of the bottle cap on a small foam sphere secured by a layer of clay, plaster, and Mod Podge.

The somatic cell is used only to show binding of any non-HIV virus and the immune system response so it is glued to the board as a whole because the cellular virus process is not shown with the somatic cell. However, since our project is created to show the process of HIV infection, the helper T cell splits opens in order to demonstrate the intracellular mechanisms and lysis. The bottom half of the helper T cell is attached to the board via three screws that are placed through aluminum tracks that are used as a guide to open the cell. The two screws on the outside have two nuts and small locking washers that act as guides during lysis. The center screw has a larger washer that can be easily tightened to secure the cell closed and loosened to allow the cell to open. This way the operator only has to adjust the wing nut to split open the cell. There is also a nucleus on the display board, which is projected from the inside of the helper T cell. The nucleus is composed of an acrylic hemisphere with a tube that is wrapped around a rod to represent the injection of viral RNA into the nucleus of the host cell. The top of the tube contains a slot which holds a syringe that can be filled with colored liquid so the injection can be seen from a distance. The bottom of the tube contains a clamp so the liquid will not leak out and can stay in the nucleus for the entire presentation.

The last section of our project is the representation of the immune system. It consists of a black foam board that is projected out from the display board. The

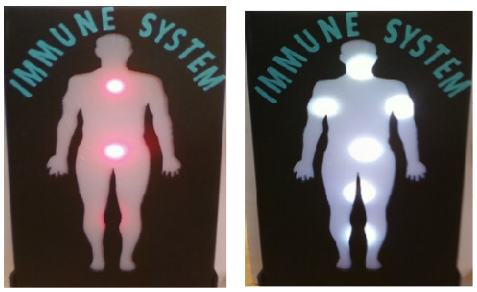


Figure 8 : The figure on the left shows the red circuit lit up to represent death. The figure on the right shows the white circuit lit up to represent the immune system strength

silhouette of a man is cut out of this box and a vinyl sheet is placed behind the man so the lights from the circuit behind it can be illuminated across this sheet. Two circuits were created and placed inside this box. The first circuit consists of six white LEDs connected in parallel to a flip switch and a 1k-5k ohm potentiometer. The potentiometer is a variable resistor and it is connected to a knob that can be accessed behind the display board in order to make the white lights dim after they are turned on with the flip switch. The white lights are placed in general areas where the lymph nodes are concentrated in the body. The second circuit consists of three red LEDs connected in parallel to a flip switch with a 217ohm resistor. Both of the circuits run on two D-batteries. The batteries are easily accessible from behind the display board so they can be replaced when needed. The circuits are covered by the back display board. The two switches and the potentiometer knob are also easily accessible behind the display board near the edge so the operator can access them while giving a lecture without having to strain to reach them.

Figure 9: View from behind board (switches, potentiometer knob, and batteries)

Budget

Date Purchased	Store	Item Purchased	Price
11/3/2009	Hobby Lobby	3 foam display boards	$5.97
		2" Styrofoam balls	$4.27
		Tax	$0.56
	Plasteel Corporation	8" Smoothfoam ball	$12.08
		shipping and handling	$4.95
11/13/2009	Hobby Lobby	Activ-Clay	$14.99
		modeling clay	$7.99

		paintbrushes	$4.47
		acrylic paint (x6)	$5.94
		black poster board	$5.99
		Tax	$2.17
11/17/2009	Hobby Lobby	(-)modeling clay	($7.99)
		(-) tax	($0.44)
		Plaster	$2.99
		Mod Podge	$4.47
		Tax	$0.41
11/20/2009	Dollar Tree	shower curtain liner	$1.00
		Panasonic battery	$1.00
		Tax	$0.11
	RadioShack	zip coil	$4.39
		3 white LED 2 pk	$5.97
		3 red LED	$5.97
		2 rocker switches	$5.98
		battery holder	$1.79
		potentiometer	$2.99
		Tax	$1.47
11/24/2009	True Value	miscellaneous hardware	$6.00
11/27/2009	Michaels	acrylic sphere	$1.99
		Tax	$0.10
		TOTAL	**$107.58**

