Medical Microbiology (BI 158)  
Virology Section  
Spring 2000  
FINAL EXAM  
May 11, 2000

This is a 1.5 hour exam covering the Virology section of BI 158. There are 135 points on this exam and it is worth 27% of your final grade.

1. (4 points) Define the following terms:

   A. **Virion** - A complete infectious unit consisting of nucleic acid, any proteins required for packaging & initial infection, a capsid, and an envelope if appropriate.

   B. **Capsid** - A protein shell, coded for by the viral genome, which protects the viral genes from the environment & allows infectivity/receptor binding.

   C. **Envelope** - A plasma membrane containing virally coded glycoproteins which is obtained when budding from the host nucleus, golgi, or cytosol.

   D. **Nucleocapsid** - An inner protein shell which directly surrounds the viral genome. Seen in viruses such as HIV.
2. Describe the following regarding HIV-1:

A. (2 pts) the mechanism by which the virus acquires an envelope
   
   Bulding from the host cell membrane.

B. (2 pts) the composition and origin of the envelope
   
   Phospholipid Bilayer - Host
   Glycoproteins - Virus

C. (2 pts) the major envelope glycoprotein(s)
   
   gp41 & gp120
3. (4 pts) Mutation are introduced into the HIV genome at two different steps in the life cycle of the virus. Name these two steps and the enzymes involved at each step.

- During the initial reverse transcription from (+) ssRNA to dsDNA by **Viral RT**.
- During transcription of provirus to mRNA by **host cell RNA polymerase**.

4. Illustrate or describe how the following viruses produce mRNA (include critical enzymes involved and indicate whether they are virus encoded or host cell encoded).

**Herpesviruses**

Viral Genome is dsDNA → Host Cell RNA Pol → mRNA

**Paroviruses**

- Genome is (+) ssRNA → Viral RNA Dep RNA Pol → mRNA
- Genome is (+) mRNA → (can be either)

- 2
(2 pts) Hepatitis C virus

Viral genome is (+) mRNA

(2 pts) Hepatitis A virus

Viral genome is (+) mRNA

(2 pts) HTLV-1

Genome is (+) RNA $\xrightarrow{\text{Viral RT}}$ ds DNA $\xrightarrow{\text{Host RNA pol}}$ mRNA

Viral integrated

Integration

(2 pts) Coltivirus

Genome is (-) RNA $\xrightarrow{\text{Viral RT}}$ +RNA $\xrightarrow{\text{RNA dep RNA pol}}$ (-) mRNA
5. Graph the following types of infections where the X-axis = time and the Y-axis = virus titer. Give one example for each type of infection.

(2 pts) Acute – Hep A

(2 pts) Chronic – Hep B

(2 pts) Latent (include reactivation) – HTLV-1
6. Define the following terms:

(2 pts) incubation period
   Time from viral infection to onset of symptoms
   ✓

(2 pts) viremia
   Presence of virus in the bloodstream. Represents a systemic infection.

(2 pts) tropism
   Preference for a particular tissue or cell-type by a virus.
   ✓

7. What is the incubation period for the following viral infections:

(2 pts) Flu (influenza A)  1-5 days  ✓

(2 pts) Common Cold (rhinovirus)  1-3 days

(2 pts) Chicken Pox (VZV)  5-15 days
8. BRIEFLY describe the general mechanism by which each of the following types of retrovirus induce tumors?

A. (2 pts) Transducing Retroviruses:
   
   The virus captures a host proto-oncogene on its genome, this gets mutated over time and is expressed in an oncogenic form. Example - V-erbA

B. (2 pts) cis-Activating Retroviruses:
   
   A tightly controlled host proto-oncogene comes under control of a viral LTR after viral integration.

C. (2 pts) trans-Activating Retroviruses
   
   Virally encoded proteins block the actions of host cell tumor suppressors. Example: HTLV-I tax protein

9. (4 pts) Overview the process of reverse transcription?

   Viral RNA dependent DNA polymerase synthesizes a DNA strand from the viral RNA template. Often this template is destroyed.

   The viral RNA/DNA dependent DNA polymerase synthesizes a complement to the ssDNA, producing a dsDNA copy of the original viral genome.

