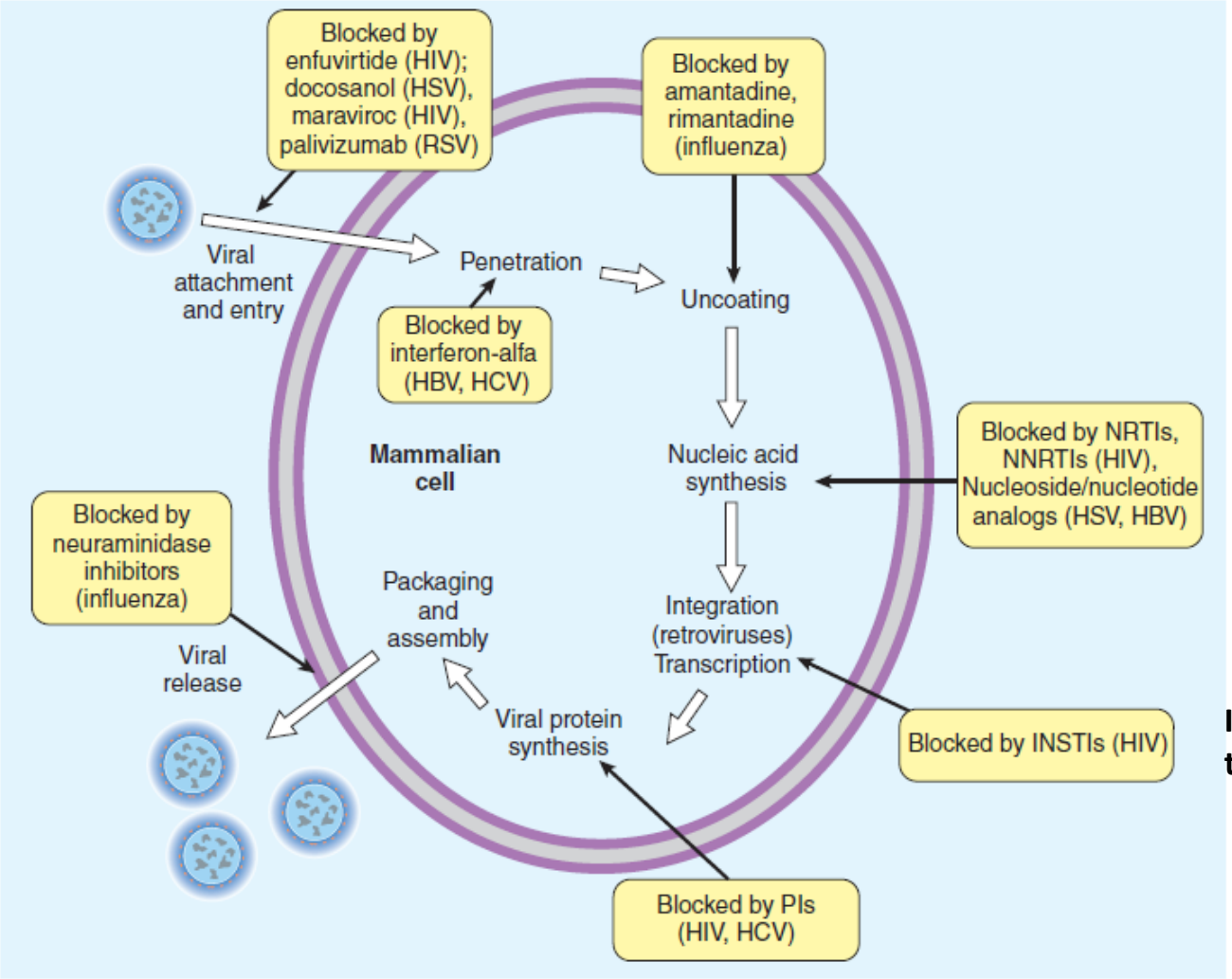
Drugs for Some Viruses Affecting Hematolymphatics

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Integrase strand transfer inhibitors

FIGURE 49–1 The major sites of antiviral drug action. *Note:* Interferon alfas are speculated to have multiple sites of action. (Modified and reproduced, with permission, from Trevor AJ, Katzung BG, Masters SB: *Pharmacology: Examination & Board Review*, 9th ed. McGraw-Hill, 2010. Copyright © The McGraw-Hill Companies, Inc.)

Agents for Cytomegalovirus (CMV)

- CMV infections occur in the setting of advanced immunosuppression, and are typically due to reactivation of latent infection.
- Dissemination of infection results in end organ disease: blood diseases (CMV-induced hemolytic anemia, thrombocytopenia, leukopenia, CMV mononucleosis, bone marrow suppression), retinitis, colitis, esophagitis, CNS disease (ventriculoencephalitis, encephalitis, polyradiculopathy , myelitis), and pneumonitis.