How to Operate Model

1) Turn on white lights with switch to show immune system at full strength
2) Fill syringe to halfway with red food colored water and insert syringe into the smaller slot in the top of the tube behind the board. Keep the bottom of the tube unclamped.
3) CASE 1:
    a. Bind virus to somatic cell

b. Dim white lights down half way with potentiometer knob to show the strength of the immune system is weakened by virus
c. Turn potentiometer so the white lights return to full strength to show the immune system is able to fight off the virus
d. Unbind virus from somatic cell

4) CASE 2:
   a. Bind HIV to helper T cell
   b. Injection stage – push down the syringe to fill the tube in the nucleus. Make sure to hold the bottom of the tube upward so it does not leak out the bottom. Once the tube is full you can clamp the bottom so it stays filled throughout the presentation. This represents the viral DNA being incorporated into the DNA of the helper T cell. Once injected, HIV takes over the functionality of the host cell and uses it to continue replication.
   c. Dim the lights about half way down with the potentiometer knob to show the strength of the immune system is weakened by the virus
   d. Lysis stage - loosen the center bolt behind the board and guide the bottom of the helper T cell so it splits from the top. Inside the helper T cell there are mutated HIV which are able to rebind to the CD4 receptors.
   e. Dim the white lights almost all of the way off. This shows that since the HIV are mutating during the replication process, the immune system is not able to fight off this virus as fast as it is able to fight off a normal virus. Also since the HIV are rebinding to helper T cells, the number of helper T cells in the immune system is declining steadily as they split. Helper T

cells are what send the signals to the immune system to fight off the virus, so since the number of helper T cells is declining, the strength of the immune system is declining and not able to respond to full strength.

f. Rebind virus to somatic cell

g. Turn on the red lights to show death since the strength of the immune system is so low due to the death of the helper T cells; they are not able to send signals to the immune system to fight off this other virus. It is the infection of the body from this opportunistic virus that eventually kills a person infected with HIV.

Ethics

HIV/AIDS is a controversial subject and should be discussed a professional manor. Because the students in this class are from very diverse backgrounds, the description of HIV infection must be scientific. The final product will be purely under the control of the client, so the misuse of the model is not a concern.

Ergonomics

The torque required to attach the viruses to the cells is minimal and they can be unscrewed with ease. The syringe and clamp require a minimal force to push the liquid through the tube. In the lysis stage, the wing nut is twisted tight by a few turns with a single hand. The potentiometer is equipped with a large knob for ease of dimming the white LED circuit. Two switches have been incorporated into the design to allow for easy operation of the circuits. The battery pack is accessible for replacing the battery in the

future. The whole model is fitted with two supports, which allows the model to stand independently.

Future Work

If future work on the model occurs, a few aspects of the design and construction could be improved. Researching materials that are more durable than the clay and plaster mix could be used to improve the longevity of the individual viruses. If the budget were to be expanded there are several parts of the model that could be molded out of plastic to allow for a smoother appearance to the model. The plastic molds would have to be designed and sent out to a company to pour. Cost, resilience, and user safety must still be taken into account in considering changes to the model structure and construction.

Works Cited

"The Human Immune System: Our Defense Mechanism." Davidson College. 5 October 2009.<http://www.bio.davidson.edu/Courses/Molbio/MolStudents/spring2003/Cobain/geneprotein.html>

Cichocki, M. "The HIV Life Cycle" about.com. Medical Review Board. 5 October 2009. <http://aids.about.com/od/newlydiagnosed/ss/livecycle.htm>

"Computer Generated Model of HIV in Bloodstream." Getty Images. 5 October 2009. <cache.gettyimages.com>

Noble, Rob. "HIV Structure and Life Style." Avert. 18 September 2009. <http://www.avert.org/hiv-virus.htm>

Nogrady, Bianca. "T Cell Turnoff." *Scientific American*. December 2007. Vol.297.Pgs.24-26 10 October, 2009. EBSCO Host.