10. (2 pts) Where does reverse transcription take place in the infected cell?

     Cytosol.
11. (8 pts) Compare and contrast the mechanisms of action of two classes of drugs targeted at RT (be sure to include the general name of each class of drug).

The two classes which target RT are NRTIs (Nucleoside Reverse Transcriptase Inhibitors) and NNRTIs (Non-nucleoside Reverse Transcriptase Inhibitors).

NRTIs are nucleoside analogs. They compete with normal dNTPs to be incorporated into the chain. However, since they lack an 3'-OH they prevent elongation of the backbone once incorporated. An example of this class is AZT.

NNRTIs are non-competitive inhibitors of viral RT. These are not chain terminators, but bind to RT at a site other than the active site & shut down the enzyme. One example is delavirdine.

NRTIs can be toxic to the host, both directly & indirectly. NNRTIs are usually non-toxic, since the host does not have RT. Mutations to circumvent both classes have been observed.
12. (3 pts) Which of the following Herpesviruses:
HSV-1, HSV-2, CMV, EBV, VZV
establish latent infections in:

A. Neurons HSV-1 /2 & VZV
B. Monocytes CMV
C. B cells EBV

13. (4 pts) Of the Herpesviruses listed above which would you most likely treat and under what circumstances with:

acyclovir? HSV-2 (Genital Herpes) in an infected, pregnant mother to prevent vertical transmission.

gancyclovir? CMV in an immunocompromised patient or a patient with CMV reactivations.
14. (4 pts) Describe the molecular basis for the selectivity of acyclovir for Herpesvirus infected cells.

Acyclovir is a prodrug that requires three phosphorylations to become active. The first phosphorylation is done exclusively by a herpesvirus encoded thymidine kinase. The other two can be done by the host.

15. (2 pts) Which of the Herpesviruses is the etiological agent of genital herpes?

HSV-2
16. (8 pts) During one of your clinical rotations a older gentleman is brought in with a single but severe bite wound to his left hand. He describes how he was bitten by a red fox that he was attempting to feed. The fox was not captured and the rabies status of the animal is unknown. Describe to the gentleman your treatment strategy and the rationale for your decision.

I would begin by assuming that the fox was carrying rabies. Given this assumption, there is a 15% chance that the gentleman will become infected from the bite. If he begins to develop symptoms, he will most certainly die. (100% case-fatality rate). Given the dismal outcome, I would clean the wound to reduce infectivity if local spread. I would give him pooled gamma globulin (human) to passively immunize him to spread. I would also vaccinate him to give him active immunity in case the IgG fails to clear the initial infection. If pooled IgG & vaccine are unavailable, I'd amputate his hand and possibly lower arm, since retrograde spread to the CNS is slow.
17. (8 pts) During your next clinical rotation in the neonatal intensive care unit you observe a 3 month old infant who is having difficulty breathing and presents with nasal discharge and a low grade fever. Following 3 days of treatment consisting of oxygen and suctioning of secretions the infant's condition worsened considerably. Cultures identified RSV in the nasal secretions. Explain to the parents what RSV is and how you plan to treat their infant.

RSV is a member of the pneumovirus genus, paramyxovirus family. It has a negative stranded RNA genome which must be copied to a (+)RNA before viral proteins are expressed. The infection is characterized by bronchectasis, which explains the child's difficulty breathing and formation of syncitial bodies.

At three months the child is relatively immunocompromised and will have difficulty fighting the infection. I would treat him/her with aerosolized Ribavirin. Ribavirin is a broad spectrum anti-viral, but is toxic if given IV. Giving it by spray ensures that it is delivered only to the area that needs it (respiratory tract.)
18. Describe the mechanism of action of the following drugs and indicate which viruses you would treat with them:

(2 pts) Amantadine-HCL

Rx for Influenza A.
Blocks M2 proton pore, inhibiting uncoating of the virus.

(2 pts) Zidovudine

aka AZT
Rx for HIV
Chain terminator. Looks like a thymidine residue, but is didemine.

(2 pts) Nevirapine

Rx for HIV
Non-competitive inhibition of viral RT.