Agents for Cytomegalovirus

Ganciclovir (and valganciclovir prodrug):

- **It is an acyclic guanosine analog that requires activation by triphosphorylation.**
- **Initial phosphorylation is catalyzed by virus-specified protein kinase in CMV infected cells.**
- **Because it requires virus enzymes first for activation, the active metabolites accumulate in infected cells.**

Agents for Cytomegalovirus

- **The activated compound competitively inhibits the viral DNA polymerase and causes termination of viral DNA elongation.**
- **Resistance with long-term use is due to mutation in the kinase which results in less triphosphorylated active form of ganciclovir.**
- **The elimination half-life is 4 hours, and the intracellular half-life is 16–24 hours**
- **Administered IV because it is poorly absorbed orally**
- **Its clearance is related to creatinine clearance.**

Agents for Cytomegalovirus

Adverse Effects:

1. Bone marrow suppression (leukopenia, anemia, thrombocytopenia, pancytopenia), the most common
2. Gastrointestinal distress (nausea, vomiting, diarrhea, abdominal pain, loss of appetite, Hepatotoxicity)
3. Renal impairment
4. Hypomagnesemia, hypokalemia, hypocalcemia
5. Peripheral neuropathy
6. CNS toxicity (headache, confusion, seizures, psychosis)
7. Retinitis and retinal detachment
8. Infertility, aspermatogenesis and may impact ova production
9. Embryotoxicity (birth defects)
10. Fever
11. Vitreous hemorrhage and retinal detachment.
12. May be carcinogenic

Agents for Cytomegalovirus

Foscarnet (phosphonoformic acid):

Mechanism of Action:

- It is an inorganic pyrophosphate analog that inhibits viral DNA polymerase, RNA polymerase, and HIV reverse transcriptase directly without requiring activation by phosphorylation.
- It blocks the pyrophosphate binding site of these enzymes and inhibits cleavage of pyrophosphate from deoxynucleotide triphosphates.

Agents for Cytomegalovirus

Mechanism of Resistance:

- **Is due to point mutations in the DNA polymerase gene and is typically associated with prolonged or repeated exposure to the drug.**

Agents for Cytomegalovirus

Pharmacokinetics:

- **Foscarnet is available in an intravenous formulation only**
- **Although the mean plasma half-life is 3–7 hours, up to 30% of foscarnet may be deposited in bone, with a half-life of several months.**
- **Clearance of foscarnet is primarily renal and is directly proportional to creatinine clearance.**

Agents for Cytomegalovirus

Therapeutic Uses:

- **Foscarnet is effective in the treatment of end-organ CMV disease (retinitis, colitis, and esophagitis), including ganciclovir resistant cases**
- **The combination of ganciclovir and foscarnet is synergistic.**
- **However, toxicity is also increased when these agents are administered concurrently.**

Agents for Cytomegalovirus

Adverse Reactions:

1. **Renal impairment, hypo- or hypercalcemia, hypo- or hyperphosphatemia, hypokalemia, and hypomagnesemia**
2. **Genital ulcerations**
3. **Nausea, & vomiting**
4. **Elevation of liver enzymes and fatigue**
5. **Anemia**
6. **Headache, hallucinations, and seizures**

Cidofovir

- It is an acyclic cytosine nucleotide analog.
- Acivated by phosphorylation to the diphosphate independent of viral enzymes.
- It acts both as a potent inhibitor of and alternative substrate for viral DNA polymerase, competitively inhibiting DNA synthesis, and becoming incorporated in viral DNA.
- Cidofovir-resistant isolates tend to be cross-resistant with ganciclovir but not foscarnet.

Cidofovir

- Half-life of the active metabolite is much longer than the parent (~ 40 vs ~ 3 hours).
- CSF penetration is poor.
- Eliminated by active tubular secretion.

Uses (IV + Probenecid high dose):

- CMV retinitis – with aggressive hydration.
- Dose should be adjusted with changes in calculated creatinine clearance
- It is contraindicated in pre-existing renal insufficiency.

Cidofovir

Adverse effects:

