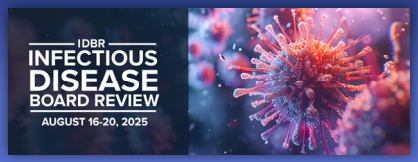

Core Concepts: Antiviral Drugs

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8/4/2025

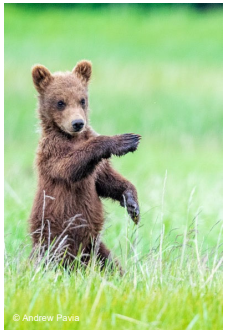
1

Disclosures of Financial Relationships with Relevant Commercial Interests

- Antimicrobial Therapy Inc.
- Haleon

2

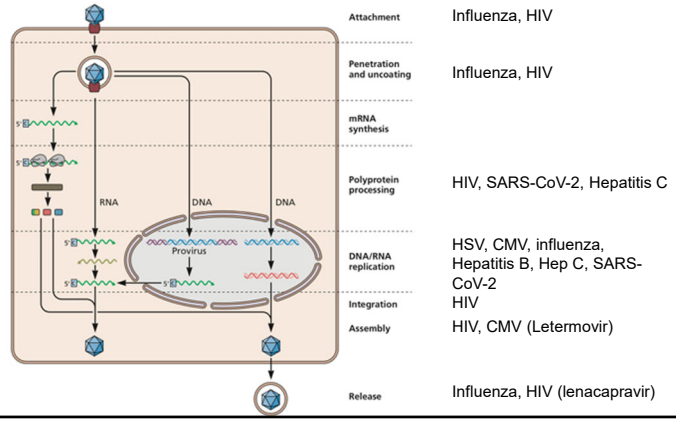
What You Need to Know



- Common basic mechanism e.g., target and drug type
  - Target: Polymerases (including reverse transcriptase)
    - Types: nucleoside/nucleotide analogs, NNRTI's, mutagens
  - Target: Entry
  - Target: Uncoating
  - Target: Integration
  - Target: Budding or release
- Clinically important resistance mechanisms and cross resistance – most testable
- It is possible that remdesivir, Paxlovid, or molnupiravir will be on the exam by mechanism

3

Antiviral Mechanisms of Action



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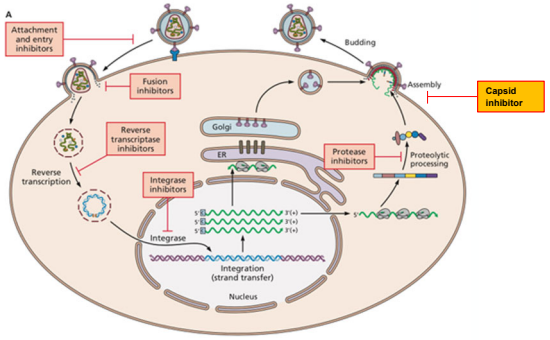
HIV Antiretroviral Targets in the Life Cycle

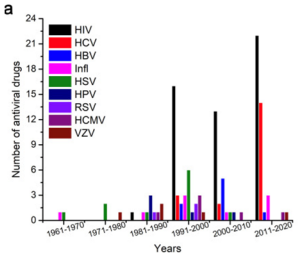


5

Limited Antivirals, Limited Targets

DNA Viruses
- Herpes Viruses
  - HSV
  - CMV
- Smallpox, mPox
- Hepatitis B
- Adenovirus

RNA viruses
- HIV
- Hepatitis C
- Influenza
- SARS-CoV-2
- Ebola, Lassa



Int J Biol Macromol. 2021 Mar 1:172

6

General Concepts

- Viruses use host mechanisms for part of their life cycle
- Need to inhibit a viral target without inhibiting host cellular target
- For acute infections, window of efficacy is generally short
- If replication is not completely inhibited, resistant mutants are likely to be selected
- The longer the duration of replication with drug exposure and the less effective the host response, the greater the risk of resistance. Combination therapy proven in chronic viral infections e.g., HIV, hepatitis C
- Pre-exposure prophylaxis important for HIV, CMV, and to a lesser extent influenza