(2 pts) Saquinivir

Rx for HIV
Protease inhibitor - mimics transition state & blocks the viral Asp-protease

(2 pts) Gancyclovir

Rx for CMV
Thymidine analog - chain terminator (didemine) which is activated by viral thymidine kinase.
19. (32 points) Fill in the missing information:

<table>
<thead>
<tr>
<th>FAMILY</th>
<th>GENUS</th>
<th>SPECIES</th>
<th>Enveloped (+/-)</th>
<th>Replication in N or C</th>
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<tr>
<td>Picornaviridae</td>
<td>Hepatitisvirinae</td>
<td>hepatitis A virus</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paramyxoviridae</td>
<td>Rubulavirusae</td>
<td>mumps virus</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Bunyaviridae</td>
<td></td>
<td>coxsackievirus</td>
<td>-</td>
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<tr>
<td>Flaviviridae</td>
<td>Alphavirusae</td>
<td>EEE</td>
<td>+</td>
<td>-</td>
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<td>Togaviridae</td>
<td>Rubivirusae</td>
<td>Rubella virus</td>
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<td>Flaviviridae</td>
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<td>West Nile Fever</td>
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<td></td>
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<td>Hepatitis C virus</td>
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<tr>
<td>Reoviridae</td>
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<td>coltivirus</td>
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</table>
3. (2 pts) In one sentence state your definition of a virus.

"A virus is an obligate intracellular parasite that infects living organisms such as animals, bacteria, and plants but not other viruses."  

4. (5 pts) The mutation rate for DNA viruses is at least 10,000 fold less than the mutation rate for RNA viruses. Why?

"RNA viruses use RNA polymerases that lack proofreading ability whereas DNA viruses use DNA polymerases that do have proofreading ability."  

5. (5 pts) Does vaccination with an inactivated or killed virus vaccine such as the Salk polio vaccine generate herd immunity? Why, or why not?

"No, vaccination with an inactivated vaccine such as the Salk polio vaccine do not generate herd immunity because it is injected and generates no gut immunity (equal). The Sabin vaccine on the other hand is given orally and confers gut immunity. It generates herd immunity consequently by fecal-oral spread."  

6. (2 pts) Which of the following viruses are transmitted via the respiratory route? (circle all correct answers)

A. HTLV-1
B. Influenza C Virus
C. Rhinovirus
D. HIV-2
7. (5 pts) Vaccines based on papillomavirus L1 and L2 proteins generate a good systemic IgG response but a poor mucosal IgA response. Given what you know about the pathogenesis of HPV infection do you expect that systemic IgG will prevent HPV infection at mucosal surfaces. Discuss why or why not?

Yes, the systemic IgG will prevent HPV infection at mucosal surfaces. The HPV infection resides in the basal cells of the skin of the cervix for example and only begins to produce mature viral proteins as the cells mature and rise to the top. In order to be infected by HPV, there must be a break or a tear at the mucosal surface to expose the basal layers to the viruses. Hence, mucosal immunity is of little consequence since infection takes place in the basal layers but the systemic IgG may help prevent infection at those basal, deep layers when the break in epithelium occurs.

8. (2 pts) Polyomaviruses produce a single protein that interacts with two tumor suppressor proteins in the infected cell. Name these two tumor suppressor proteins.

p53
Rb

9. (2 pts) Papillomaviruses dedicate two proteins to do the same job as the one polyomavirus protein discussed above. Name these two papillomavirus proteins.

E6 → binds p53
E7 → binds Rb
10. (2 pts) Which of the following polyomaviruses is the etiological agent of progressive multifocal leukoencephalopathy? CIRCLE ALL CORRECT ANSWERS

A. SV40
B. BKV
C. LPV
D. JCV

11. (2 pts) Which of the following groups of papillomaviruses are strongly associated with the development of cervical cancer? CIRCLE ALL CORRECT ANSWERS

A. HPV-1, 3, 28, 41
B. HPV-5, 15, 17, 23
C. HPV-2, 6, 11, 32
D. HPV-16, 18, 31, 45

12. (2 pts) Which of the following statements are true about cervical cancer. CIRCLE ALL CORRECT ANSWERS

A. The leading cancer among women worldwide
B. 50% of sexually active young adults have been infected with HPVs that have malignant potential.
C. The E6 and E7 proteins are the only HPV proteins expressed in cervical carcinoma
D. Therapeutic vaccines targeting these two proteins are currently being developed
13. (2 pts) The hemagglutination assay and the hemagglutination inhibition assay measure two different things. What are they?