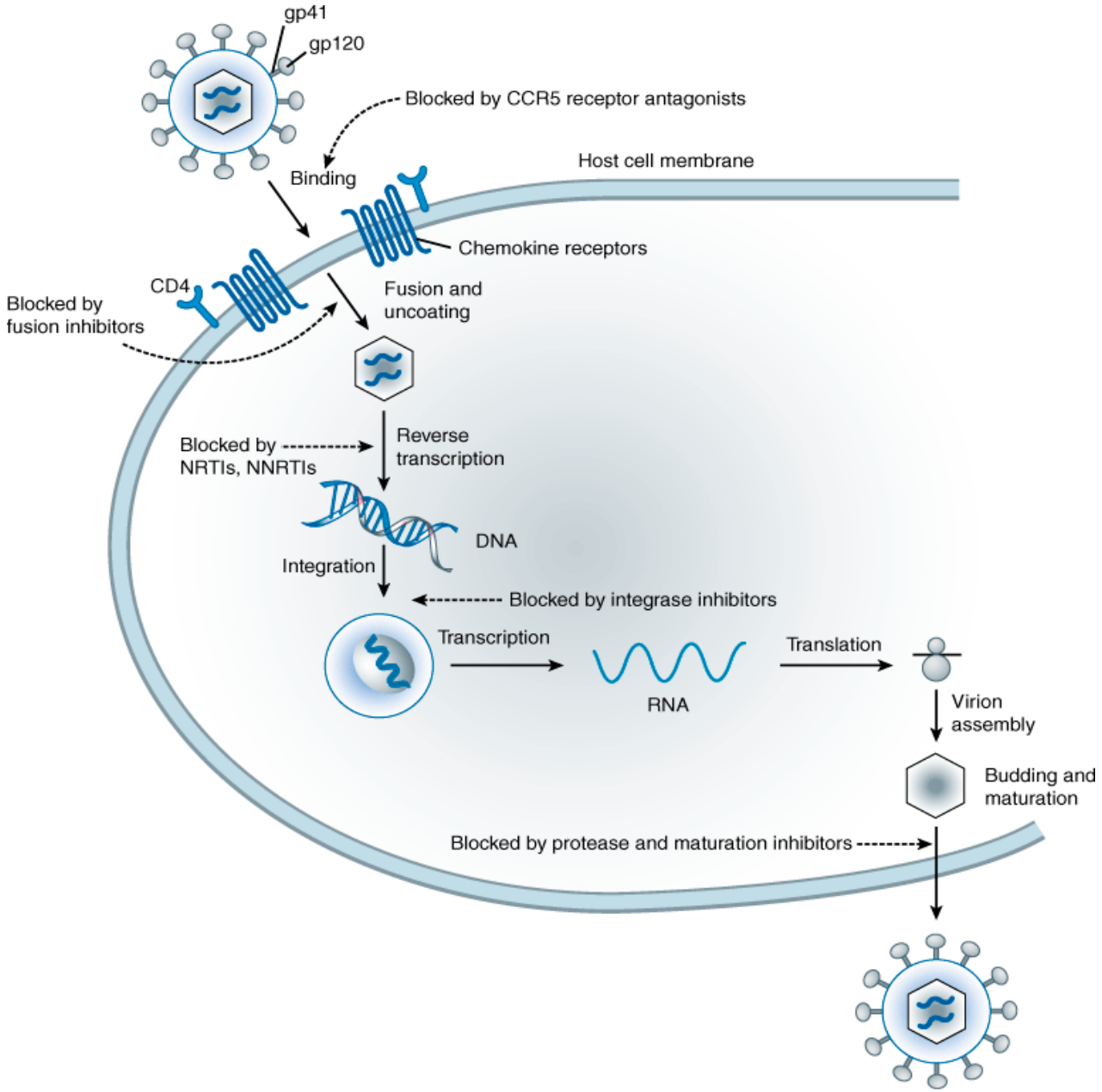
1. **Dose-dependent proximal tubular nephrotoxicity, which can be reduced by pre-hydration with normal saline.**
2. **Proteinuria, azotemia, metabolic acidosis, and Fanconi's syndrome.**
3. **Avoid use of other nephrotoxic agents.**
4. **Uveitis, ocular hypotony, and neutropenia.**
5. **Mutagenic, gonadotoxic, and embryotoxic and may be carcinogenic.**

Agents for Epstein-Barr (EBV/HHV-4) Virus

- **No specific and effective drug is available against this virus.**

Agents for Human Immunodeficiency Virus

- **Combination therapy with maximally potent agents reduce viral replication to the lowest possible level and decrease the likelihood of emergence of resistance.**
- **Typically 3-4 antiretroviral agents, has become the standard of care.**



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

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Life cycle of HIV:

1. **Binding of viral glycoproteins to host cell CD4 and chemokine receptors precedes fusion and entry into the cell.**
2. **After un-coating, reverse transcription copies the single-stranded HIV RNA genome into double-stranded DNA, which is integrated into the host cell genome.**
3. **Gene transcription by host cell enzymes produces messenger RNA, which is translated into proteins that assemble into immature noninfectious virions that bud from the host cell membrane.**
4. **Maturation into fully infectious virions is through proteolytic cleavage.**

NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside/nucleotide reverse transcriptase inhibitors.

Agents for Human Immunodeficiency Virus

1. Nucleoside & Nucleotide Reverse Transcriptase Inhibitors (NRTIs): Abacavir, Didanosine, Emtricitabine, Tenofovir.
2. Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs): Delavirdine, Nevirapine, Efavirenz.
3. Protease Inhibitors (PIs): Atazanavir, Indinavir, Ritonavir, Saquinavir.
4. Fusion Inhibitors: Enfuvirtide.
5. Entry Inhibitors: Maraviroc.
6. Integrase Strand Transfer Inhibitors (INSTIs): Raltegravir, Elvitegravir.