7

Question #1

PREVIEW QUESTION

IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

A patient with HIV infection (CD4 count of 15 cells/μL, VL 2 million) has a 3-year history of a recurrent perianal herpes simplex that had previously responded to acyclovir or valacyclovir. On this occasion, the painful ulcers has not responded to a 10-day course of acyclovir 400 mg TID followed by a 10-day course of valacyclovir 1g bid. The patient has been adherent to his regimens.

What is the best therapeutic option?

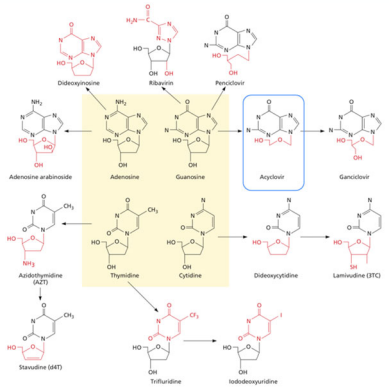
1. Intravenous ganciclovir
2. Intravenous acyclovir
3. Intravenous foscarnet
4. Valganciclovir
5. Famciclovir

8

Herpes Viruses

9

Nucleoside and Nucleotide Analogs



10

Acyclovir and Valacyclovir

- Acyclic guanosine nucleoside analogs, act as chain terminators
- Must be phosphorylated to tri-phosphate
- Therapeutic uses:
  - HSV-1, HSV-2, VZV but NOT CMV or EBV
- Resistance occurs almost exclusively in immunosuppressed hosts (especially HSCT recipients and advanced HIV)
  - More common with HSV than VZV
  - When acyclovir resistant HSV or VZV disease is successfully treated, usually with foscarnet, if recurrent disease occurs, the recurrent isolate is characteristically wild type, i.e., acyclovir sensitive
  - Secondary resistance (due to drug pressure) is more common than primary (the acquired virus is resistant)

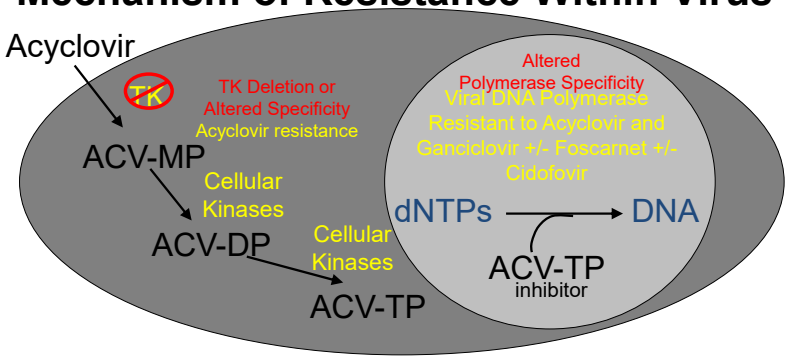
11

Acyclovir and Valacyclovir

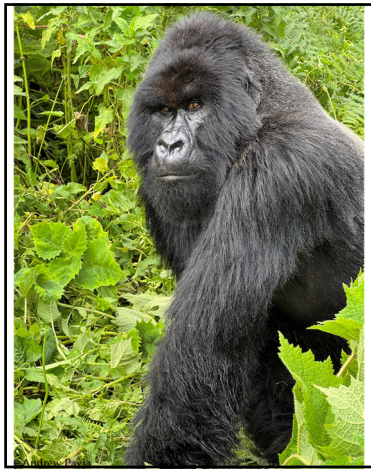
- Mechanisms of resistance
  - Thymidine kinase deficient viral mutants (absent TK)
    - Acyclovir and ganciclovir resistant viruses remain sensitive to foscarnet, cidofovir
  - Thymidine kinase alterations
    - Same as above
  - DNA Polymerase mutations (UL 54 mutation)
    - Acyclovir resistant: may also be resistant to ganciclovir or foscarent or cidofovir