The hemagglutination assay is measuring for the presence of virus.

The hemagglutination inhibition assay is measuring for the presence of antibody to the virus.

14. (2 pts) What test is initially used to determine whether a patient is sero-positive for HIV-1?

The ELISA test is initially used to determine whether a patient is sero-positive for HIV-1.

15. (2 pts) What second test is used to confirm the sero-positive status of a patient?

The second test used to confirm the sero-positive status of a patient is the Western Blot test.
16. (2 pts) What two tests are used to measure HIV viral load in patients.

1. The reverse transcriptase PCR test
2. Branch enzyme-linked test

17. (2 pts) If a patient presents with high HIV viral load and is treated with a combination of anti-retroviral drugs—what two things would you want to measure to determine whether the patient is responding to the drugs.

1. Viral load after drug treatment
2. CD4+ T cell count
18. (5 pts) Picornaviruses produce a protease that plays a critical role in the life cycle of the virus. This protease also has a profound inhibitory effect on host cell protein synthesis. Name the protease, describe its role in the life cycle of the virus, and discuss how it manages to inhibit host cell protein synthesis without affecting picornaviral protein synthesis.

The name of the protease is the 2A protease. The virus needs to be translated during its lifecycle to produce proteins. However, it lacks the 5' Cap needed for recognition by ribosomes. Host cell mRNAs have this cap present. The 2A protease cleaves the cap binding complex from host cell mRNA which shifts protein synthesis toward viral protein synthesis since host cell protein synthesis is now inhibited. Picornaviral protein synthesis remains unaffected because it uses an IRES (internal ribosome entry site) for recognition by the ribosome.

19. (2 pts) Which of the following influenza viruses has an animal reservoir? CIRCLE ALL CORRECT ANSWERS

A. Influenza A
B. Influenza B
C. Influenza C
2. (2 pts) Which of the following influenza viruses is responsible for global pandemics? CIRCLE ALL CORRECT ANSWERS

A. Influenza A  
B. Influenza B  
C. Influenza C

21. (2 pts) Amantadine-HCL is used prophylactically to prevent which of the following virus infections? CIRCLE ALL CORRECT ANSWERS

A. RSV  
B. measles  
C. Influenza B  
D. Influenza A

22. (5 pts) Describe the mechanism of action of amantadine-HCL?

Normally the influenza virus is taken up within an endosome. This endosome fuses with a lysosome causing the pH to drop. The drop in pH activates the M2 protein which is an ion channel forming protein. As a consequence, H+ rush into the vesicle causing a viral protein to be activated and fuse the viral particle to the vesicular membrane to be released into the cell. Amantadine is an M2 protein ion channel blocker which prevents the virus from uncoating and entering the cell by preventing H+ ions from entering.

23. (5 pts) Why does actinomycin D inhibit orthomyxovirus replication but has no effect on paramyxovirus replication?

Actinomycin D inhibits orthomyxovirus replication but has no effect on paramyxovirus replication because it primarily works in the nucleus where orthomyxoviruses replicate. Paramyxoviruses, on the other hand, replicate in the cytoplasm.
24. (2 pts) What drug is used to treat severe cases of RSV infection?

Ribavirin

25. (2 pts) What combination of therapies are used to treat a suspected exposure to rabies?

gamma globulin and vaccination

26. (5 pts) What two places in the life cycle of HIV-1 do mutations occur and why?

The two places in the life cycle of HIV-1 where mutations occur are:

1. When reverse transcriptase is transcribing viral RNA to DNA

2. When the DNA provirus is being replicated with DNA-dependent RNA polymerase

Mutations occur because RT and the RNA polymerase lack proofreading abilities

27. (2 pts) What two steps in the life cycle of HIV-1 are currently targeted by anti-retroviral drugs?