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

- Act by competitive inhibition of HIV-1 reverse transcriptase.
- Incorporation into the growing viral DNA chain results in premature chain termination due to inhibition of binding with the incoming nucleotide.
- All NTRIs may produce mitochondrial toxicity due to inhibition of mitochondrial DNA polymerase gamma.
- Can produce fatal lactic acidosis with hepatic steatosis (fatty liver).
- There may be an increased risk of myocardial infarction (MI) (?).

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

Abacavir:

- It is a guanosine analog.

Adverse Effects:

- Hypersensitivity reaction, occasionally fatal have been reported in 3-5% of patients. Test HLA-B*5701 allele before use.
- Symptoms which occur in the first 6 weeks of therapy: fever, vomiting, diarrhea, and anorexia.

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

- Respiratory symptoms (dyspnea, pharyngitis, and cough).
- Elevation of aminotransferases and creatine kinase levels.
- Pancreatitis
- Risk of MI.

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- They bind directly to HIV-1 reverse transcriptase, resulting in allosteric inhibition of RNA- and DNA-dependent DNA polymerase.
- Do not require phosphorylation to be active.
- As a class NNRTIs tend to be associated with GIT intolerance and skin rash that can be serious (Steven-Johnson syndrome).
- Metabolized by CYP3A4 → tremendous drug-drug interactions.

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Delavirdine:

Adverse effects:

- **Skin rash develops in ~ 40% of patients during the first 1-3 weeks of therapy.**
- **Severe rash – erythema multiforme and Steven-Johnson syndrome - is rare.**
- **Headache, fatigue, vomiting, diarrhea, and elevated serum aminotransferase levels.**
- **Pregnancy should be avoided.**
- **Extensively metabolized by CYP3A and CYP2D6 and also inhibits CYP3A4 and CYP2C9 → drug interactions.**

Protease Inhibitors

- During the later stages of HIV growth cycle, polyproteins that become immature budding particles are formed.
- Protease is responsible for processing of these proteins to produce the final structural proteins of the mature virion core.
- Protease inhibitors inhibit this post-translational cleavage of polyproteins, resulting in the production of immature, noninfectious viral particles.
- They are active against HIV-1 and HIV-2.
- They do not need intracellular activation.

Protease Inhibitors

- **A syndrome of redistribution and accumulation of body fat, resulting in central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral and facial wasting, breast enlargement, and a Cushingoid appearance has been observed with the use of these drugs.**
- **This has been concomitantly associated with elevated LDL and triglycerides, hyperglycemia and insulin resistance (except atazanavir). Cause is unknown.**
- **All are extensively metabolized by CYP3A4.**

Protease Inhibitors

Atazanavir:

Adverse effects:

- **Diarrhea, nausea, and vomiting.**
- **Peripheral neuropathy.**
- **Indirect hyperbilirubinemia and jaundice due to inhibition of UGT1A1 glucuronidation enzyme.**
- **Prolongation of PR interval and QTc interval.**

Fusion Inhibitors

- **The process of entry of HIV-1 into host cells entails binding of the viral envelope glycoprotein complex (gp120 & gp41) to its cellular receptor CD4.**
- **This binding induces conformational changes in gp120 that enable access to the chemokine co-receptors.**
- **Co-receptor binding induces further conformational changes in gp120, allowing exposure to gp41 → leading to fusion of the viral envelope with the host cell membrane → entry of viral core into cellular cytoplasm.**

Fusion Inhibitors

Enfuvirtide:

- It is a synthetic peptide fusion inhibitor that blocks entry into the cell.
- It binds to gp41 subunit of the viral envelope preventing the conformational changes required for the fusion of the viral and cellular membranes.
- Must be administered by sc injection.
- Eliminated by proteolytic hydrolysis.

Adverse effects:

- Injection site reactions
- Hypersensitivity and eosinophilia.
- Increased rate of bacterial pneumoni

Integrase Strand Transfer Inhibitors

Raltegravir:

- **It is a pyrimidine analog that binds integrase.**
- **Integrase is a viral enzyme essential to the replication of both HIV-1 and HIV-2.**
- **It inhibits strand transfer, the third and final step of provirus integration, thus interfering with the integration of reverse-transcribed HIV DNA into the chromosomes of host cells.**

Integrase Strand Transfer Inhibitors

- **Polyvalent cations (Ca^{2+}, Mg^{2+}, Fe^{2+}) may bind the drug and interfere with its activity.**
- **Adverse effects include diarrhea, nausea, headache.**
- **Increased creatine phosphokinase**