12

Acyclovir Mechanism of Action Mechanism of Resistance Within Virus



13



CMV

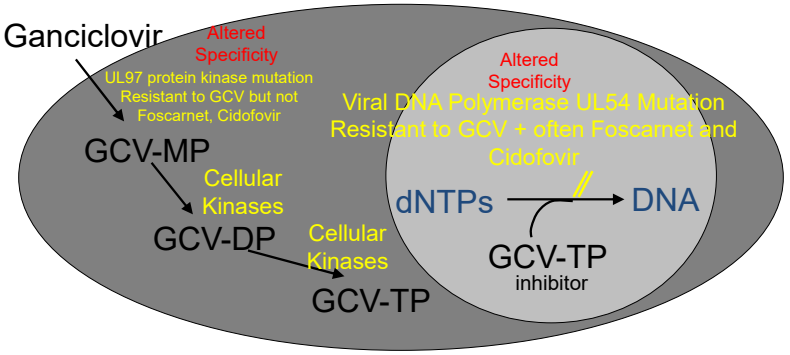
14

Ganciclovir and Valganciclovir

- Guanosine analog
  - Active against **CMV, HSV-1, HSV-2, VZV, +/- HHV-6**
- Requires initial phosphorylation by CMV UL97 ser/thr kinase
- Triphosphate inhibits viral DNA polymerase
- Resistance usually due to drug pressure (secondary resistance) rather than primary (transmitted virus)
  - UL 97-only (kinases) resistant to ganciclovir ("The last shall be first")
    - Usually appear first
    - Sensitive to foscarnet, cidofovir, marabavir
  - UL 54 (polymerase)-resistant to ganciclovir and often to foscarnet and /or cidofovir

15

Mechanism of Action of Ganciclovir Mechanism of Resistance Within Virus



16

Foscarnet

- Activity
  - Binds to DNA polymerase
  - Active against HSV, VZV, CMV, HHV-6A, HHV-6B
  - Active against resistant HSV, UL 97 mutant CMV
- Resistance
  - DNA Polymerase mutations
  - (UL54 and others, but not UL 97)

17

Cidofovir

- Mechanism of action
  - Acyclic phosphonate nucleotide analog
  - Inhibitor of phosphorylation by viral DNA Polymerase
- Activity
  - HSV-1, HSV-2, CMV
  - pox viruses, adenovirus, polyoma virus, papillomavirus
  - Probable efficacy for adenovirus, polyoma viruses
- Resistance
  - Viral DNA polymerase mutations (not UL 97)
- Use with caution
  - Significant renal toxicity

18

Letermovir

- Mechanism of action
  - Inhibitor of viral terminase subunit pUL56, a component of the terminase complex involved in DNA cleavage and packaging
- Activity
  - CMV
  - NOT HSV, VZV
- Use for prophylaxis approved
  - Limited data on treatment
- Drug Interactions
  - Cytochrome p450 3A inhibitor: increases cyclosporine, tacrolimus, sirolimus and decreases voriconazole
- Resistance
  - Emerges on therapy; de novo resistance rare
  - Not likely testable: UL56 gene of terminase complex. No cross resistance

19

Maribavir

- Mechanism of action
  - Non-nucleoside inhibitor of UL97
- Activity
  - CMV
  - NOT HSV, VZV
- Use for treatment of refractor CMV infections
- Drug Interactions
  - Cytochrome p450 3A substrate; inhibitors increase maribavir concentration
  - Inhibitor of P-gp
- Resistance
  - Emerges on therapy; mutations in UL97 but most different from ganciclovir