The two steps in the life cycle of HIV-1 that are currently targeted by anti-retroviral drugs are:

1. Where reverse transcription takes place (NRTI, NNRTI)

2. Where the activation of capsid protein by proteases takes place (e.g., gag-pol precursors)
28. (5 pts) Compare and contrast NRTIs and NNRTIs?
Both NRTIs and NNRTIs target the reverse transcriptase step of the HIV lifecycle where viral RNA is transcribed to viral DNA. They differ, however, by their mechanism of action. NRTIs are nucleoside analogs that are incorporated into the transcribed DNA by reverse transcriptase. They cause termination of DNA chain production through their incorporation. NNRTIs work by inhibiting reverse transcriptase.

29. (5 pts) Describe the sequence of events that take place in the initial steps of the HIV life cycle (attachment and entry)?

1. GP120 is located on the virus and is an attachment molecule. It recognizes CD4 on T lymphocytes in the host and binds to it. This binding causes a conformational change.

2. A chemokine receptor binding site is revealed on GP120 as a consequence of the conformational change. This receptor binding site binds to a chemokine receptor on the membrane of the T cell (e.g., CXC-R4 or CCR5). This binding causes a conformational change.

3. As a result of the 2nd conformational change, a fusogenic site is revealed on GP41.

4. HIV-1 virus core is inserted into the host.
30. (2 pts) Why are rotaviruses so difficult to control in hospital settings, especially in pediatric wards.

Rotaviruses are so difficult to control in hospital settings because they are easily transmitted through the fecal-oral route and there is a high density of virus in the stool.

31. (4 pts) Which cell type is targeted by the B19 virus and what is the effect of B19 infection in the following patient groups?

A. immunocompetent child

B. immunosuppressed child

C. fetus

Bone marrow erythroid progenitor cells are targeted by the B19 virus. In the immunocompetent child, B19 virus infection leads to Fifth Disease. In the immunosuppressed child, infection leads to a transient aplastic anemia or a chronic anemia. In the fetus, B19 infection leads to hydrops fetalis (death) or a chronic anemia.
32. (4 pts) Name the Herpes Virus (virus and subtype) most often associated with the following:

Ocular Herpes: *beta herpesvirus - HerV*

Oral Herpes: *alpha herpesvirus - HSV-1*

Genital Herpes: *alpha herpesvirus - HSV-2*

Encephalitis: *alpha herpesvirus - HSV-2*

33. (5 pts) Name the Herpes virus associated with the following disorders:

Chicken Pox *Varicella Zoster Virus (VZV)*

Shingles *Varicella Zoster Virus (VZV)*

Infectious Mononucleosis *Epstein-Barr Virii*

Burkitt’s Lymphoma *Epstein-Barr Virii*

retinitis in immunosuppressed patients *cytomegalovirus*

34. (5 pts) Why does the drug acyclovir specifically target Herpes virus infected cells?

The drug acyclovir specifically targets Herpes virus infected cells because the virus encodes a specific kinase (thymidine kinase) needed for the activation of acyclovir. When acyclovir initially enters the cell, it is inactive. Then it is phosphorylated once by thymidine kinase and subsequently two more times by host cell kinases to reach its fully activated state. Once activated, it incorporates into the DNA being produced during replication and prevents viral replication. Only herpesviruses encode for this thymidine kinase.
35. (2 pts) Which of the following viruses are associated with chronic hepatitis? CIRCLE ALL CORRECT ANSWERS

Hepatitis A

Hepatitis B

Hepatitis C

Yellow Fever Virus

36. (5 pts) Describe the unusual life cycle of hepadnaviruses

Hepadnaviruses are partially double stranded, partially single stranded DNA. Upon entry to the cell, the genome enters the nucleus where the single stranded DNA portion of the genome is repaired to yield ds DNA. This ds DNA is subsequently transcribed into mRNA. The mRNA leaves the nucleus and enters the cytoplasm (there is both mRNA and a special subgenomic RNA). Translation occurs in the cytoplasm of viral proteins from the mRNA. The subgenomic RNA is incorporated into a viral capsid where it undergoes reverse transcription into negative stranded DNA. The reverse transcriptase has RNAase H ability that degrades the RNA as the DNA is being made. Subsequently, the positive strand of DNA is made but is halted part of the way due to a lack of nucleotides. Hence, the genome is partially double stranded, partially single stranded. The virus particle then buds off the cell to infect other cells.