ANTI-HERPES ANTIVIRALS

	ACYCLOVIR (Zovirax)	VALACYCLOVIR (Valtrex)	FAMCICLOVIR (Famvir)
Info/Notes	Guanine nucleoside analogue	L-valine ester **prodrug of acyclovir**	Diacetyl-ester prodrug of the acyclic guanosine analogue 6-deoxypenciclovir (Denavir)

Uses	• Most effective against HSV-1 (oral) followed by HSV-2 (genital)
	  ○ Parenteral or topical – herpes simplex
	  ○ Oral – initial txt of genital herpes & prevention of recurrences
	• Varicells-zoster virus
	• Epstein-Barr Virus
	• Preferred in visceral, disseminated or CNS involvement (effective in latent state)
	• Acyclovir doesn't effectively treat active CMV (cytomegalovirus) disease
	• Severe cases of recurrent diseases treated parenterally (slow IV infusion)
		• Herpes zoster
		• Herpes simplex genitalis
		• Herpes labialis
			• Acute herpes zoster (shingles)
			  ○ Effective in reducing pain & healing time
			  ○ As effective as acyclovir for HSV treatment
			• In immunocompetent patients, is approved for treatment and prophylaxis of recurrent genital herpes
			• For HIV-infected patients, is approved for treatment of all recurrent mucocutaneous HSV infections

Mechanism of Action	• Acyclovir in therapeutic range has no effect on a cell not affected by a virus
	1. Acyclovir is taken up by the virus infected cells
	2. Acyclovir is converted to its active metabolite via 3 phosphorylation steps
	  a. Viral **thymidine kinase** converts acyclovir → acyclovir monophosphate
	  b. Host cell enzymes convert mono → diphosphate by cellular **guanylate kinase**
	  c. Several cellular enzymes convert di → acyclovir triphosphate (active compound)
	3. Acyclovir triphosphate is incorporated into viral DNA → irreversible inactivation of DNA polymerase
	• Triphosphate is present in 40-100 x higher concentrations in HSV-infected cells than uninfected cells
			1. Upon oral administration, famciclovir is converted to penciclovir by first-pass metabolism
			2. Penciclovir → monophosphate by viral thymidine kinase
			3. Mono → tri- phosphate by cellular kinases
			4. Penciclovir triphosphate acts as a competitive inhibitor of viral DNA polymerase (but doesn't cause chain termination like acyclovir)

Pharmaco-kinetics	• Oral bioavailability: 15-21% • Protein binding: < 20% • CSF: ⅓ of plasma levels • Half-life: 2.5 -3 hours • Primarily excreted renally: 60 – 91% by glomerular filtration & tubular secretion	• Oral bioavailability 3-5x greater (55-70%) than oral acyclovir (dose less frequently) • Actively transported by peptide transporter in intestine • During passage through intestine & liver, completely covered to acyclovir by **esterases** (→ higher plasma levels and improves clinical efficacy in certain conditions) • Excreted in urine as acyclovir • Half-life = 3 hour	• Penciclovir available as topical, absorption through skin undetectable • Famciclovir well-absorbed following oral administration ○ Converted to penciclovir = 77% bioavailability • Penciclovir < 20% bound to plasma proteins • Elimination half-life of penciclovir 2-3 hours; intracellular half-life of penciclovir triphosphate is 7-20 hours in infected cells • Penciclovir plasma half-life increased with renal insufficiency
Mechanism of Resistance	• Decreased thymidine production (altered substrate specificity) • Alteration in thymidine kinase that decrease its activity (exhibit cross-resistance to other antivirals that require thymidine kinase inactivation) • Alteration of viral DNA polymerase (decreased affinity for drugs)		• Mutations in DNA polymerases or thymidine kinases • Acyclovir-resistant HSV strains that exhibit thymidine kinase deficiency are also resistant to fam/pen-ciclovir