Poeschla, E. M. "The HIV-1 Life Cycle." Mayo Clinic. 5 October 2009. <http://mayoresearch.mayo.edu/mayo/research/poeschla/life_cycle.cfm>

"Replication Cycle of HIV." National Institute of Allergies and Infectious Diseases. 5 October 2009. <www3.niaid.nih.gov/topics/HIVAIDS/Understanding/How+HIV+Causes+AIDS/howhiv.htm>

APPENDIX A

Educational model to illustrate HIV infection cycle
Product Design Specification Report

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Jonathan Mantes – *Team Leader*
Kim Carlson – *Communicator*

Problem Statement

Our client, Marge Sutinen of the UW School of Medicine and Public Health, works to educate students on the permanent effects of HIV in her Contemporary Issues in HIV/AIDS Prevention course. She has asked our team to develop a three dimensional model that captivates the attention of a class of undergraduates and visually illustrates the HIV attachment to CD4 receptors on helper T cells, the permanent effect it has on the body, as well as the differences between HIV and other viruses. This model will be used as an aid in demonstrating the irreversibility of contracting the HIV virus to persuade students to use preventative measures to protect themselves.

Client Requirements

- The model must be able to be easily transported to and from the classroom.
- The model must be clearly seen from a distance of 6 meters.
- The model must be 3 dimensional and color coordinated.
- The model should be directed towards college undergraduate students with minimal scientific knowledge.
- The number of separate pieces and need for assembly should be minimized.
- The model must be audience captivating.
- The model must show the difference between HIV and other viruses

Design Requirements

Physical and Operational Requirements

a) *Performance Requirements* – The device will only be used for about one lecture every semester. It should be durable enough for handling and viewing in the classroom and be able to be passed around by the students. It should also be functional after being in storage for a long time between uses.
b) *Safety* – The model should have an absence of sharp edges and an abrasive surface. There must be no parts that provide a safety hazard to our client during transportation or operation. It must be able to be handled often.
c) *Accuracy and Reliability* – It does not need to be biologically proportional to an actual cell. It is not intended for exact structure and scientific use. It only needs to be a general representation of the structure, emphasizing the parts involved in the

process. The parts should not deform once the model is disassembled and the parts should fit back together for easy assembly.

d) *Life in Service* – The parts should not wear over time. The model will be a teaching tool for undergraduate students during its lifetime.
e) *Shelf Life* – The model will spend the majority of its time in storage as it will only be used for about one lecture every semester. Thus the model should not be composed of any materials that will degrade while in storage.
f) *Operating Environment* – The model will be displayed and operated by one person as a teaching tool for students. The model will be operated at room temperature and pressure.
g) *Ergonomics* – Model must not injure or cause harm to user. Parts should be large enough to handle easily. The torque required for screwing on and off and releasing parts should be reasonable. It should run smoothly and efficiently during each run.
h) *Size* – The model should be easily transported by one person to and from class. Approximate size no larger than 1 m x 1 m x .5 m.
i) *Weight* – The model should be easily carried by one person. Approximate weight no more than 5 kg.
j) *Materials* – All materials need to be non-radioactive, non-flammable, and non-corrosive.
k) *Aesthetics* – The model should be pleasant to touch, comfortable to hold, and have soothing colors.

Product Characteristics

a) *Quantity* – One prototype
b) *Target Product Cost* – Must be around $100.

Miscellaneous

a) *Standards and Specifications* – N/A
b) *Customer* – The model must be easy to view and be understandable by undergraduate students with minimal scientific background.
c) *Patient-related concerns* – The model should be able to be sterilized to prevent contact transmission of viruses such as H1N1.
d) *Competition* – There are similar items on the market but none that are marketed towards our target audience and effectively demonstrate the severity of HIV.