20

Hepatitis B

21

Therapy for Hepatitis B

- Lamivudine
  - Active against both HIV and HBV
  - Resistance:
    - Most common: YMDD motif in viral DNA polymerase, (similar to M184V in HIV)
    - Relatively common in patients chronically treated with lamivudine monotherapy
- Tenofovir (TDF and TAF)
  - Activity: HIV and HBV
  - Nothing testable about mechanism of resistance
- Telbivudine
  - Active against HBV only – DNA polymerase inhibitor
  - Nothing testable about mechanism of resistance
  - Not active against HIV
- Adefovir, Entecavir
  - Active against HBV and has some anti HIV activity
  - Entecavir can induce M184V mutation in HIV

22

Resistance Concerns if Patient Has HBV/HIV Coinfection

- Emtricitabine (FTC), lamivudine (3TC), and tenofovir (TDF) have activity against both HIV and HBV
  - When HBV and HIV treatment is needed, ART should be initiated with the combination of TDF + FTC or TDF + 3TC as the (NRTI) backbone of antiretroviral (ARV) regimen.
- If HBV treatment is needed and TDF cannot safely be used, entecavir is recommended in addition to a fully suppressive ARV regimen
- Entecavir has activity against HIV
  - Use without ARV in HIV/HBV co-infected patients may select for M184V mutation that confers HIV resistance to 3TC and FTC.
- If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, ARV drugs active against HBV should be continued for HBV treatment in combination with suitable HIV regimen

Red = testable

23

Influenza

24

Question #2

PREVIEW QUESTION

IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

A 65-year-old man in on the hematology oncology ward receiving conditioning prior to HSCT. He develops fever and an oxygen need. A PCR is positive for influenza A H1N1.

Which of the following regimens is appropriate AND least likely to lead to the emergence of resistance?

A. Rimantidine
B. Oseltamivir
C. Baloxavir marboxil
D. Rimantidine and Zanamivir
E. Letermovir

25

Influenza Therapy

- Adamantanes (Rimantidine, Amantadine)
  - Mechanisms of action
    - M2 protein
  - Activity
    - Influenza A only
  - Not recommended because resistance is widespread and stable
- Neuraminidase Inhibitors (Oseltamivir, Zanamivir, Peramivir)
  - Mechanisms of action
    - Inhibits release of new virions from surface of infected cell
  - Activity
    - Influenza A and B
  - Resistance:
    - H274Y mutation is most common (oseltamivir only, not zanamavir) which occurs mostly in Influenza A, confers partial resistance to peramivir
    - Occasionally emerges in HSCT patients on prolonged treatment or with prophylaxis

26

Influenza Therapy

- Baloxavir Single dose active against Influenza A and B
  - Mechanisms of action
    - Inhibits replication of viral RNA by interfering with polymerase complex via Cap-Dependent Endonuclease
  - Resistance
    - Several mutations (don't memorize) predominantly changes to I38X (Thr, Phe or Met)
    - **Treatment emergent resistance in 5% to as high as 20% in children**
    - Resistance more common in H3N2 than H1N1 and rare in influenza B
    - Do date, only limited transmission of resistant variants

27

SARS-CoV-2

28

SARS-CoV-2

- Remdesivir
  - Mechanism
    - Acts as adenosine nucleoside analog
    - Inhibits RNA-dependent RNA polymerase
  - Resistance
    - Resistant mutant selected for by serial passage in vitro, but none detected in clinical samples (with very limited data)
- Nirmaltrevir/ritonavir (Paxlovid)
  - Inhibits Mpro (main protease)
  - Drug-Drug interactions
  - Several mutations identified in Mpro that confer resistance but at fitness cost
  - Clinical importance of mutations remains under investigation
- Molnupiravir
  - Mechanism
    - Acts as cytidine nucleoside analog
    - Causes “catastrophic errors” in replication

29

See Antiviral Resistance Primer Online

Good Luck on the Exam!

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30