Side/Adverse Effects; Toxicities	• IV: phlebitis, reversible, nephrotoxicity
	• Oral acyclovir: nausea, vomiting, rash, headache, vertigo – infrequent
	• Topical: stinging sensations
	• Other: loss of appetite, stomach pain, headache, light-headedness, swelling in hands/feet
	• CNS: lethargy, confusion, tremor (1-3%)
	• Reversible renal dysfunction (5%)
	• Allergy: hives, difficulty breathing, swelling of face/lips/tongue/throat
	• Potentially serious SEs:
	  ○ Kidney problems and **low platelet count**
	  ○ Lower back pain
	  ○ Urinating less than usual or not at all
	  ○ Easy bruising or bleeding, or unusual weakness
	• Patients with poor liver or kidney function need special attention (GFR most important measure of kidney related toxicity)
	  ○ Most adverse effects associated with decreased renal function (drug serum > 25 mcg/mL)
			• No significant adverse effects to topical penciclovir
			• Oral famciclovir generally well-tolerated (headache, N/D)
			• Confusion may occur (elderly), hallucinations and urticarial reported

Warnings & Contra-indications	• Contraindicated in hypersensitive patients • Use with caution in immune-compromised pts (potential risk of thrombotic thrombocytopenic purpura (TTP) or hemolytic urine syndrome (HUS)) • Use in caution in patients with renal impairment & those receiving nephrotoxic drugs • Treatment should begin with 24 hours of rash appearance • Maintain adequate hydration during PO or IV therapy • Avoid rapid infusion because of risk of renal damage (renal failure → death has occurred)		• Chronic famciclovir administration may be **tumorigenic & impair spermatogenesis** (animal studies) • Dose adjustment necessary with renal impairment
Special Populations	Pregnancy: Appears to be safe in pregnancy Renal failure: Half-life and clearance dependent on renal function; dosage adjustment recommended Geriatrics: Plasma concentrations greater (age-related renal insufficiency); dose adjustment required Pediatrics: PK comparable to adults		
Drug Interactions	• Co-administration of **probenecid** and IV acyclovir increased half-life + AUC of concentration-time curve; urinary excretion & renal clearance reduced • **Interferon**: synergistic effects when administered with acyclovir; use acyclovir with caution when pt receiving IV interferon		• May interact with **probenecid** or other drugs eliminated by renal tubular secretion (increased drug concentrations)

ANTI-INFLUENZA ANTIVIRALS			
	M2 INHIBITORS	NEURONAMIDASE INHIBITORS	
	Amantadine (Symmetrel) & Rimantadine	Zanamavir (Relenza)	Oseltamivir (Tamiflu)
Info/Notes	Virus specific: influenza B is unaffected	Sialic acid analogues	
Uses	• Used for prevention & treatment of viral respiratory illnesses (influenza A strain) – works best within 48 h of symptom onset (70-90% effective) o For high risk in elderly patients with influenza o Duration of therapy: 3-5 days (decreases length of illness by 1 day) • Also used for Parkinson's Disease	• Act against both Influenza A and Influenza B (80% effective) o Must be administered < 48h after infection o Decrease symptoms and length of illness by 1 day • Inhalation dry power • Txt > 7 years old	• Oral • Txt > 1 year, prophylaxis > 13 years
Mechanism of Action	• Inhibits ion channel function of M2 → increased pH may inhibit membrane fusion → inhibits uncoating step (reduces shedding) → blocks infusion of virus with cell	• Blocks neuraminidase in InF-A and Inf-B → prevents viral release	
Pharmaco-kinetics	• Well absorbed • Renal excretion (amantadine), metabolized (rimantadine)	• Small amount is absorbed after inhalation • Excreted by kidney • Half-life = 2 – 5 h	• Converted in body to active drug
Mechanism of Resistance	• Resistance develops due to mutations in M2 proteins (30% of treated patients)	• Resistance is uncommon	
Side/Adverse Effects; Toxicities	• SEs usually seen at higher doses: orthostatic hypotension, CHF depression, psychosis, urinary retention, tremor/hallucinations • GI: nausea, anorexia • CNS: nervousness, insomnia, lack of concentration • Serious neurotoxic reaction could be fatal → may occur in association with high amantadine plasma concentration and is likely to occur in elderly patients with renal complications	• Bronchospasm in some individuals = **contraindicated in patients with asthma** • SEs: headache, dizziness, nausea, rashes	• SEs: nausea, vomiting and diarrhea • Abdominal pain (due to gastric irritation) – take with water • Insomnia, skin reaction (not common)
Warnings & Contra-indications	• Does not interfere with immunizations		
Drug Interactions	• Changes in DA neurotransmission occur = antihistamine, anticholinergic, hydrochlorothiazide and sulfa drugs may increase DA		• When concurrently used with probenecid, dose can be halved